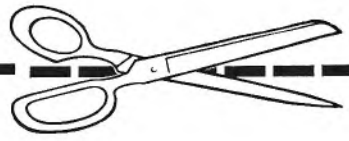
VOLUME 35 FEBRUARY 1970 NUMBER 2 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED MONTHLY BY THE AMERICAN CHEMICAL SOCIETY



Fill yourself in on reagents for:

Synthesis of aromatic aldehydes.

N-Methyl-N-phenylcarbamoyl Chloride
(EASTMAN 10912)

Under Friedel-Crafts conditions, N-methyl-N-phenylcarbamoyl chloride reacts with an aromatic compound to form an amide. Lithium aluminum hydride reduction of the amide yields the corresponding aldehyde. [Fieser and Fieser, *Reagents for Organic Synthesis*, John Wiley & Sons, Inc., New York, 1967, p. 494.]

Modification of α-chymotrypsin.

Methyl p-Nitrobenzenesulfonate
(EASTMAN 10958)

The modification of α-chymotrypsin through specific methylation of histidine-57 is accomplished with methyl p-nitrobenzenesulfonate in 0.1 M sodium phosphate buffer at pH about 7.9. Radioisotope studies confirm an almost stoichiometric reaction with α-chymotrypsin. Amino acid analysis pinpointed the modified active site of the enzyme as histidine-57. [*J.A.C.S., 91,* 1566 (1969).]

Poisoning Rosenmund-reduction catalyst.

Quinoline-Sulfur Reagent (EASTMAN 10979)

The Rosenmund reaction for reducing acid chlorides to their corresponding aldehydes requires a supported Pd catalyst. The quinoline-sulfur poison inhibits further hydrogenation under the normal reaction conditions. [*Ber., 54,* 425 (1921).]

Protein modification.

1-Nitroguanyl-3,5-dimethylpyrazole
(EASTMAN 10910)

Free amino groups of bovine serum albumen are modified by nitroguanidation with 1-nitroguanyl-3,5-dimethylpyrazole. Such modification is desirable, since it replaces a positively charged ammonium group with the non-basic nitroguanidino group. The modified proteins allow a study of the effect of changes in the net charge on physicochemical properties, as well as on their biological activity. Tyrosine, tryptophan, and histidine residues are unaffected by the reagent. [*Biochim. Biophys. Acta., 93,* 533 (1964).]

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THE JOURNAL OF Organic Chemistry

Published monthly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania

Published monthly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Easton, Pa.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, ANDREW J. D'AMELIO.

Advertising Office: Reinhold Publishing Corporation, 600 Summer St., Stamford, Conn. 06904

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VOLUME 35, NUMBER 2

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Intermediates in Nucleophilic Aromatic Substitution. VII.[1] Kinetic, Calorimetric, and Proton Magnetic Resonance Studies of the Formation of Meisenheimer Complexes of the Isomeric 2,4,6-Dicyanonitroanisoles

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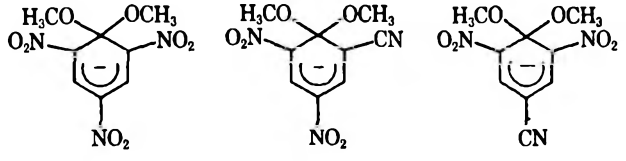
Received May 28, 1969

The rate and equilibrium constants, k_1 and K, for the formation of the 1,1-dimethoxy complexes of 2,6-dicyano-4-nitroanisole (**4**) and 2,4-dicyano-6-nitroanisole (**5**) together with the rate constants for their decomposition, k_2, have been determined in methanol and methanolic dimethyl sulfoxide solutions. The stabilities of **4** and **5** in methanol (K_4 = 35 l. mol^{-1}, K_5 = 10 l. mol^{-1}) are considerably smaller than those for their cyanodinitro- and trinitro-substituted analogs, and replacement of the two nitro groups in the 2 and 4 positions by cyano groups results in a greater decrease in K than the corresponding replacement of the 2- and 6-nitro groups. The observed linear increase in log K with increasing molarity of DMSO in methanol has been shown to be a composite effect of an increase in k_1 and a decrease in k_2. The structures of **4** and **5** are substantiated by pmr spectra of both the isolated and *in situ* generated complexes. In the *in situ* generation of **5**, but not of **4**, by the reaction of methanolic methoxide ion with the parent ether in DMSO-d_6 solution, the formation of an unstable transient, 1,3-dimethoxy-2,4-dicyano-6-nitrocyclohexadienylide ion, is observed by pmr. The formation of this transient also has been observed at *low* substrate concentrations by calorimetry.

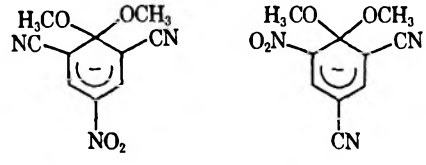
In the preceding part of this series,[1] we reported kinetic and thermodynamic data on the formation and decomposition of the 2,4,6-trinitro- (**1**), 2-cyano-4,6-dinitro- (**2**), and 4-cyano-2,6-dinitro-1,1-dimethoxycyclohexadienylides (**3**). These data indicated that the relative order of complex stabilities is **1** > **2** > **3** in



1 **2** **3**

methanol, and that the replacement of a *para* nitro group by a cyano group causes a more dramatic decrease in the stability of the complex than the corresponding replacement in the *ortho* position.

In order to substantiate these conclusions, we have prepared, isolated, and studied **4** and **5** as crystalline complexes and report our studies on the effect of replacing two nitro groups by cyano groups on the structure and stability of these complexes. We also wish to present calorimetric and pmr evidence for the formation of a transient 1,3-dimethoxy complex in the formation of **5**, as well as dimethyl sulfoxide (DMSO) solvent effects on the formation and decomposition of **5** and on the equilibrium constant of **4**.



4 **5**

Experimental Section

The solvents and reagents were prepared, purified, and standardized as previously described.[3] Solutions of sodium methoxide in methanolic DMSO were freshly prepared from the purified solvents by the appropriate dilutions.

1-Bromo-2,4-dicyanobenzene (**6**) and 1-bromo-2,6-dicyanobenzene (**7**) were prepared from 4-bromoisophthalic acid (**8**) and 2-bromo-*m*-xylene (**9**), respectively, according to procedures similar to that used by Wallenfels, *et al.*, for the preparation of 1-bromo-2,4,6-tricyanobenzene.[4] 4-Bromoisophthalamide (**10**) was prepared by refluxing 14.27 g (58 mmol) of **8** in 85 ml of thionyl chloride for 24 hr, followed by removal of the excess thionyl chloride by rotary evaporation. The residue was dissolved

(1) Part VI: J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, **34**, 689 (1969); presented, in part, at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969.

(2) (a) University of Pittsburgh; (b) Carnegie–Mellon University; (c) The University of Toledo; (d) University of Tennessee.

(3) W. E. Byrne, E. J. Fendler, J. H. Fendler, and C. E. Griffin, *J. Org. Chem.*, **32**, 2506 (1967).

(4) K. Wallenfels, F. Witzler, and K. Friedrich, *Tetrahedron*, **23**, 1353 (1967).

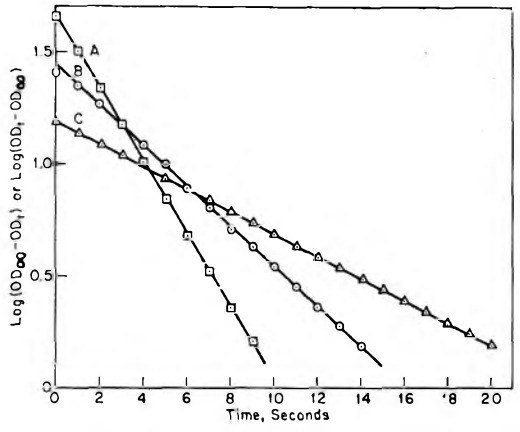


Figure 1.—(A) Plot of log ($OD_t - OD_\infty$) against time for the decomposition of **4** in methanol at 25.00°. (B) Plot of log ($OD_t - OD_\infty$) against time for the decomposition of **5** in methanol at 25.00°. (C) Plot of log ($OD_\infty - OD_t$) against time for the attainment of equilibrium of **5** in DMSO–MeOH, 10:90 (v/v), at 25.00°; [**15**] = $9.0 \times 10^{-5} M$, [$NaOCH_3$] = $1.86 \times 10^{-3} M$.

in 250 ml of dry benzene and ammonia was bubbled through the stirred reaction mixture for *ca.* 8 hr. The white precipitate of ammonium chloride and **10** was filtered, dried at 90–100°, and suspended in 200 ml of water. Filtration gave colorless, crystalline **10**, which was washed with water and dried at 90–100°, mp 248–249°. The dinitrile **6** was prepared by refluxing a mixture of 10.0 g (41 mmol) of **10**, 5.4 g of sodium chloride, and 50 ml of phosphorus oxychloride for 4 hr. The excess phosphorus oxychloride was removed by rotary evaporation at 0.1 mm and the residue was poured into *ca.* 100 ml of ice water. The precipitate was filtered, washed with water, and dried *in vacuo* over phosphorus pentoxide. After recrystallization from benzene, the colorless crystals of **6** melted at 193–193.5°.

2-Bromoisophthalic acid (**11**) was prepared by alkaline potassium permanganate oxidation of **9**. A mixture of 25 g (135 mmol) of **9**, 6.25 g of sodium hydroxide, 132 g of potassium permanganate, and 625 ml of water was refluxed for 15 hr; an additional 50 g of potassium permanganate was added, and the mixture was refluxed for a further 7 hr. The excess potassium permanganate was decomposed with methanol, the hot solution was filtered, and the manganese dioxide precipitate was washed four times with *ca.* 200-ml portions of hot water. The combined filtrates were concentrated to *ca.* 250 ml by distillation and acidified with concentrated nitric acid. The precipitate was filtered, washed with cold water, and dried *in vacuo* over phosphorus pentoxide. The colorless crystals of **11** melted at 216–218° (lit.[5] mp 218°). 2-Bromoisophthalamide (**12**) was prepared from **11** by a procedure analogous to that described for **10**. **7** was prepared by the dehydration of **12** with phosphorus oxychloride as previously described and melted at 190–190.5°.

2,4-Dicyanoanisole (**13**) was prepared by the addition of 2.62 ml (15 mmol) of 5.73 *M* potassium methoxide in methanol to a solution of 1.92 g (10 mmol) of **6** in 20 ml of methanol. The reaction mixture was refluxed for 7 hr, cooled, and poured onto 50 g of ice. The colorless crystals of **13** were filtered, washed with distilled water, and dried *in vacuo* over phosphorus pentoxide, mp 205–206°.

The same procedure was used to prepare 2,6-dicyanoanisole (**14**), mp 90–90.5°, from 6.93 ml (35 mmol) of 5.05 *M* potassium methoxide in methanol and 5.76 g (30 mmol) of **7** in 30 ml of methanol, with the exception that the reaction mixture was refluxed for 19 hr, cooled, and poured onto 100 g of ice.

2,4-Dicyano-6-nitroanisole (**15**) was prepared by the addition of 1.75 g of **13** to 35 ml of fuming nitric acid (*d* 1.52). The reaction mixture was stirred at 60–70° for 2 hr and at room temperature for 15 hr, cooled, and poured onto 100 g of ice. The solution was neutralized slowly with rigorous stirring to pH 6 by the addition of concentrated sodium hydroxide at 0°. The colorless, crystalline precipitate was filtered, washed with distilled water, and dried *in vacuo*. After recrystallization from aqueous methanol, the colorless needles of **15** melted at 119–120°.

(5) E. A. Coulson, *J. Chem. Soc.*, 1298 (1937).

Anal.[6] Calcd for $C_9H_5N_3O_3$: C, 53.25; H, 2.48; N, 20.68. Found: C, 53.43; H, 2.48; N, 20.36.

The same procedure and reactant quantities were used to prepare 2,6-dicyano-4-nitroanisole (**16**) from **14**. After recrystallization from methanol, the colorless needles of **16** melted at 148.5–149.5°.

Anal.[6] Calcd for $C_9H_5N_3O_3$: C, 53.25; H, 2.48; N, 20.68. Found: C, 53.41; H, 2.33; N, 20.65.

Potassium 1,1-dimethoxy-2,4-dicyano-6-nitrocyclohexadienylide (**5**) was prepared by the addition of 0.211 ml (1.07 mmol) of 5.05 *M* potassium methoxide in methanol to a solution of 0.204 g (1.08 mmol) of **15** in 0.25 ml of dry dioxane. The red crystals which formed immediately on slight cooling were filtered under dry nitrogen and were washed with dry benzene and anhydrous ether. The crystalline product did not decompose completely at temperatures <280°. This material contained approximately 0.5 mol of dioxane of crystallization (by pmr integration of dioxane singlet, τ 6.43 ppm[8]).

Anal.[6] Calcd for $C_{10}H_8N_3O_4K \cdot 0.5C_4H_8O_2$: C, 45.3; H, 4.05; N, 13.2; K, 12.3. Found: C, 40.79; H, 3.58; N, 11.92; K, 16.28.

The same procedures and reactant quantities were used for the preparation of potassium 1,1-dimethoxy-2,6-dicyano-4-nitrocyclohexadienylide (**4**) from **16** in 0.50 ml of dry dioxane. The yellow crystals, which formed upon evaporation of a small amount of the solvents with dry nitrogen, were filtered and washed with dry benzene and anhydrous ether in an atmosphere of dry nitrogen. The yellow crystals turned red at *ca.* 140°, but did not decompose completely at temperatures <280°. This material contained approximately 0.34 mol of dioxane of crystallization (pmr integration).

Anal.[6] Calcd for $C_{11}H_8N_3O_4K \cdot 0.3C_4H_8O_2$: C, 44.80; H, 3.49; N, 14.01; K, 13.04. Found: C, 42.03; H, 2.73; N, 13.95; K, 13.02.

The analyses for complexes **5** and **4** are rather poor and duplicate analyses showed a considerable lack of reproducibility which suggests that these results could be due to loss of dioxane or methanol during the analyses or the presence of potassium carbonate in the ash. The purity of these complexes was, however, found to be greater than 98% by pmr integration, and no impurities could be detected in their infrared spectra obtained under conditions of maximum resolution on a Perkin-Elmer 221 spectrophotometer.

The attainment of the equilibrium for the formation of complex **5** and **15** in methanol and in methanolic DMSO was followed at 480 mμ in the thermostated cell compartment of a Beckman DU-2 spectrophotometer. The temperature was measured inside the cells and was maintained within ±0.02°. The mixing techniques for fast reactions have been described previously.[1]

The decomposition of complexes **4** and **5** was initiated by injecting a freshly prepared concentrated solution of the complex (50–100 μl in DMSO) into the thermostated methanol or methanolic DMSO contained in the cell compartment of the spectrophotometer. The rate of color disappearance was followed at the appropriate wavelength. Since the concentration of **15** was kept a hundredfold smaller than that of the sodium methoxide, and since the concentrations of the complexes were in the order of $10^{-4} M$, pseudo-first-order kinetics were observed for both the attainment of the equilibrium for **5** and for the decomposition of complexes **4** and **5**. Such first-order plots for typical runs are given in Figure 1.

Rapid mixing techniques[1] were used to determine the absorbance due to the complexes at the various methoxide ion concentrations in methanol and in methanolic DMSO. The blank in each case contained the same concentration of methoxide ion in the corresponding solvent.

Calorimetric studies were carried out with a dual calorimeter similar to that described by Arnett, Bentrude, Burke, and Duggleby.[7]

The apparatus was checked at least once a month by measuring the heat of solution of potassium chloride in water. The values obtained usually agreed within ±1% of the accepted value[8] and always agreed within ±2%.

(6) Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(7) E. M. Arnett, W. G. Bentrude, J. J. Burke, and P. M. Duggleby, *J. Amer. Chem. Soc.*, **87**, 1541 (1965).

(8) V. B. Parker, "Thermal Properties of Aqueous Uni-univalent Electrolytes," National Bureau of Standards, Washington, D. C., Patent NSRDS–NBS2.

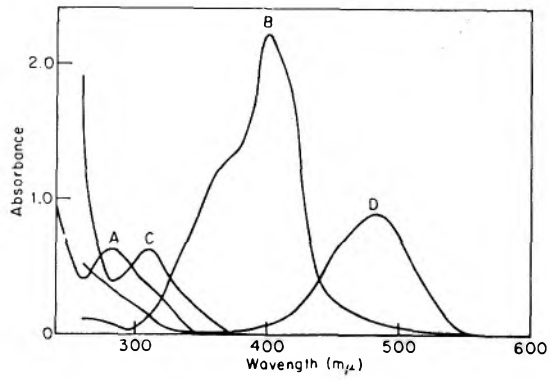


Figure 2.—Absorption spectra of 2,6-dicyano-4-nitroanisole (**16**) (6.75×10^{-5} *M*) in methanol (A) and in 2.99 *M* methanolic sodium methoxide (B). Absorption spectra of 2,4-dicyano-6-nitroanisole (**15**) (3.96×10^{-5} *M*) in methanol (C) and in 2.99 *M* methanolic sodium methoxide (D) (all in matched 1.00-cm cells).

The 60-MHz pmr spectra were obtained with a Varian Associates A-60 spectrometer at 25° (probe temperature maintained with a V6040 variable-temperature controller). Unless otherwise noted, all spectra were determined on solutions in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard; chemical shifts (τ, parts per million) are given relative to TMS (τ 10.00 ppm) and are accurate to ±0.03 ppm. Chemical-shift data were taken from spectra determined at sweep widths of 500 Hz. The reported coupling constants are the average of at least three determinations at 50-Hz sweep widths and are accurate to ±0.02 Hz.

Results

The absorption spectra of 2,4-dicyano-6-nitroanisole (**15**) and 2,6-dicyano-4-nitroanisole (**16**) in methanol and in 2.99 *M* methanolic sodium methoxide are shown in Figure 2. The data for the interaction of **15** with sodium methoxide at 25.00° are given in Table I for methanolic solutions and in Table II for methanolic

TABLE I
INTERACTION OF 2,4-DICYANO-6-NITROANISOLE (**15**) (7.29×10^{-5} *M*) WITH METHANOLIC SODIUM METHOXIDE AT 25.00°

10^2[NaOCH$_3$], *M*	Absorbance at 480 mμ[a]	$10k_{obsd}$, sec^{-1}
0[b]		1.79
0[b]		1.81
0[b]		2.09
0[b]		2.25
1.03	0.132	2.34
2.06	0.260	2.62
3.09	0.363	3.77
4.12	0.460	2.69
5.18	0.528	2.71

[a] Using a pair of matched 10-mm cells. [b] Decomposition of the solid complex **5**.

DMSO. Values and standard deviations of k_1 for **15** in these solvents have been calculated by least-mean-squares treatments of the data. Attempts were made to obtain k_1 values at different temperatures in order to calculate the Arrhenius parameters for the formation of complex **5**. The standard deviations for these kinetic runs were, however, even greater than for those at 25.00°. Similarly, attempts to obtain k_1 values for the reaction of **16** with methoxide ion in methanol or in methanolic DMSO were completely frustrated by irreproducible k_{obsd} values. Kinetic measurements in methanolic DMSO systems yielded better data; the standard deviations in the k_1 values are considerably

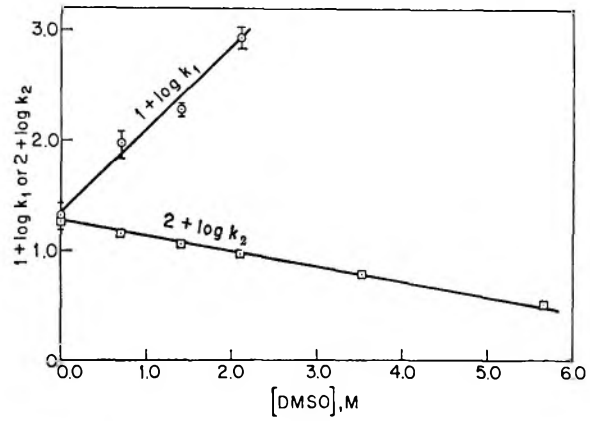


Figure 3.—Plot of 1 + log k_1 and 2 + log k_2 for **5** in methanolic dimethyl sulfoxide at 25.00°.

TABLE II
INTERACTION OF 2,4-DICYANO-6-NITROANISOLE (**15**) WITH SODIUM METHOXIDE IN METHANOLIC DIMETHYL SULFOXIDE AT 25.00°

[DMSO], *M*	10^2[NaOCH$_3$], *M*	10^2k_{obsd}, sec^{-1}	k_1, l. mol^{-1} sec^{-1}
0			2.06 ± 0.83[a]
0.70[b]	0[c]	15.4	
	0[c]	14.3	
	0[c]	13.9	
	3.94	17.5	
	7.38	22.5	
	9.85	20.7	
	12.30	25.3	
	14.74	30.4	9.55 ± 1.06
1.41[b]	0[c]	11.7	
	0[c]	10.8	
	0[c]	12.0	
	1.86	11.7	
	2.80	12.4	
	3.73	16.3	
	4.60	17.3	
	9.32	27.1	
	11.65	32.7	
	16.3	42.5	
	18.6	45.0	19.1 ± 0.8
2.10[d]	0[c]	9.43	
	0[c]	9.43	
	2.20	16.33	
	4.40	24.2	
	6.60	24.6	
	8.80	58.9	
	11.00	103.5	
	13.2	131.8	87.4 ± 14

[a] For details see Table I. [b] [**15**] = 9.0×10^{-5} *M*. [c] Decomposition of the solid complex **5** in the appropriate methanolic DMSO. [d] [**15**] = 8.0×10^{-5} *M*.

smaller in 0.70 and 1.41 *M* DMSO in methanol than in pure methanol (Table II). The uncertainty in k_1 values in the 2.10 *M* DMSO system is due to the very high k_{obsd} values. A linear relationship has been found between log k_1 and log k_2 and molar DMSO concentration (Figure 3). Using the absorbance data in Table I and the form of the Benesi–Hildebrand equation[9] shown

$$\frac{[15] \text{ or } [16]}{A} = \frac{1}{\epsilon} + \frac{1}{K\epsilon[\text{NaOCH}_3]} \quad (1)$$

(9) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703 (1949).

TABLE III
DECOMPOSITION OF POTASSIUM 1,1-DIMETHOXY-2,4-DICYANO-6-NITROCYCLOHEXADIENYLIDE (5) IN METHANOLIC DIMETHYL SULFOXIDE

	[DMSO], M			
	0	1.41	2.10	3.52
10^2k_2, sec^{-1} at 25.00°	19.8	11.5	9.43	6.52
10^2k_2, sec^{-1} at 14.45°	9.07	5.51	4.16	2.47
E_2, kcal mol^{-1}	12.4 ± 1.0	11.9 ± 1.0	13.3 ± 1.0	15.7 ± 1.0
$\Delta S^{\pm}$, eu	−22 ± 3	−24 ± 3	−20 ± 3	−13 ± 3

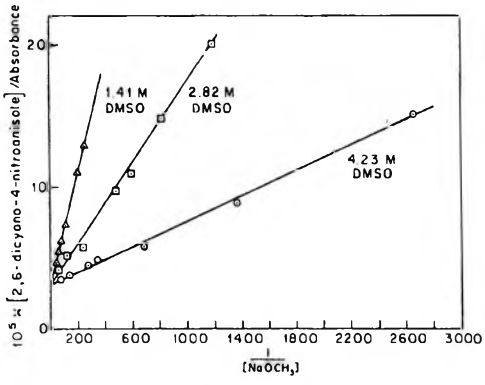


Figure 4.—Benesi–Hildebrand plots for the formation of **4** in methanolic dimethyl sulfoxide.

where A is the absorbance in a 1.0-cm cell, ϵ is the extinction coefficient, and K is the equilibrium constant for the complex, a good linear relationship was obtained on plotting [**15**]/A *vs.* 1/[$NaOCH_3$] indicating that a simple 1:1 equilibrium prevails.[1,3,10] Since the intercept of the Benesi–Hildebrand plot (*i.e.*, $1/\epsilon$) is susceptible to large errors, ϵ was determined independently by dissolving known amounts of **5** in DMSO and in various DMSO–methanol mixtures and measuring the absorbance (using the appropriate blanks) at 480 mμ. A value of $\epsilon_{480} = (2.1 \pm 0.1) \times 10^4$ cm^{-1} l. mol^{-1} represents the mean of five independent measurements and was used in conjunction with eq 1 to obtain $K = 15$ l. mol^{-1}. This value is in agreement with that of $K = 10 \pm 5$ l. mol^{-1} obtained from the kinetic data (k_1/k_2 in Table II). Table III contains the kinetic and thermodynamic data for the decomposition of **5** in methanol and methanolic DMSO.

Equation 1 was used to calculate K for the formation of **4** at 25.00° in methanol and methanolic DMSO. The data are given in Table IV and typical Benesi–Hildebrand plots are shown in Figure 4. The extinction coefficient obtained from the intercept of Figure 4 for **4**, $\epsilon_{400} = 3.12 \times 10^4$ cm^{-1} l. mol^{-1}, is in very good agreement with that of $\epsilon_{400} = (3.1 \pm 0.5) \times 10^4$ cm^{-1} l. mol^{-1} obtained from direct measurements by dissolving known amounts of **4** in DMSO and DMSO–methanol mixtures and measuring the absorbance at 400 mμ against the appropriate solvent blanks. A satisfactory linear relationship of log K *vs.* [DMSO], M, for **16** has also been obtained. Table V contains the kinetic and thermodynamic data for the decomposition of **4** in methanol and in methanolic DMSO.

The heats of formation of several Meisenheimer complexes from the corresponding anisoles and sodium methoxide in solution are given in Table VI, together with free energies calculated from the data in Tables II and IV. The heats of formation were obtained by

(10) E. J. Fendler, J. H. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 4141 (1968).

TABLE IV
INTERACTION OF 2,6-DICYANO-4-NITROANISOLE (16) WITH SODIUM METHOXIDE IN METHANOLIC DIMETHYL SULFOXIDE AT 25.00°

[DMSO], M	10^3[$NaOCH_3$], M	Absorbance at 400 mμ[a]	K, l. mol^{-1}[b]
0[c]	5.25	0.079	
	10.5	0.136	
	21.0	0.205	
	31.5	0.262	
	42.0	0.316	
	52.5	0.336	33.5
1.41[d]	9.45	0.332	
	12.18	0.390	
	18.90	0.442	
	23.63	0.548	
	28.35	0.515	
	37.80	0.560	77.0
2.82[b]	0.84	0.121	
	1.68	0.222	
	2.10	0.249	
	3.60	0.330	
	4.20	0.421	
	8.40	0.468	
	12.6	0.545	
	16.8	0.578	
	21.0	0.618	221
4.23[e]	0.368	0.109	
	0.735	0.200	
	1.47	0.278	
	2.21	0.325	
	2.94	0.336	
	3.68	0.362	
	7.35	0.428	
	14.7	0.477	695

[a] Using a pair of matched 10-mm cells. [b] Obtained from eq 1. [c] [**16**] = 1.89×10^{-5} M. [d] [**16**] = 2.43×10^{-5} M. [e] [**16**] = 1.65×10^{-5} M.

subtracting the heat of solution of the solid substituted anisole in the indicated solvent from the heat of solution of the same compound in the solvent containing sodium methoxide. Concentrations of the reactants were kept below 0.013 M. The above method is applicable only when the equilibrium constant for complex formation is large. When this is not the case, the heat of complex formation (H_f) was calculated from

$$H_f = H_{obsd}/[c]V$$

where [c] is the concentration of the complex, V is the volume of solution in the calorimeter (210.0 ml), and H_{obsd} is the difference in the heat of solution of the substituted anisole in the pure solvent and in the solvent containing sodium methoxide. The concentration of the complex, [c], was calculated from

$$[c] = \frac{([A] + [B] + 1/K) \pm \sqrt{([A] + [B] + 1/K)^2 - 4[A][B]}}{2}$$

TABLE V

DECOMPOSITION OF POTASSIUM 1,1-DIMETHOXY-2,6-DICYANO-4-NITROCYCLOHEXADIENYLIDE (4) IN METHANOLIC DIMETHYL SULFOXIDE

	[DMSO], M				
	0	1.41	2.82	4.32	5.64
10^2k_2, sec^{-1} at 25.00°	37.3	21.16	12.90	6.30	3.29
10^2k_2, sec^{-1} at 14.45°	14.37	6.80	4.37		
10^2k_2, sec^{-1} at 7.60°	7.95	3.71	2.29		
E_2, kcal mol^{-1}	14.6 ± 0.8	16.7 ± 0.8	16.7 ± 0.8		
$\Delta S^{\ddagger}$, eu	−20.4 ± 2.0	−6.9 ± 2.0	−7.8 ± 2.0		

TABLE VI

THERMODYNAMIC VALUES FOR FORMATION OF MEISENHEIMER COMPLEXES AT 25°

Complex	Solvent (vol. % DMSO in methanol)	ΔF, kcal/mol	ΔH, kcal/mol[a]	ΔS, eu
	0	−2.1	Endothermic	
4	20	−3.2	−2.23 ± 0.55	+3.3
	30	−3.9	−2.46 ± 0.64	+4.7
5	15	−3.4	−0.82 ± 0.49	+8.7
19	15		(+3.05 ± 0.64)[b]	
1	0	−5.77	−4.86 ± 0.30	+3.0
18	0		−1.48 ± 0.50[c]	

[a] Errors are standard deviations (σ) from the mean. [b] This is a minimum value calculated assuming that K for the 1,3 complex is the same as K for the 1,1 complex. [c] Calculated assuming that K for the 1,3 complex is large, *i.e.*, that the complex formation is essentially complete.

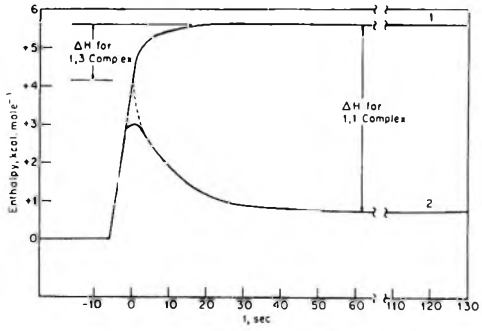


Figure 5.—Plots of enthalpy, ΔH, *vs.* time for solid **17** in pure methanol (curve 1) and the same amount of **17** in 0.01 M methanolic sodium methoxide (curve 2).

where [A] and [B] are the initial concentrations of anisole and base and K is the equilibrium constant.

The behavior of 2,4,6-trinitroanisole (**17**) and **15** toward sodium methoxide in methanol and in 15% (v/v) DMSO in methanol indicates that a complex forms prior to the formation of the more stable 1,1 complex. Two typical calorimetric runs are superimposed in Figure 5. Curve 1 is typical of the injection of solid **17** into pure methanol. Curve 2 reproduces an injection of the same amount of **17** into methanol containing 0.01 M sodium methoxide. Normally, one-step complex formation yields a curve identical with 1 but displaced along the enthalpy axis. Extrapolation of the lines on opposite sides of the peak yields an intersection point considerably below the displacement due to the endothermic solution of **17** in methanol. With **15**, the curve is displaced in an endothermic direction from the curve generated by the dissolution of the anisole in the solvent. In both cases, the calorimeter results indicate formation of a transient. In contrast, **16** gives no evidence for transient formation. As shown by curve 2, the transients are converted in an exothermic process into the final products, the 1,1 complexes. The rate of formation of the 1,1 complex **1** from the transient calculated from curve 2 is in fair agreement with the rate reported by Gold[11] (4 l. mol^{-1} sec^{-1}). The first-order rate of formation of **5** from the transient in 0.01517 M sodium methoxide in methanol is roughly $k = 0.20$ sec^{-1}. This is too fast to enable an accurate determination using the calorimeter. The method of Bolles and Drago[12] has been applied to the calorimetric data yielding values of K in rough agreement with those obtained from absorption spectroscopy. Using this method[12] the values of K obtained for the 1,1 and 1,3 complexes were the same within a rather large experimental error. This result indicates that the two K values are at least of the same order of magnitude.

Table VII allows an intercomparison of kinetic and thermodynamic data for the formation and decomposition of complexes **1** and **5** in methanol at 25.00°. The pmr data for the dicyanonitroanisoles and the 1,3- and 1,1-dimethoxycyclohexadienylides are given in Table VIII.

Discussion

The absorption maxima of **15** and **16** in methanolic sodium methoxide at 400 and 480 mμ are assigned to complexes **4** and **5** since the spectra of the isolated complexes have the same maxima. In each case the absorption maximum is reached at approximately 10^{-1} M sodium methoxide and remains essentially constant at higher concentrations; *i.e.*, the equilibria given in eq 2

$$\text{16 or 15} + \text{NaOCH}_3 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{4 or 5} \qquad (2)$$

prevail. As in the case of the Meisenheimer complex formations previously studied,[1] the increase of absorbance at 480 mμ for **5** at lower methoxide ion concentrations was followed as a function of time. Under the experimental conditions, the observed first-order rate constant, k_{obsd}, for equilibrium attainment is given by[1]

$$k_{obsd} = k_1[\text{NaOCH}_3] + k_2 \qquad (3)$$

where k_1 is the second-order rate constant for the formation of the complex and k_2 is the first-order rate constant for its decomposition. We have successfully used eq 3 previously for calculating k_1 and k_2 values for a number of Meisenheimer complexes.[1,3,10] However, plots of k_{obsd} against sodium methoxide concentration for **15** showed considerable scatter. The reason for these difficulties lies mainly in the unfavorably small equilibrium constants. With the present technique, it appears that optimum conditions for obtaining k_1 and k_2 values prevail when K is reasonably high and when

(11) V. Gold and C. H. Rochester, *J. Chem. Soc.*, 1987 (1964).
(12) T. F. Bolles and R. S. Drago, *J. Amer. Chem. Soc.*, **87**, 5015 (1965).

TABLE VII

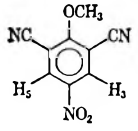
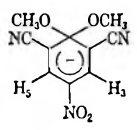
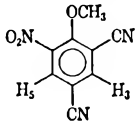
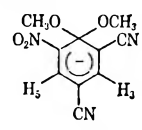
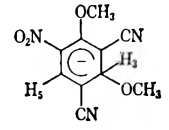
KINETIC AND THERMODYNAMIC PARAMETERS FOR THE FORMATION AND DECOMPOSITION OF TRINITRO-, CYANODINITRO-, AND DICYANONITRO-SUBSTITUTED MEISENHEIMER COMPLEXES IN METHANOL AT 25.00°

	1[a]	2[a]	3[a]	4	5
k_1, l. mol^{-1} sec^{-1}	17.3	18.8	6.1	~12[b]	2.0
10^3k_2, sec^{-1}	1.04	7.20	22.0	373	198
K, l. mol^{-1}	17,000	2600	280	34	10
E_1, kcal mol^{-1}	13.5 ± 1.0	17.8 ± 0.8	13.9 ± 0.8		
$\Delta S_1^{\ddagger}$, eu	−9.4 ± 2.0	+5.0 ± 2.0	−10.4 ± 2.0		
E_2, kcal mol^{-1}	19.0 ± 1.0	14.4 ± 0.8	9.6 ± 0.8	14.6 ± 0.9	12.4 ± 1.0
$\Delta S_2^{\ddagger}$, eu	−4.8 ± 2.0	−20 ± 2.0	−32.0 ± 2.0	−20.4 ± 2.5	−22.0 ± 3.0

[a] Data obtained in ref 1. [b] Calculated from k_1 and K.

TABLE VIII

PMR SPECTRA OF DICYANONITROANISOLES AND THE CORRESPONDING 1,3- AND 1,1-DIMETHOXYCYCLOHEXADIENYLIDES[a]

	 16	 4[b]	 15	 5[b]	 19[c]
τ_1 (OCH_3)	5.53	7.02	5.78	7.08	5.78
τ_3 (OCH_3)				7.03	
τ_3 (H)	1.00	2.10	1.24	2.70	4.88
τ_5 (H)	1.00	2.10	1.14	2.00	2.12
J_{35}			2.7	2.3	2[d]

[a] Except where noted, spectra determined in DMSO-d_6 at 25°. Details of method are given in Experimental Section. [b] Spectra determined on samples of isolated complexes. [c] Spectrum determined in MeOH–DMSO-d_6 mixtures. [d] J_{35} estimated from 500-Hz sweep width spectra.

the methoxide ion concentration is kept in the region of 10^{-2}–10^{-3} M. Carbon dioxide may interfere at lower methoxide ion concentrations and changes in ion activities introduce uncertainties at higher concentrations.

The order of stabilities of the 2,4,6-trisubstituted Meisenheimer complexes parallels the electron-withdrawing power of the substituents at these positions. The stabilities of the trinitro- (**1**),[1] cyanodinitro- (**2**, **3**),[1] and dicyanonitro- (**4**, **5**) substituted Meisenheimer complexes are best expressed by the equilibrium constants of their formation in methanol at 25.00°: $K_1 > K_2 > K_3 > K_4 > K_5$. Replacing two nitro groups in the 2 and 4 positions by cyano groups results in a greater effect on K than replacing two nitro groups in the 2 and 6 positions: $K_1/K_4 = 500$, $K_1/K_5 = 1700$. The present results substantiate our earlier[1] findings of $K_1/K_2 = 6.5$ and $K_1/K_3 = 60$, and those of others who observed greater activating power for *p*-nitro compared with *o*-nitro groups for methoxydehalogenations.[13] Molecular orbital calculations have also demonstrated that the *para* substituent carries the bulk of the negative charge in Meisenheimer complexes.[14]

Changes in the equilibrium constants for complexes **1**–**5** are dependent to a greater extent on the changes in k_2 than those in k_1 (Table VI). A similar situation has been encountered in comparisons of the k_1 and k_2 values for the methoxyl complexes of 1-methoxy-2,4-dinitronaphthalene[10] and 2,4-dinitroanisole.[15] Lack of experimental data does not allow the comprehensive discussion of the Arrhenius parameters for complexes **4** and **5** which was possible for complexes **1**–**3**.[1]

It has been known for some time that dipolar aprotic solvents enhance the stability of Meisenheimer complexes.[3] Indeed, this fact has been used extensively to facilitate the isolation of crystalline potassium or sodium cyclohexadienylides.[1,3,10,16] Kinetic results on the interaction of **15** and **16** with sodium methoxide in methanol and methanolic DMSO (Tables II and IV, Figure 3) allows a quantitative treatment of this observation. The similarity of the dielectric constants of methanol (30) and DMSO (47)[17] renders this solvent pair particularly useful for kinetic studies. The equilibrium constant for the formation of **4** is higher by a factor of approximately 20 in 4.23 M DMSO in methanol (DMSO–MeOH, 30–70 v/v) than in pure methanol. Furthermore, this increase in the equilibrium constant with increasing amounts of DMSO in the solvent pair is a composite effect of an increase in k_1 and a decrease in k_2 (Table II and Figure 3).

As a first approximation, the enhancement of k_1 obtained by an enrichment of the solvent in DMSO can be attributed to the difference in the hydrogen-bonding power of these solvents. It has been generally recognized that such strong hydrogen-bond acceptors as methoxide ions become considerably less solvated in dipolar aprotic than in protic solvents.[18] The methoxide ion in the DMSO-rich solvent is, therefore, less extensively hydrogen bonded and can consequently become a stronger nucleophile than in pure methanol. A similar rationalization can be extended to the effect of DMSO as a cosolvent on k_2. Since the negative charge is delocalized in the Meisenheimer complex, the aprotic DMSO solvates this large ionic species to a greater

(13) J. F. Bunnett and R. J. Morath, *J. Amer. Chem. Soc.*, **77**, 5051 (1955); W. Greizerstein and J. A. Brieux, *ibid.*, **84**, 1032 (1962).

(14) P. Caveng, P. B. Fischer, E. Heilbronner, A. L. Miller, and H. Zollinger, *Helv. Chim. Acta*, **50**, 848 (1967).

(15) C. F. Bernasconi, *J. Amer. Chem. Soc.*, **90**, 4982 (1968).

(16) G. S. Gitis, A. I. Glaz, and A. Ya. Kaminskii, *J. Gen. Chem. USSR*, **33**, 3229, (1963); S. Nagakura, *Tetrahedron Suppl.*, **19**, 361 (1963).

(17) D. Martin, A. Weise, and H.-J. Niclas, *Angew. Chem. Intern. Ed. Engl.*, **6**, 318 (1967), and references cited therein.

(18) A. J. Parker, *Quart. Rev.* (London), 163 (1962); *Advan. Org. Chem.*, **5**, 1 (1965); *Advan. Phys. Org. Chem.*, **5**, 173 (1967); *Chem. Rev.*, **69**, 1 (1969).

extent than methanol and hence enhances its stability.

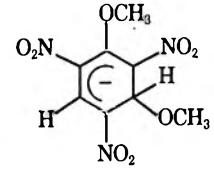
The arguments presented so far are, however, gross oversimplifications. Any serious consideration of solvent effects on rates has to include changes in the activity coefficients of the reactants and of the transition state as a function of solvent changes. The pioneering work of Parker and his coworkers has laid the foundation for this type of treatment.[19] From solubility and electrochemical measurements these workers have demonstrated quantitatively that polar reactants and large polarizable SNAr transition states are more, but small negative ions are less, solvated by DMSO than by methanol. This conclusion qualitatively fits our data, but quantitative treatment must wait until activity coefficient data are available for **15** and **16** or similar aromatic ethers. It is realized that "solvent sorting" could possibly occur in mixed solvents such as methanolic DMSO. This "solvent sorting" would result in further complications by producing cybotactic regions whose composition is different from that of the bulk solvent.[20] Such a situation is more likely to occur in DMSO-rich solvents (>95% DMSO) where the effects of extensive ion pairing of the methoxide ion also need to be considered.[21]

Linear correlations have been obtained between log k_1, log k_2, and log K *vs.* molar DMSO concentration for compounds **15** and **16** (Figure 3). Similar results have been found for the reactions of alkoxides and amines with 4-fluoronitrobenzene and 2,4-dinitrochlorobenzene in methanolic DMSO.[22] Kingsbury observed that the slopes of log k *vs.* [DMSO], M, have a fairly constant value of 0.275 and concluded that the DMSO "catalysis" is relatively independent of the system involved.[22] Values of 0.75 and −0.14 for the slopes of log k_1 and log k_2 *vs.* [DMSO], M, for the reaction of **15** with methoxide ion clearly render this conclusion untenable. In the light of the numerous parameters influencing the solvent effects (*vide supra*), it is unwarranted to attach any mechanistic significance to the linearity of this type of plot. Once such linearity has been established, however, this relationship may be used profitably to obtain K values in methanol for such nucleophilic aromatic substitutions where $k_1/k_2 < 1$. We have successfully used this method for estimating the equilibrium constant for the interaction of methoxide ion with tricyanoanisole in methanol from the data obtained in various methanolic DMSO solutions.[23]

A large body of experimental evidence for nucleophilic aromatic substitutions where the rate-determining step is the formation of the intermediate complex indicates that dipolar aprotic solvents more strongly affect the enthalpy than the entropy of activation.[18] Unfortunately, the lack of data on the temperature effect on k_1 for the reaction of methoxide ion with **15** and the large uncertainties in the calorimetric determination of ΔH values for **4** do not allow us to substantiate this generalization. The decomposition of Meisenheimer complexes (k_2) in different methanolic DMSO mixtures are governed to a greater extent by entropy changes (Tables III and V). Increasing the DMSO concentration caused an increase in $\Delta S^{\ddagger}$. This is explicable in terms of a greater solvation difference between the ground and transition states in methanol than in DMSO.

The structures of the 1,1-dimethoxy complexes **4** and **5** are confirmed by their pmr spectra (Table VIII). The observed parameters are in full accord with expectations based on the spectra of the corresponding cyanodinitro[1] (**2** and **3**) and trinitro[1,24] (**1**) complexes. Since the salient characteristics and structural implications of the pmr spectra of Meienheimer complexes have been discussed in detail elsewhere,[1,3,10,24,25] no further comments on the spectra of **4** and **5** are warranted.

Calorimetric studies indicate the formation of transients in the reactions leading to **1** and **5**; however, no conclusions regarding structures can be drawn on the basis of calorimetric studies. In the light of previous work,[1,24,26] it appears most likely that the transients detected are 1,3 complexes, formed by rapid attack of methoxide ion at the 3 position of the anisoles. Servis[24] has provided pmr evidence for the formation of **18** as a transient in the reaction of 2,4,6-trinitroanisole with methoxide ion; **18** undergoes rapid conversion into the



18

1,1 complex **1**.[27] Pmr studies of the *in situ* generation of **5** from **15** and potassium methoxide confirm the calorimetric detection of a transient and provide evidence for its structure. Addition of 1 drop of 5.73 M potassium methoxide in methanol to a solution of **15** in DMSO-d_6 at 25° results in a broadening[28] of the protons of **15** and the development of weak doublets of equal intensities at τ 2.12 and 4.88 ppm at the expense of the signals attributable to **15**. Within 18 min of the addition of the potassium methoxide, the transient doublets are undetectable and only the multiplet due to **15** and the doublets at τ 2.00 and 2.70 ppm are observable. Similar behavior is observed on the addition of the second and third drops of 5.73 M potassium methoxide. The rate of disappearance of the transient signals

(19) A. J. Parker and R. Alexander, *J. Amer. Chem. Soc.*, **90**, 3313 (1968); R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *ibid.*, **90**, 5049 (1968).

(20) A. H. Fainberg and S. Winstein, *ibid.*, **78**, 2770 (1956); J. B. Hyne, R. Willis, and R. E. Wonkka, *ibid.*, **84**, 2914 (1962).

(21) E. C. Steiner, R. O. Trucks, J. D. Starkey, and J. H. Exner, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, No. POLY-18.

(22) C. A. Kingsbury, *J. Org. Chem.*, **29**, 3262 (1964).

(23) W. G. Ernsberger, E. J. Fendler, J. H. Fendler, and C. E. Griffin, unpublished results.

(24) K. L. Servis, *J. Amer. Chem. Soc.*, **89**, 1508 (1967).

(25) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966); M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969).

(26) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev.* (London), **22**, 123 (1968).

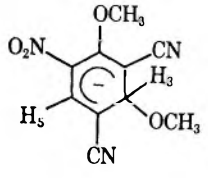
(27) Throughout this paper we have referred to the 1,3-dimethylcyclohexadienylide complexes as transients. However, by the use of this terminology in the formation of the 1,1 complexes, we do not intend to imply that the 1,3 complexes are direct precursors of the 1,1 complexes. Indeed, it is more probable that concurrent equilibria exist and that the 1,1 complexes are formed *via* the aromatic ethers or similar ion-paired species, formed by the dissociation of the 1,3 complexes.

(28) This effect is most probably the result of the formation of a paramagnetic species, although this postulate has not been verified experimentally. The formation of the anion radical of 3,5-dinitrobenzonitrile by reaction of that aromatic with methoxide ion in methanol has been demonstrated recently.[29]

(29) N. L. Arthur E. J. Fendler, J. H. Fendler, and C. E. Griffin, unpublished results.

increases with increasing concentrations of methanol and methoxide ion. Thus, after the addition of the third drop of methanolic potassium methoxide, the transient signals disappear within 3 min. The intensity of the signals due to **15** decrease with successive methoxide additions, disappearing after the addition of the third drop. The persistent spectrum is identical with that obtained for the isolated complex **5**, *i.e.*, doublets at τ 2.00 and 2.70 ppm.

Similar evidence for the formation of a transient species is obtained by examination of the high-field portion of the spectrum. Addition of potassium methoxide to a solution of **15** results in a reduction in the intensity of the methoxyl singlet of **15**, τ 5.78 ppm, and the appearance of a singlet at τ 7.03 ppm. The intensity of the latter singlet is three times the intensity of either the 2.12- or 4.88-ppm doublet at the same elapsed time after methoxide addition. With time, the 7.03-ppm singlet decreases in intensity with the simultaneous development of a singlet at τ 7.08 ppm. Ultimately, the lower field singlet completely disappears. The intensity of the 7.08-ppm singlet is three times that of either the 2.00- or 2.70-ppm doublet. The rates of disappearance and appearance of these singlets parallels the behavior of the lower field resonances. The same behavior is observed on the addition of the second and third drops of potassium methoxide solutions; the rate of disappearance of the 7.03-ppm singlet increases with successive additions. After the addition of the third drop of methoxide solution, the 5.78-ppm signal disappears and the persistent spectrum is that of the isolated complex **5**, namely a singlet at 7.08 ppm. In addition, resonances due to methanol and DMSO-d_5 are observed in this region of the spectrum. The transient signals consisted of a two-proton AX system (τ 2.12, 4.88 ppm, J_{AX} = 2 Hz) and a methoxyl singlet at τ 7.03 ppm, assignable as the H-5, H-3, and C-3 methoxyl signals, respectively, of 1,3-dimethoxy-2,4-dicyano-6-nitrocyclohexadienylide (**19**).[30] These as-



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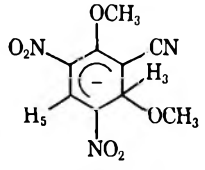
signments are based on the chemical shifts previously reported for the 1,3-dimethoxycyclohexadienylides **18**, **20**, and **21**[1] formed by the reactions of methoxide ion



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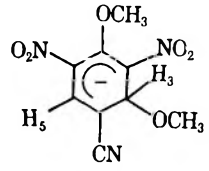
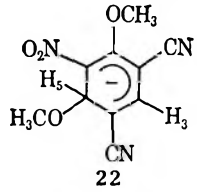


21

with methyl picrate, 2-cyano-4,6-dinitroanisole, and 4-cyano-2,6-dinitroanisole, respectively. These comparisons unequivocally establish the transient to be a 1,3-dimethoxycyclohexadienylide.

The 1,3-dimethoxycyclohexadienylides **18** and **19** have also been observed calorimetrically in solutions containing low concentrations of reactants and DMSO (Results and Table VI), indicating that 1,3 complex formation does not require either the high concentrations of reactants or the use of dipolar aprotic solvents previously employed.[1,24,25,31] In the light of these calorimetric results, the rapidly formed species, presumed to be a charge-transfer complex, observed in a kinetic investigation of **17** and ethanolic sodium ethoxide prior to 1,1 complex formation[32] might, in fact, be the 1,3 complex.

However, **15** is unsymmetrical with respect to attack by methoxide ion at the unsubstituted ring positions and two isomeric complexes **19** and **22** could be formed. The spectrum of complex **22** would possess the same



22

gross features as **19**, but a consideration of chemical shifts supports the latter structure. In **22** the environment of H-5 is identical with that of H-3 in both **20** and **21** and would consequently be expected to display the same chemical shift, *i.e.*, τ 4.50–4.52 ppm.[1] However, the proton bonded to sp^3-hybridized carbon in the transient is more strongly shielded, τ 4.88 ppm. This shielding effect is consistent with the environment of H-3 in **19** since it has been shown that the deshielding effect of cyano groups is considerably less than that of nitro groups on the ring protons (attached to either sp^2- or sp^3-hybridized carbons) of Meisenheimer complexes.[1] A consideration of the chemical shift of the lower field proton of the transient similarly supports structure **19**. The shift (τ 2.12 ppm) of this proton, H-5 of **19**, is very similar to that of H-5 of **21** (τ 2.25 ppm), reflecting their essentially identical environments. H-3 of **22** is flanked by two cyano groups and would be expected to be much more strongly shielded.[33] Thus, the structure **19** is established for the transient.

The selectivity observed in the reaction of methoxide ion with **15** to yield the 1,3 complex **19**, rather than the isomeric **22**, is further evidence for the greater stabilizing effect of nitro groups compared with cyano groups in Meisenheimer complex chemistry (*vide supra*). In **19**, the entering methoxy group is *para* to the nitro function, while an *ortho* relationship is present in **22**. This selectivity now appears to be quite general for the formation of complexes from nitro cyano aromatics, and is manifested by the relative stabilities of complexes **4** and **5**, and **2** and **3**,[1] by the selectivity observed in the formation of the 1,3-dimethoxycyclohexadienylide precursors (**20** and **21**) of **2** and **3**,[1] and in the attack of

(30) The C-1 methoxyl signal of **19** has approximately the same chemical shift as the methoxyl of **15** (τ 5.78 ppm) and is not resolved. Similar chemical-shift behavior has been observed for the C-1 methoxyl signals of **18**, **20**, and **21** and the C-1 methoxyl signals of the starting anisoles.

(31) M. R. Crampton and V. Gold, *J. Chem. Soc.*, *B*, 893 (1966).

(32) J. B. Ainscough and E. F. Caldin, *ibid.*, 2528 (1956).

(33) H-5 of **18** and **20** (τ 1.47–1.59 ppm)[1,24] is more strongly deshielded than H-5 of **21** (τ 2.25 ppm).[1] The replacement of one flanking nitro group by a cyano group thus produces a shielding effect of *ca.* 0.75 ppm. It might be argued that similar replacement of the second nitro group would produce a similar shielding effect to give τ 3.00 ppm for H-3 of **22**.

methoxide ion on 3,5-dinitrobenzonitrile.[29,34] The failure to observe formation of a transient species by either pmr or calorimetric probes in the reaction of methoxide ion with **16** is also consistent with this reactivity and stability pattern. In the symmetrical anisole **16**, attack is directed to the 1 position (*para* to nitro) to yield the 1,1 complex **4** as both the kinetic and thermodynamic product of the reaction. From these and our preceding studies,[1] it is clear that the same substitutional factors which determine the relative stabilities of the thermodynamically stable 1,1 complexes also determine the occurrence and position of attack in the formation of 1,3 complexes.

(34) M. I. Foreman and R. Foster, *Can. J. Chem.*, **47**, 729 (1969).

Registry No.—**4**, 12384-95-1; **5**, 12384-96-2; **6**, 22433-89-2; **7**, 22433-90-5; **10**, 22487-60-1; **11**, 22433-91-6; **13**, 22433-92-7; **14**, 22433-93-8; **15**, 22414-19-3; **16**, 22433-95-0; **18**, 12244-75-6; **19**, 12384-97-3; sodium methoxide, 124-41-4.

Acknowledgment.—This study was supported in part by grants from the U. S. Atomic Energy Commission and the Research Corporation (to J. W. L.). A portion of the pmr studies was carried out with instrumentation provided by a grant (FR 00292-03) from the National Institutes of Health. One of us (J. W. L.) gratefully acknowledges the advice and assistance of Mr. Otto Prater in the construction of the calorimeter.

Oxidation of Nitronates with Persulfate and with Silver Ions

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Received June 6, 1969

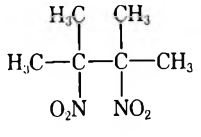
Sodium or ammonium persulfates convert salts of primary nitro compounds into secondary vicinal dinitro compounds ($RCHNO_2CHNO_2R$) and aldehydes. Silver ion catalyzes the oxidation–reduction reactions, and advantageous specific procedures using buffers and heterogeneous extractants are described for effecting oxidative dimerization. Experimental methods have been developed which minimize transformation of the oxidative dimers to conjugated nitro olefins and their addition products. Salts of phenylnitromethane, 1-nitropropane, 1-nitrobutane, and 2-methyl-1-nitropropane are converted by persulfates into their corresponding vicinal dinitro derivatives. In the absence of an extractant, ammonium persulfate oxidizes sodium phenylmethanenitronate to *cis*-α-nitrostilbene, α,β,γ-triphenyl-α-nitropropene, 3,4,5-triphenylisoxazoline oxide, and 3,4,5-triphenylisoxazole, along with benzaldehyde. Sodium 1-phenyl-1-ethanenitronate, sodium 9-fluorenenitronate, and sodium 1-(1-cyclohexenyl)-1-ethanenitronate, secondary nitronates having conjugating unsaturated centers, are converted effectively into acetophenone, fluorenone, and 1-cyclohexenyl methyl ketone, respectively. Potassium 1-nitropentane-1-nitronate and ammonium persulfate yield pentanoic acid and pentanamide. Various mechanisms for oxidation of nitronates by persulfates have been considered. An effective method for oxidizing secondary nitronates to tertiary vicinal dinitro compounds ($R_2CNO_2CNO_2R_2$) by reaction with equivalent quantities of silver nitrate in aqueous dimethyl sulfoxide or acetonitrile has been developed. 9-Nitrofluorene, 1-phenyl-1-nitroethane, nitrocyclohexane, and 2-nitropropane have thus been oxidized advantageously to 9,9′-dinitro-9,9′-bifluorenyl, 2,3-dinitro-2,3-diphenylbutanes, 1,1′-dinitrobicyclohexyl, and 2,3-dimethyl-2,3-dinitrobutane. Oxidative dimerization of silver salts of primary nitro compounds to secondary vicinal dinitro compounds is complicated by competitive oxidative nitration of the silver nitronates by silver nitrite to primary geminal dinitro alkanes.

Salts of secondary nitro compounds are oxidized by persulfates in the pH range of 9.5–7.0 at 0–5° to vicinal tertiary dinitro compounds (eq 1) and ketones (eq 2).[1]

$$2R_2C{=}NO_2^- + S_2O_8^{2-} \xrightarrow{H^+} R_2C(NO_2)-CR_2 + 2SO_4^{2-} \quad (1)$$

$$R_2C{=}NO_2^- + 2S_2O_8^{2-} \xrightarrow{2H_2O} R_2C{=}O + 4H^+ + NO_3^- + 4SO_4^{2-} \quad (2)$$

Thus alkaline solutions of 2-nitropropane, 2-nitrobutane, and nitrocyclohexane, respectively, with ammonium or sodium persulfates yield 2,3-dimethyl-2,3-dinitrobutane (**1**, 51–62%) and acetone (8–27%), 3,4-dimethyl-3,4-dinitrohexane[2] (37%) and 2-butanone (48%), and 1,1′-dinitrobicyclohexyl (**2**, 14–30%) and cyclohexanone (67%). Oxidation of salts of primary nitro compounds by persulfates has been limited to nitroethane, which results ultimately in 3,4,5-trimethylisoxazole (**3**, *ca.* 25%),[1] and to phenylnitromethane[3] (**4**), which gives *meso*- (**5**, 5%) and *dl*- (**6**, 33%) 1,2-dinitro-1,2-diphenylethanes along with benzaldehyde (**7**).



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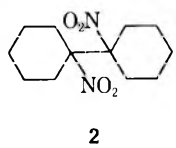

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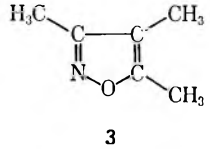

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The present investigation was initiated to determine the reactions of persulfates with salts of primary nitroalkanes, unsaturated primary and secondary nitro compounds, and 1,1-dinitro alkanes. The study was expanded to include the catalytic effects of silver ion on oxidation of salts of primary and secondary nitro compounds with persulfates. These efforts led to investigation of the actions of stoichiometric quantities of silver ion on representative alkane nitronates and to development of an advantageous method for converting silver salts of secondary nitro alkanes into their vicinal oxidative dimers.

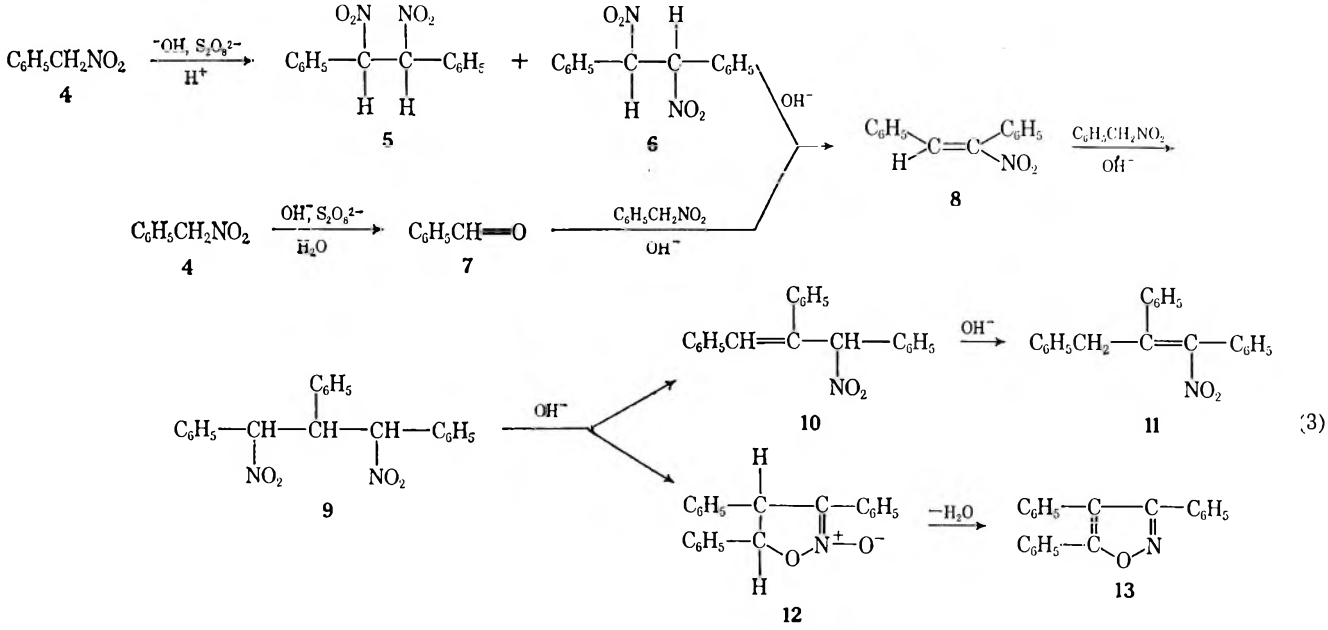
Oxidation of phenylnitromethane (**4**) by ammonium

(1) H. Shechter and R. B. Kaplan, *J. Amer. Chem. Soc.*, **75**, 3980 (1953).

(2) The stereochemistry of the 3,4-dimethyl-3,4-dinitrohexane is not known.

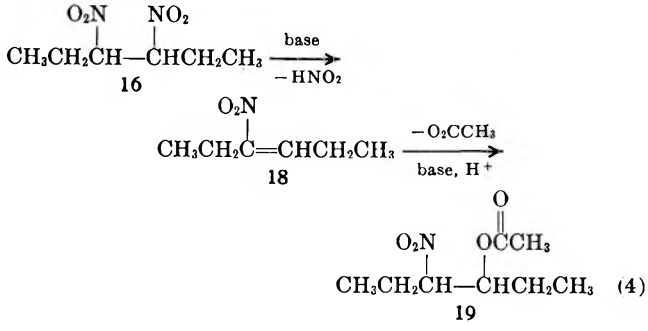
(3) (a) A. Dornow and K. Fust, *Chem. Ber.*, **90**, 1774 (1957). (b) Reference 3a describes the oxidative dimers of **4** as α- and β-1,2-dinitro-1,2-diphenylethanes. The α and β oxidative dimers are **5** and **6**, respectively. The stereochemistry of **6** is established upon its partial resolution by less than 1 equiv of brucine: H. Shechter, J. J. Gardikes, and A. H. Pagano, *J. Amer. Chem. Soc.*, **81**, 5420 (1959).

persulfate in aqueous sodium hydroxide at 0–5° in 20 hr over the pH range of 11.7–6.0 yields benzaldehyde (**7**, 23%), *cis*-α-nitrostilbene (**8**, 58%),[4] α,β,δ-triphenyl-α-nitropropene (**11**, 2.0%), 3,4,5-triphenylisoxazoline oxide (**12**, 1.3%), 3,4,5-triphenylisoxazole (**13**, 2.4%), and regenerated **4** (12%). Under the lengthy alkaline oxidative conditions, **8**, **11**, **12**, and **13** are apparently derived from **5** and **6** or from **7** and **4** by sequences as shown in eq 3.[5,6] To control the system so that satisfactory yields of the initial oxidation products could be obtained, the reactions were effected in the presence of heterogeneous extractants (chloroform or benzene) and the pH was controlled at 9.7–7.0 by use of sodium acetate as a buffer. Salts of **4** are thus oxidized by excess ammonium persulfate at various ratios of oxidant to nitro compound (Table I) to **5** (10–18%) and **6** (34–65%) along with **7** (12–16%), **12** (0.4%), **13** (0.4–2.6%), benzoic acid (**14**, 1.0–7.8%), and benzamide (**15**, 0.4–2.5%). Under the conditions of the persulfate oxidations, using chloroform as a heterogeneous extractant, neither **5** nor **6** isomerizes and their conversions into **8** and subsequent products are minimal. In the absence of the extractant, **5** and **6** are converted essentially quantitatively into **8** by aqueous sodium acetate or methanolic piperidine; reaction of **6** with 30% aqueous sodium hydroxide at 90–100° yields **13**.



(3)

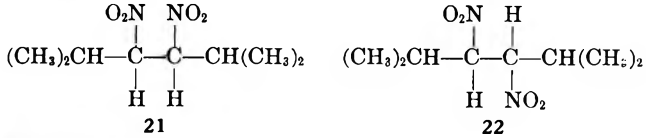
Oxidations of alkaline solutions of other primary nitro compounds with buffered persulfate ion in the presence of chloroform were effected as with **4**. Sodium 1-propanenitronate and sodium persulfate give 3,4-dinitrohexanes (**16**, *ca.* 41%),[7] propionaldehyde (**17**, 45–59%), 3-nitro-3-hexene (**18**, 2%), 4-acetoxy-3-nitrohexane (**19**, 3%), and 1-nitropropane (**20**). Similarly, sodium 1-butanenitronate yields isomeric 4,5-dinitrooctanes (12%, stereochemistry unknown), butyraldehyde (18–27%), 4-nitro-4-octene (32%), and 5-acetoxy-4-nitrooctane. Oxidation of the 1-butanenitronate anion with ammonium persulfate results in butyramide (4%) and butyric acid (12%), along with the previous products.[8] It is apparent that the 3-nitro-3-hexene (**18**) and the 4-nitro-4-octene obtained in the persulfate oxidations of 1-propanenitronate and 1-butanenitronate ions, respectively, are derived from the oxidative dimers, 3,4-dinitrohexane (**16**, eq 4) and



(4)

4,5-dinitrooctane, by base-catalyzed elimination of nitrous acid. Nucleophilic addition of acetate ion to the conjugated nitro alkenes in the protonic environment results in the formation of vicinal nitroacetates (eq 4).

Oxidation of sodium 2-methyl-1-propanenitronate, a relatively hindered nitronate, results in *meso*- (**21**) and *dl*-2,5-dimethyl-3,4-dinitrohexanes (**22**) (10%), iso-



(4) The stereochemistry of **8** (the phenyl groups are *cis*) has been assigned by J. P. Freeman and T. E. Stevens, *J. Org. Chem.*, **23**, 136 (1958).

(5) Conversions of **4** and **7** into **11**, **12**, and **13** have been studied by (a) F. Heim, *Chem. Ber.*, **44**, 2016 (1911); (b) E. P. Kohler and G. R. Barrett, *J. Amer. Chem. Soc.*, **46**, 2105 (1924); (c) D. E. Worrall, *ibid.*, **57**, 2299 (1935); (d) P. Ruggli and B. Hegedüs, *Helv. Chim. Acta*, **22**, 405 (199); (e) K. Rorig, *J. Org. Chem.*, **51**, 391 (1950); (j) A. Dornow and A. Frese, *Justus Liebigs Ann. Chem.*, **578**, 122 (1952); (g) A. T. Nielsen and T. G. Archibald, *Tetrahedron Lett.*, 3375 (1968).

(6) Oxidation of nitroethane to **3** by alkaline persulfate presumably follows a course analogous with that of **4**.

(7) The isomeric 3,4-dinitrohexanes (**16**) could not be separated readily, and thus their stereochemistry was not determined.

(8) (a) A blank experiment with sodium 1-butanenitronate in which ammonium persulfate is omitted results in recovery of 99% of the initial 1-nitrobutane and only 1% as butyraldehyde (as its 2,4-dinitrophenylhydrazone). It is concluded that the oxidizing agent is necessary to produce significant amounts of carbonyl compounds from nitronates and that the yield of aldehyde from Nef reaction[8b] in competition with that from persulfate oxidation is very small. (b) W. E. Noland, *Chem. Rev.*, **55**, 137 (1955).

TABLE I

REACTION OF SODIUM PHENYLMETHANENITRONATE WITH AMMONIUM PERSULFATE (EQ 3)

$[C_6H_5CH{=}NO_2Na]$, mol	$[(NH_4)_2S_2O_8]$, mol	Temp, °C	Time,[a] hr	Yield,[b] % 5	6	7	12	13	14	15	4[c]
0.1	0.2[d]	0–10	3.5	15.5	41.5	11.6	0.4	2.6	1.0		6.0
0.25	0.5[d]	−5 to −10	6.0	9.5	34.2	16.3		0.4	7.8		7.3
0.1	0.2[d]	12–15	0.37	18.5	44.0	15.0	0.4	2.5	1.3	0.4	5.6
0.095	0.285[d]	10–20	1.0	10.7	65.0	16.3	0.4	2.3	1.9	2.5	6.4

[a] Time elapsed between pH *ca.* 11 to 6.5; the reaction mixtures were then analyzed. [b] Yields are based on sodium phenylmethanenitronate consumed. [c] Recovery, per cent, of **4**. [d] Ammonium persulfate was added to the alkaline solution of **4**.

TABLE II

UNCATALYZED OR SILVER ION CATALYZED REACTIONS OF SODIUM 1-PROPANENITRONATE[a] WITH PERSULFATES

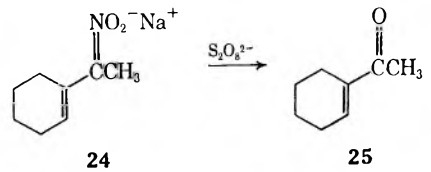
$[C_3H_6NO_2Na]$,[a] mol	$[S_2O_8^{2-}]$,[b,c] mol	Temp, °C	Time, min	Yield, % 16[d,e]	17[e,f]	20[g,h]
0.3	0.9[i]	10–20	90[j,k]	30[l]	24	10
0.3	0.9[m,n]	10–20	60[j,k]	50[l]	40	3.1
0.3	0.9[i]	0–5	390	27	25	11
0.3	0.9[m,n]	0–5	240	23	58	5.3
0.3	0.9[o]	10–20	90[j,k]	18[l]	48	12
0.3	0.9[n,p]	10–20	240	41[l]	46	4.8
0.3	0.9[q]	10–20	15[j,k]	45	29	17

[a] Sodium 1-propanenitronate. [b] Persulfates. [c] The persulfate reagents were added to sodium 1-propanenitronate. [d] 3,4-Dinitrohexanes. [e] Yields based on **20** consumed. [f] Propionaldehyde, isolated as its 2,4-dinitrophenylhydrazone. [g] 1-Nitropropane. [h] Recovery of **20**. [i] Sodium persulfate (Becco Chemical Division, Food Machinery and Chemical Corp.) catalyzed with aqueous 10% silver nitrate (10 ml, 5.9×10^{-3} mol). [j] Time elapsed between pH *ca.* 11 to pH *ca.* 6.5 when reaction mixtures were worked up. [k] At the same temperature, catalyzed Becco sodium persulfate did not decrease the reaction time as much as catalyzed Eimer and Amend sodium persulfate. [l] Yields for oxidative dimers were lower with catalyzed or uncatalyzed Becco sodium persulfate than with catalyzed or uncatalyzed Eimer and Amend sodium persulfate. [m] Sodium persulfate (Eimer and Amend) catalyzed with aqueous 10% silver nitrate (10 ml, 5.9×10^{-3} mol). [n] In all cases Eimer and Amend sodium persulfate was less soluble than Becco persulfate. [o] Sodium persulfate (Becco) uncatalyzed. [p] Sodium persulfate (Eimer and Amend) uncatalyzed. [q] Ammonium persulfate (J. T. Baker) catalyzed with aqueous 10% silver nitrate (7.7 ml, 4.5×10^{-3} mol).

butyraldehyde (20%), and 4-acetoxy-2,5-dimethyl-3-nitrohexanes (15%), along with regenerated 2-methyl-1-nitropropane. The stereochemistry of oxidative dimerization in this system is similar to that for **4** in that **22** (the *dl* isomers) is formed in greater yield than is **21** (the *meso* isomer, the ratio of **22**/**21** is 4.5:1). The stereochemical assignments for the isomers are made on the basis that *l*-brucine effects elimination of nitrous acid from *l*-2,5-dimethyl-3,4-dinitrohexane to form 2,5-dimethyl-3-nitro-3-hexene at a greater rate than from the *d* isomer.

Since oxidative dimerizations of alkane nitronates and particularly α-aryl alkane nitronates such as from **4** occur so slowly, a study was made of the influence of small proportions of silver ion (the mole ratio of Ag^+ to $RCH{=}NO_2^-$ is less than 1:60) on the oxidations.[9] Oxidative dimerizations of 1-propanenitronate, 1-butanenitronate, 2-methyl-1-propanenitronate, and phenylmethanenitronate ions are greatly accelerated by silver ion. Reaction times were reduced by more than 80% in most cases (from 1–7 hr to 0.25–1 hr). The products and yields resulting from the silver-catalyzed method are essentially identical with those obtained in the absence of catalyst. The slightly improved yields with silver ion as catalyst are attributed more to improved techniques in isolation of the products than to any effect by silver ion. The results for uncatalyzed and for silver ion catalyzed reactions of sodium 1-propanenitronate with persulfates are summarized in Table II.

Oxidations of secondary alkane nitronates having a conjugating aryl group or carbon–carbon double bond were also effected with persulfates. Reactions of sodium 1-phenyl-1-ethanenitronate (**23**) and of sodium 1-(1-cyclohexenyl)-1-ethanenitronate (**24**), respectively, give acetophenone (70–72%) and 1-cyclohexenyl methyl ketone (**25**, 61–66%, eq 5). No oxidative dimers could



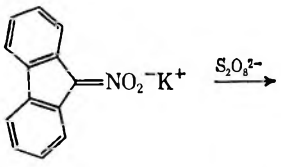
24 **25** (5)

be isolated in either case. *Transformation of* **24** *to* **25** *by persulfate indicates that the oxidation method may be of general value for converting unsaturated nitronates into their corresponding unsaturated carbonyl derivatives.* From potassium 9-fluorenenitronate (**26**) the major product is fluorenone (**27**, 72%); the oxidative dimer **28** (13%) is also obtained (eq 6).

(9) Monopositive silver ion is oxidized by persulfates to dipositive and tripositive silver, possibly according to the following equations; in the presence

$$Ag^+ + S_2O_8^{2-} \longrightarrow Ag^{2+} + \cdot SO_4^- + SO_4^{2-}$$
$$Ag^{2+} + S_2O_8^{2-} \longrightarrow Ag^{3+} + \cdot SO_4^- + SO_4^{2-}$$
$$2 \cdot SO_4^- \longrightarrow S_2O_8^{2-}$$

of reducing agents, tripositive and possibly dipositive silver ions are converted rapidly into monopositive silver and the oxidized form of the reducing agent. For discussion of this system and variants thereof, see D. M. Yost, *J. Amer. Chem. Soc.*, **48**, 152 (1926), and C. E. Bawn and D. Margerison, *Trans. Faraday Soc.*, **51**, 925 (1955).



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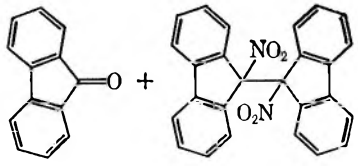
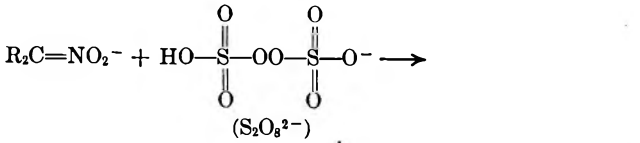


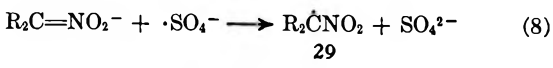
27 28 (6)

There are no simple observable correlations between the effects of structure of primary and secondary nitronates and the major products obtained in their oxidation with persulfates; each compound has its own disciplines of oxidation. For preparative purposes it is advantageous to effect oxidation of secondary rather than primary nitronates, because formation and isolation of vicinal tertiary dinitro compounds are not complicated by products derived from or after base-catalyzed elimination of nitrous acid, as in the case of vicinal secondary dinitro compounds. It is clear also that conversion of primary and secondary nitronates into aldehydes (and acids) and ketones is enhanced at elevated temperatures and in dilute solution. It will also be seen that oxidation of primary nitronates by persulfates is more efficient for preparing vicinal secondary dinitro alkanes than is decomposition of silver salts of primary nitro compounds.

The detailed mechanisms of reactions of mononitronates with persulfates are not known. Oxidation of salts of mononitro compounds apparently involves transfer of one electron to hydropersulfate and/or persulfate ion and to sulfate radical ions, as in eq 7 and 8.

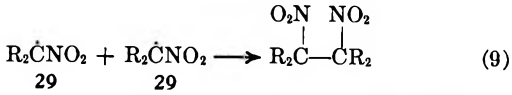


(7)



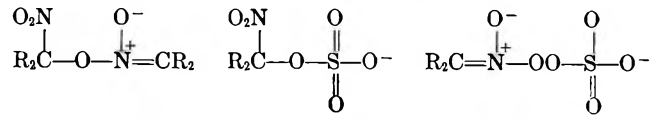
(8)

The nitroalkyl radicals (**29**) possibly dimerize to vicinal dinitro compounds (eq 9) and the isomeric α-nitro alkyl



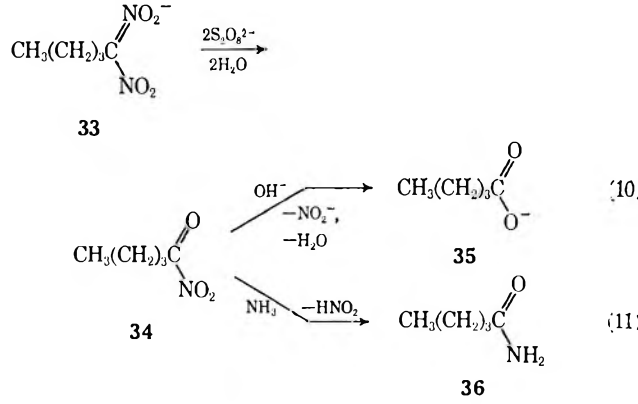
(9)

alkane nitronates (**30**, nitronic esters) or pair with sulfate radical ions. Hydrolysis of **30**, **31**, and **32** thus can give the carbonyl product, nitrous acid, and the parent mononitro compound;[10] displacement of **30**, **31**, and **32** by alkane nitronate may result in vicinal dinitro compounds.



30 31 32

The possible oxidation of 1-nitro alkane nitronates [$RC(NO_2)=NO_2^-$] by persulfates to their corresponding tetranitro compounds has been investigated. Exposure of the potassium salt of phenyldinitromethane to persulfate ion for 12 hr results in recovery of *ca.* 90% of the initial materials. In the oxidation of potassium 1-nitropentane-1-nitronate (**33**) with ammonium persulfate, 5,5,6,6-tetranitrodecane is not obtained; pentanoic acid (**35**, 35%) and pentanamide (**36**, 55%) are formed. The interesting transformations of **33** to **35** and **36** are explainable on the assumption that **34** undergoes nucleophilic reaction with hydroxide ion and with ammonia (eq 10 and 11).



33 (10) 34 35 (11) 36

The results of oxidation of nitronates with persulfates, the catalytic effects of silver ion on such systems, and previous knowledge of oxidative nitration of nitronates and nitrite ion to geminal dinitro compounds by silver ion[11] have led to study of decomposition of silver salts of mononitro and 1,1-dinitro compounds in homogeneous solution as a possible improved method for preparing vicinal dinitro derivatives. Silver salts of primary nitronates have been previously reported to decompose in heterogeneous media to silver and the corresponding vicinal secondary dinitro compounds.[12] Thus silver salts of nitroethane and 1-nitropentane, respectively, decompose heterogeneously in water to 2,3-dinitrobutane and 5,6-dinitrodecane and silver in unspecified yields.[12a] Similarly, silver phenylmethanenitronate in benzene slowly gives 1,2-dinitro-1,2-diphenylethane and silver.[12b] In previous work[1] from this laboratory, aqueous mixtures of silver nitrate and sodium 2-propanenitronate have been observed to convert impractically into acetone (30%), 2,3-dimethyl-2,3-dinitrobutane (11%), and 2-nitropropane (*ca.* 30%).

(10) There are other routes by which nitro alkyl radicals (**29**) can give vicinal dimers and carbonyl compounds which fit the present facts. Of particular note are possible reactions of nitro alkyl radicals and/or sulfate radical anions with nitronate ions by carbon and/or oxygen alkylation to give intermediate nitroxyl radical anions such as $R_2C(NO_2)CR_2(NO_2)^{\mp}$, $R_2C{=}NO_2CR_2(NO_2)^{\mp}$, $^-O_3SO_2CR_2(NO_2)^{\mp}$, and $^-O_3SO_2N(O^-)\dot{C}R_2$, which are then oxidized to vicinal dinitro compounds, **30**, **31**, and **32**. The radical anions $R_2C(NO_2)CR_2(NO_2)^{\mp}$ have been proposed as intermediates by G. A. Russell and W. C. Danen [*J. Amer. Chem. Soc.*, **88**, 5663 (1966)] in conversion of the 2-propanenitronate ion by 2-halo-2-nitropropanes into 2,3-dimethyl-2,3-dinitrobutane.

(11) R. B. Kaplan and H. Shechter, *J. Amer. Chem. Soc.*, **83**, 3535 (1961).

(12) (a) A. Angeli and L. Alessandri, *Atti Accad. Naz. Lincei, Rend., Cl. Fis. Mat. Nat.*, **191**, 784 (1910); (b) R. L. Shriner and G. B. Brown, *J. Org. Chem.*, **2**, 376 (1937).

It has now been found that, upon addition of concentrated solutions of sodium 2-propanenitronate at 30–32° to silver nitrate dissolved in acetonitrile or, preferably, dimethyl sulfoxide containing small proportions of water,[13] silver 2-propanenitronate is formed, which decomposes, possible *via* the complex ion $(R_2C{=}NO_2)_2\text{-}Ag^-Ag^+$, to silver and **1** (61–84%, eq 12). Acetone

$$2(CH_3)_2C{=}NO_2Ag \longrightarrow \underset{\substack{| \\ O_2N}}{\underset{|}{(CH_3)_2C-C(CH_3)_2}} + 2Ag \quad (12)$$

$$\mathbf{1}$$

(8–20%), 2-nitropropane (6–23%), and nitrous acid are also formed (eq 13). In this system dimethyl sulfoxide and, to a considerable extent, acetonitrile dissolve silver 2-propanenitronate and decomposition occurs quickly to give **1** in markedly improved conversions compared with previous heterogeneous methods. With either dimethyl sulfoxide or acetonitrile as solvent, silver 2-propanenitronate decomposes essentially completely at *ca.* 30° in the dark in less than 0.5 hr. In either solvent conversion of silver 2-propanenitronate (Table III) into **1** is increased and conversion into acetone is lowered as the temperature is raised from −10 to 33°. Decomposition of sodium 2-propanenitronate and silver nitrate to products is considerably faster in water–dimethyl sulfoxide than in methanol–dimethyl sulfoxide (5 hr). Silver 2-propanenitronate is photosensitive; upon exposure to light in acetonitrile, its conversion into acetone is enhanced.

$$2(CH_3)_2C{=}NO_2Ag \xrightarrow{H_2O} CH_3\overset{\overset{O}{\|}}{C}CH_3 + CH_3\overset{\overset{NO_2}{|}}{C}HCH_3 + HNO_2 + 2Ag \quad (13)$$

TABLE III

DECOMPOSITION OF SILVER 2-PROPANENITRONATE

Solvent (ml)	Temp, °C	Time,[a] hr	Yield, % 1[b]	C_3H_6O[b,c]	$C_3H_7NO_2$[d]
CH_3CN (350)	−10 to −5	17.0	10	51	12
CH_3CN (350)	0–5	17.0	34	31	19
CH_3CN (300)	30–32	5.0	66	20	16
CH_3CN (400)	30–32	0.5	61	39	11
CH_3CN (400)	80[e]	1.0	53	23	28
DMSO (150)	0–5	12.0	39	20	30
DMSO (150)	30–32	5.0	61	19	23
DMSO (350)	32–34	5.0	77[f]	13	6.0
DMSO (350)	30–31	4.0	77	8	6.0
H_2O (170)	0–5	12.0	20	49	31

[a] Total storage time of the reaction mixture. Reaction at *ca.* 30° was essentially complete in 0.5 hr. [b] Yield based on 2-nitropropane not recovered. [c] Acetone, isolated as its 2,4-dinitrophenylhydrazone. [d] Recovered 2-nitropropane. [e] The reaction mixture was refluxed. [f] Yields of **1** as high as 84% have been obtained under these conditions.

Silver salts of other secondary nitro compounds decompose rapidly in water–dimethyl sulfoxide to oxidative dimers in good yields. On the basis of the secondary nitronates studied, the method is reliable and of general advantage for preparing vicinal tertiary dinitro compounds. Thus silver 9-fluorenenitronate, cyclohexanenitronate, and 1-phenyl-1-ethanenitronate, respectively, give 9,9′-dinitro-9,9′-bifluorenyl (**28**, 60%) and fluorenone (**27**, 33%), 1,1′-dinitrobicyclohexyl (**2**, 49%) and cyclohexanone (40%), and isomeric 2,3-dinitro-2,3-diphenylbutanes (63%) and acetophenone.

Decompositions of silver 1-propanenitronate, a primary nitronate, were effected homogeneously in dimethyl sulfoxide or acetonitrile as above for secondary nitronates and heterogeneously in water as described previously.[1] In all experiments the yields of oxidative dimers and propionaldehyde are low, and the products are more complex than those from silver salts of secondary nitro compounds. Decomposition of silver 1-propanenitronate thus yields 3,4-dinitrohexanes (**16**, 6–23%) and propionaldehyde (**17**, 6–12%); 1-nitropropane (**20**), 1,1-dinitropropane (**37**, 10–22%), and 3-nitro-3-hexene (**18**, trace) are also formed.[14] With water–acetonitrile as solvent, **16** is not obtained; the products are 4-nitro-3-hexanol (22–28%), **37** (17–22%), **17** (6%), and **20**. Silver 2-methyl-1-propanenitronate in water–dimethyl sulfoxide decomposes very inefficiently to *dl*-2,5-dimethyl-3,4-dinitrohexane (**22**); the major reactions lead to 2-methyl-1,1-dinitropropane (32%) and isobutyraldehyde (18%) and regeneration of 2-methyl-1-nitropropane. Decomposition of such silver primary nitronates is not a satisfactory synthetic method for preparing vicinal secondary dinitro alkanes. It is apparent that oxidative decomposition of these silver alkane nitronates leads in part to silver nitrite, and the silver 1-alkane nitronates undergo oxidative nitration with silver nitrite to give 1,1-dinitro alkanes (as in eq 14) in competition with oxidative dimerization

$$CH_3CH_2CH{=}NO_2Ag + AgNO_2 \longrightarrow \underset{\mathbf{37}}{CH_3CH_2CH(NO_2)_2} + 2Ag \quad (14)$$

to vicinal secondary dinitro compounds. Silver phenylmethanenitronate, however, does not undergo extensive decomposition to silver nitrite and subsequent oxidative nitration to phenyldinitromethane (2%) under the above conditions. Its principal products are *dl*-1,2-dinitro-1,2-diphenylethane (**6**, 35%), *cis*- (**8**) and *trans*-α-nitrostilbene (32%), and benzaldehyde (**7**, 18%).[15]

Possible thermolysis of silver nitronates was extended to 1,1-dinitro compounds. Reaction of the potassium salt of 1,1-dinitroethane with silver nitrate in dimethyl sulfoxide does not result in oxidative decomposition. Even after 7 days at 45°, silver is not precipitated from a homogeneous solution of silver 1-nitroethanenitronate in dimethyl sulfoxide in light. Silver salts of 1,1-dinitro alkanes are much more stable than those of mononitro compounds. Additional methods for oxidizing 1-nitro alkane nitronates are being investigated.

Experimental Section

Reagents.—Ammonium persulfate (J. T. Baker, ARG, 99.1%) was used the most extensively as the persulfate oxidant. Occasionally, sodium persulfate (Eimer and Amend, assay unknown) and potassium persulfate (Matheson Coleman and Bell, RG, 98%) were used. Technical 1-nitropropane, 2-nitropropane,

(13) Although there are experimental features which make acetonitrile more desirable than dimethyl sulfoxide as a solvent in these oxidations (see Experimental Section), dimethyl sulfoxide is preferred because higher yields of vicinal oxidative dimers are obtained.

(14) As the reaction temperature is increased, conversion into **16** decreases even further.

(15) No attempt was made to maximize conversion into oxidative dimers in this system. *meso*-1,2-dinitro-1,2-diphenylethane (**5**) was not obtained; it, along with **6**, might have undergone conversion into **8** and *trans*-α-nitrostilbene in the present experiments.

and 1-nitrobutane were washed with aqueous sodium bicarbonate (10%) and rectified over boric acid before use. 2-Methyl-1-nitropropane,[16a] 1-nitro-1-phenylethane,[16b] 1-(1-cyclohexenyl)-1-nitroethane,[16c] potassium 9-fluorenenitronate,[16d] 1,1-dinitroethane,[11] 1,1-dinitropentane,[11] and phenyldinitromethane[16e] were prepared by adaptation of known procedures.

Technical acetonitrile and dimethyl sulfoxide were used as solvents for the oxidations with silver nitrate. Acetonitrile has the advantage over dimethyl sulfoxide in that it is more easily removed, the products are cleaner, and lower reaction temperatures can be used. Dimethyl sulfoxide is superior, however, with respect to yields.

Sodium Phenylcyanomethanenitronate.[17]—A mixture of phenylacetonitrile (234 g, 2.0 mol) and amyl nitrate (373 g, 2.8 mol, Ethyl Corp., Baton Rouge, La.) at 0° was added over a 1-hr period to a well-stirred solution of sodium (4.6 g, 2.0 g-atom) in absolute ethanol (600 ml) at 4–10°. The mixture was stirred for 1 hr at 5° and stored in ice–salt for 24 hr. The precipitate was filtered and washed with ethyl ether. After the combined ether–ethanol filtrate had been vacuum evaporated to dryness, the sodium phenylcyanomethanenitronate was triturated with ether, filtered, and washed with ether, yield 360 g (98%) of white material.

Phenylnitromethane (4).[17]—Sodium phenylcyanomethanenitronate (360 g, 1.96 mol) was added in small portions over a 1-hr period to a stirred, refluxing solution of sodium hydroxide (300 g, 7.5 mol) in water (1000 ml). Copious evolution of ammonia occurred after addition of the sodium salt. The mixture was boiled for 2.5 hr and cooled to 30°, and ice (600 g) was added. The vigorously stirred mixture was acidified at 0–10° with concentrated hydrochloric acid (825 ml) and extracted with ethyl ether. The combined ether extracts were washed with cold aqueous saturated sodium bicarbonate, ice–water containing a few drops of hydrochloric acid, and ice–water. The ether solution was dried (Na_2SO_4), concentrated at reduced pressure, and distilled twice to obtain **4**: yield 195–206 g (71–75%); bp 76–79° (2 mm); $n^{25}D$ 1.5287; strong ir absorption at 6.4 μ (C–NO_2), none for C=O or C–ONO. *Caution:* fuming of **4** was experienced in initial distillation.

Homogeneous Reaction of Sodium Phenylmethanenitronate with Ammonium Persulfate.—Ammonium persulfate (15.7 g, 0.069 mol) in water (55 ml) adjusted to pH 8 by 10% aqueous sodium hydroxide was added dropwise to stirred **4** (19.0 g, 0.138 mol) in water (100 ml)–sodium hydroxide (8.1 g, 0.202 mol, pH 11.7) at <10°. Within 15 min a yellow-white solid precipitated. The pH of the reaction mixture was 9.3 upon addition of the oxidizer, remained at 8–9 for 10 hr, and changed gradually and stabilized at 6.0–6.3 during the next 10 hr.

The mixture was filtered and the solid was washed with water and dried. Addition of ethyl ether and petroleum ether to the solid gave yellow *cis*-α-nitrostilbene (**8**), yield 8.0 g (58.4%), mp 73–74° (from ethanol), no depression by authentic **8**. Concentration of the filtrate gave yellow α,β,γ-triphenyl-α-nitropropene (**11**), yield 0.25 g (1.9%), mp 101–103° (from ethanol) (lit.[18] mp 102–103°).

Anal. Calcd for $C_{21}H_{17}NO_2$: C, 80.01; H, 5.39; N, 4.47. Found: C, 80.04; H, 5.50; N, 4.50.

The alkaline filtrate and the aqueous washes were cooled, acidified to pH 4.5 with aqueous urea–acetic acid, and continuously extracted with ethyl ether. The ether extract was washed with water, 5% aqueous sodium bicarbonate, hydrochloric acid (0.1 *N*), and water, dried (Na_2SO_4), filtered, and evaporated.

The aqueous filtrate and washings were acidified further with hydrochloric acid. An aliquot of this solution, upon reaction with excess 2,4-dinitrophenylhydrazine reagent, gave benzaldehyde 2,4-dinitrophenylhydrazone (mp 235.5–236.5°, no depression by authentic sample) corresponding to 4.8% benzaldehyde (**7**, 0.0059 mol) in the combined solution.

Evaporation of the ether extract yielded an oil, from which separated white 3,4,5-triphenylisoxazole (**13**), yield 0.29 g (2.4%), mp 210–212°, no depression by authentic **13**. Distillation of the residue gave **7**, yield 2.40 g (18.5%), characterized as its semicarbazone, mp 220–221°, and **4**, yield 2.2 g (11.6%), bp 82–84° (2–3 mm), $n^{20}D$ 1.5328, ir absorption essentially identical with that of initial **4**. Crystallization of the distillation residue from petroleum ether yielded white 3,4,5-triphenylisoxazoline oxide (**12**), yield 0.17 g (1.3%), mp 161–162.5°, no depression by authentic **12**.

Heterogeneous Reaction of Sodium Phenylmethanenitronate with Ammonium Persulfate.[19]—A solution of ammonium persulfate (65 g, 0.285 mol), sodium acetate (41.2 g, 0.5 mol), and water (150 ml) was added rapidly at 10–20° to a stirred mixture of phenylnitromethane (**4**, 13.02 g, 0.095 mol), water (65 ml), sodium hydroxide (5.5 g, 0.138 mol), and chloroform (70 ml). The pH dropped from 9.1 to 6.8 over a 1-hr period. The mixture was filtered, washed with water, and air dried to give white *meso*-1,2-dinitro-1,2-diphenylethane (**5**), yield 1.28 g (10.7%), mp 239° (lit.[3] mp 235–237°).

The aqueous layer was extracted with chloroform. Concentration of the chloroform extracts and addition of ethyl ether gave white *dl*-1,2-dinitro-1,2-diphenylethane (**6**), yield 7.07 g, mp 150–152°, no depression by authentic **6**.

Concentration of the ethereal filtrate gave a residue (4.58 g) which at 0° precipitated **12**, yield 0.03 g (0.35%), mp 162–164° (from ethanol). An aliquot of the residue was converted into benzaldehyde semicarbazone, mp 222–223°; the derivative corresponds to 0.052 g (16.3%) of **7** in the residue. A second aliquot (*ca.* 0.11 g) was dissolved in aqueous sodium hydroxide (0.1 *N*, 75 ml); analysis of a 10-ml sample diluted to 1000 ml at 290 nm (pure sodium phenylmethanenitronate has an extinction coefficient of 20,000 at 291 nm) revealed that 6.4% **4** (0.83 g, 6.1×10^{-3} mol) was present. A third aliquot (0.5 g) in benzene–Skellysolve B was chromatographed on silicic acid using Skellysolve B (10 ml) as prewash and 10% ethyl ether–Skellysolve B (75 ml) as developer. The top band, on elution with ethyl ether, gave benzamide (**15**), mp 127–129°, corresponding to 0.21 g (2.5%) in the residue. The lower band gave **6**, mp 145–146°, corresponding to 0.69 g in the residue. Crystallization of the residue from ethanol resulted in **13**, yield 0.19 g (2.5%), mp 215°.

Evaporation of the aqueous extract and trituration of the residue with ethyl ether gave, upon removal of solvent, benzoic acid (**14**), mp 121°.

Conversion of *meso*-1,2-Dinitro-1,2-diphenylethane (5) by Sodium Acetate into *cis*-α-Nitrostilbene (8).—Water was added to **5** (0.20 g, 7.4×10^{-4} mol) in hot methanol (100 ml) until the solution became near-cloudy. Sodium acetate (0.061 g, 7.4×10^{-4} mol) was then added and the mixture was refluxed for 10 min. After standing for several hours, the solution was extracted with ethyl ether. The ether extract, after drying ($MgSO_4$) and vacuum evaporation, gave **8**, yield 0.16 g (97%), mp 69–70.5°, no depression by authentic **8**.

Conversion of *dl*-1,2-Dinitro-1,2-diphenylethane (6) by Sodium Acetate into *cis*-α-Nitrostilbene (8).—A mixture of sodium acetate (0.061 g, 7.4×10^{-4} mol), **6** (0.20 g, 7.4×10^{-4} mol), and methanol (20 ml) containing a few drops of water was refluxed for 10 min. The mixture was kept at 20–25° for 1 hr; **8**, yield 0.08 g, mp 71–72.5°, precipitated during this period. The alcoholic solution was extracted with ethyl ether. The combined ether extracts were dried ($MgSO_4$) and evaporated. The yellow residue (0.09 g) was dissolved in benzene (3 ml) and chromatographed on silicic acid using Skellysolve B as prewash and 10% ethyl ether–Skellysolve B as developer (35 ml). The yellow band was eluted with ethyl ether. The eluent was dried and evaporated, giving additional **8**, yield 0.07 g (91%), mp 69–70.5°.

Conversion of *dl*-1,2-Dinitro-1,2-diphenylethane (6) by Sodium Hydroxide into 3,4,5-Triphenylisoxazole (13).—Reaction of **6** (2.0 g, 0.0074 mol) with aqueous 30% sodium hydroxide (50 ml) at 80–90° for 4 hr gave a solid which was washed with water and a little ethanol and recrystallized from ethanol–acetic acid to give white **13**, yield 0.5 g (63%), mp 213–215°, no depression by authentic **13**.

Reaction of Sodium 1-Propanenitronate with Sodium Persulfate Catalyzed by Silver Ion.—This experiment is a prototype of that for oxidation of 1-propanenitronate, as summarized in Table II.

(16) (a) N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and G. F. Graham, *J. Amer. Chem. Soc.*, **78**, 1497 (1956); (b) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *ibid.*, **77**, 6269 (1955); (c) H. Fraser and G. F. Kon, *J. Chem. Soc.*, 604 (1934); (d) W. Wislicenus and M. Waldmuller, *Chem. Ber.*, **41**, 3338 (1908); (e) L. F. Fieser and W. E. Doering, *J. Amer. Chem. Soc.*, **68**, 2252 (1946).

(17) This is a significantly improved procedure over that of A. H. Blatt, "Organic Syntheses," Coll. Vol. II, 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1943, p 512.

(18) F. Heim, *Chem. Ber.*, **44**, 2022 (1911).

(19) This experiment is a prototype of those in Table I.

Sodium persulfate (205 g, 0.9 mol) and sodium acetate (123 g, 1.5 mol) in water (500 ml) and then 10% aqueous silver nitrate (5.9×10^{-3} mol) were added to a stirred mixture of 1-nitropropane (20, 26.7 g, 0.3 mol), 10% aqueous sodium hydroxide (150 ml), and chloroform (500 ml) at 10–20°. After 1 hr the pH of the mixture was 6.7. The silver deposited and the aqueous and chloroform layers were separated. The aqueous portion (A) was extracted with chloroform. The chloroform extracts were washed with 5% aqueous sodium bicarbonate and dilute hydrochloric acid, dried ($MgSO_4$), and distilled to give distillate B and residue C. The aqueous washings D were acidified.

Extract A was steam distilled into D. An aliquot of this solution, when treated with excess 2,4-dinitrophenylhydrazine, gave propionaldehyde 2,4-dinitrophenylhydrazone, mp 156–158° from ethanol, no depression by authentic sample, corresponding to 5.8 g of propionaldehyde (17) in A–D. Rectification of B and the most volatile component of C gave additional 17, 0.35 g, analyzed as its 2,4-dinitrophenylhydrazone, and 20: yield 0.83 g (3.1%), bp 49–53° (50 mm); $n^{20}D$ 1.4016–1.4020 (lit.[20] $n^{20}D$ 1.4015). The total conversion into 17 was 40%.[21]

Residue C, on distillation, gave (1) a mixture (1.26 g) of 4-acetoxy-3-nitrohexane (19) and 3-nitro-3-hexene (18), bp 52–69° (10 mm), $n^{20}D$ 1.4382–1.4555, and (2) 3,4-dinitrohexanes (16), yield 5.46 g (49.5%) of pale yellow liquid, bp 50–54° (0.3 mm), $n^{20}D$ 1.4512. Fraction 1 was separable by chromatography or by distillation to (1) 18, yield 0.3 g (1.6%), a pale yellow lachrymator, bp 62–65° (10 mm), $n^{20}D$ 1.4580 [authentic 18 from 19 and sodium acetate, bp 66–66.5° (10 mm), $n^{20}D$ 1.4580]; and (2) 19, yield 0.75 g (2.7%), a colorless liquid, bp 90–93° (10 mm), $n^{20}D$ 1.4347 (the chromatographic and the spectral properties are essentially identical with those of authentic 19).

Fraction 2 was distilled into various fractions of 19: bp 67° (1.3 mm); mp *ca.* 27°; $n^{30}D$ 1.4431.

Anal. Calcd for $C_6H_{12}N_2O_4$: C, 40.91; H, 6.83; N, 15.85. Found: C, 40.72; H, 6.97; N, 15.37.

The structure of 16 was confirmed upon its reaction (1.0 g, 5.68×10^{-3} mol) with aqueous sodium hydroxide (6.1×10^{-3} mol) for 45 min, extraction of a subsequent ethereal solution with dilute hydrochloric acid, work-up, and vacuum distillation to 18: yield 0.62 g (85%); $n^{20}D$ 1.4575; ir 6.6 and 7.5 (C=CNO_2) and 6.0 μ (C=C); its properties are essentially identical with those of authentic 18.

Reaction of Sodium 1-Butanenitronate with Ammonium Persulfate Catalyzed by Silver Ion.—Oxidation of a heterogeneous mixture of 1-nitrobutane (27 g, 0.26 mol) in aqueous 10% sodium hydroxide (130 ml) and chloroform (450 ml) at 10–20° was effected at pH *ca.* 11.0 upon addition of ammonium persulfate (178 g, 0.78 mol), sodium acetate (107 g, 1.3 mol) in water (300 ml), and aqueous silver nitrate (4.3×10^{-3} mol). The reaction mixture was handled essentially identically with those from sodium 1-propanenitronate and sodium persulfate. The following materials were obtained: (1) butyraldehyde, yield 4.25 g (27%), as its 2,4-dinitrophenylhydrazone, mp 121–122°, no depression by an authentic sample; (2) 1-nitrobutane, yield 4.3 g (16%), bp 76–77° (67 mm), $n^{20}D$ 1.4106 (lit.[20] $n^{20}D$ 1.4112); (3) 5-acetoxy-4-nitrooctane, yield 0.44 g (*ca.* 2%), contaminated slightly with 4-nitro-4-octene, bp 64° (2 mm), $n^{20}D$ 1.4457; (4) 4-nitro-4-octene, yield 5.63 g (32%), pale yellow lachrymator, bp 66–68° (2 mm), $n^{20}D$ 1.4590–1.4597 [lit.[20] bp 93° (10 mm), $n^{25}D$ 1.4593], ir 6.6 and 7.5 (C=CNO_2) and 6.0 μ (C=C); and (5) 4,5-dinitrooctanes, yield 2.70 g (12%), yellow oil, bp 85–87° (0.5 mm), $n^{20}D$ 1.4517, ir 6.4 and 7.5 μ (CNO_2). The dinitrooctanes were contaminated with some 4-nitro-4-octene as a result of decomposition during distillation.

Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.85; N, 13.71. Found: C, 47.52; H, 7.47; N, 13.86.

Reaction of Sodium 2-Methyl-1-propanenitronate and Ammonium Persulfate Catalyzed by Silver Ion.—Aqueous silver nitrate (4.5×10^{-3} mol) was added to a mixture of 2-methyl-1-nitropropane (30.9 g, 0.3 mol), 10% aqueous sodium hydroxide (150 ml), ammonium persulfate (205 g, 0.9 mol), sodium acetate (123 g, 1.5 mol), chloroform (500 ml), and water (300 ml) at 10°. After 1 hr the chloroform solution was washed with 5% sodium bicarbonate, dilute hydrochloric acid, and water.

Analysis of the combined aqueous extracts and an aliquot of the chloroform solution by reaction with 2,4-dinitrophenylhydrazone (mp 179.5°, no depression by an authentic sample) showed formation of isobutyraldehyde in 38% yield. Distillation of the chloroform solution gave (1) 2-methyl-1-nitropropane, yield 8.4 g (27%), bp 65–67° (60 mm), $n^{20}D$ 1.4080, identical with initial material; (2) 4-acetoxy-2,5-dimethyl-3-nitrohexane, yield 3.7 g (15%), bp 64–68° (0.5 mm), $n^{20}D$ 1.4389, essentially identical with authentic material; and (3) a residue which solidified on cooling. Addition of ethyl and petroleum ether to the semisolid gave white, unstable *dl*-2,5-dimethyl-3,4-dinitrohexane (22), yield 3.0 g (13%), mp 123–124°, upon recrystallization from Skellysolve B and acetone.

Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.88; N, 13.71. Found: C, 47.56; H, 7.67; N, 13.63.

Evaporation and recrystallization of the residue gave *meso*-2,5-dimethyl-3,4-dinitrohexane (21), yield 0.82 g (4%), mp 80–83°.

Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.88; N, 13.71. Found: C, 47.54; H, 7.65; N, 13.62.

Partial Resolution of *dl*-2,5-Dimethyl-3,4-dinitrohexane (22).—A solution of 22 (0.80 g, 3.92×10^{-3} mol) and *l*-brucine (0.52 g, 1.31×10^{-3} mol) in benzene (80 ml) was stored at 25° for 5 hr. The mixture was washed with water, hydrochloric acid (0.05 *N*), and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow-white solid: yield 0.76 g; mp 120°; $[\alpha]^{23}_{590}$ 1.4° (α 0.17°, *c* 6.0, *l* = 2 dm).

Additional *l*-brucine (0.5 g) was added to the solid in benzene (80 ml) and the mixture was refluxed for 1 hr. The solution on treatment as above yielded a yellow semisolid (0.26 g). Addition of petroleum ether gave a white solid: mp 115–118° after recrystallization from Skellysolve B–acetone; mixture melting point with 22, no depression; ir almost identical with 22; $[\alpha]^{23}_{590}$ 11° (α 0.74°, *c* 3.3, *l* = 2 dm).

The above procedure with 21 gave no optical rotation in the recovered material.

2,5-Dimethyl-3-nitro-3-hexene.—Isobutyraldehyde (42 g, 0.585 mol), 2-methyl-1-nitropropane (61 g, 0.59 mol), aqueous 10 *N* sodium hydroxide (8 ml), and 95% ethanol were stirred for 72 hr at 30–38°. The mixture was acidified with hydrochloric acid, neutralized, washed, and vacuum distilled to give 2,5-dimethyl-4-nitro-3-hexanol: yield 25.6 g (49%); bp 94–97° (10 mm); $n^{20}D$ 1.4486; ir 6.4 and 7.2 (NO_2) and 2.9 μ (OH).

2,5-Dimethyl-4-nitro-3-hexanol (25.6 g, 0.144 mol), acetic anhydride (16 g, 0.154 mol), and sulfuric acid (0.5 ml) were stirred at 40–70° for 2.5 hr and then distilled to yield 4-acetoxy-2,5-dimethyl-3-nitrohexane: yield 21.7 g (73%); bp 86–87° (2–2.5 mm); $n^{20}D$ 1.4387; ir 6.4 and 7.2 (CNO_2) and 5.7 and 8.1 μ (CO_2).

4-Acetoxy-2,5-dimethyl-3-nitrohexane (22 g, 0.101 mol) and anhydrous sodium acetate (12.0 g) were heated slowly at 115° (15 mm). The product that distilled at 70–80° (15 mm) was dissolved in ethyl ether, washed with aqueous 5% sodium bicarbonate, dilute hydrochloric acid, and water, dried ($MgSO_4$), and fractionated to give 2,5-dimethyl-3-nitro-3-hexene: yield 10.0 g (64%); bp 74–76° (10 mm); $n^{20}D$ 1.4506; ir 6.6 and 7.4 (C=CNO_2) and 6.0 μ (C=C).

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.79. Found: C, 61.28; H, 9.94; N, 8.51.

Reaction of Sodium 1-Phenyl-1-ethanenitronate (23) with Ammonium Persulfate.—Ammonium persulfate (30.6 g, 0.134 mol) and sodium acetate trihydrate (45.5 g, 0.335 mol) in water (100 ml) was added to 1-nitro-1-phenylethane (30 g, 0.067 mol) and sodium hydroxide (3.35 g, 0.0837 mol) in water (32 ml) at 0–5°. After 7 hr (pH change of *ca.* 11 to 6.5) the aqueous layer was extracted with chloroform and ethyl ether. The organic extracts were washed with 5% sodium bicarbonate, dilute hydrochloric acid, and water, dried ($MgSO_4$), and distilled to give (1) acetophenone, yield 4.96 g (71%), bp 34–36° (0.3 mm), $n^{20}D$ 1.5328–1.5334, identified as its 2,4-dinitrophenylhydrazone, mp 253–254° (from ethanol), no depression by an authentic sample; and (2) 1-nitro-1-phenylethane, yield *ca.* 1.0 g (10%), bp 53° (0.3 mm), $n^{20}D$ 1.5214, spectral and chromatographic properties identical with initial material.

Oxidation of Sodium 1-(1-Cyclohexenyl)-1-ethanenitronate (24) with Ammonium Persulfate Catalyzed by Silver Ion.—On addition of ammonium persulfate (43 g, 0.19 mol) and sodium acetate trihydrate (43.5 g, 0.32 mol) in water (60 ml) to 1-(1-cyclohexenyl)-1-nitroethane (10 g, 0.0645 mol) in 10% sodium hydroxide (33 ml) and chloroform (50 ml) at 9°, the pH changed from 11.6 to 8.7. Aqueous 10% silver nitrate (1.5 ml) was then

(20) H. B. Hass and E. F. Riley, *Chem. Rev.*, **32**, 373 (1943).

(21) In all experiments in which aldehydes or ketones were analyzed as precipitated 2,4-dinitrophenylhydrazones, the data were corrected to include losses of the derivatives owing to their solubilities under the experimental conditions.

introduced; in 1 hr the pH was *ca.* 6.0. The aqueous layer was extracted with chloroform and with ethyl ether. The organic extracts were concentrated *in vacuo*. An aliquot of the concentrate dissolved in methanol, on addition to 2,4-dinitrophenylhydrazine, gave 1-cyclohexenyl methyl ketone 2,4-dinitrophenylhydrazone, mp (from ethanol) 205–207°, no depression by an authentic sample,[22] corresponding to a yield (4.5 g) of 1-cyclohexenyl methyl ketone of 66%.

The remainder of the concentrate was stirred with excess 10% sodium hydroxide at 0° and extracted with ethyl ether. The ether extract was washed with saturated sodium chloride containing a few drops of hydrochloric acid, dried ($MgSO_4$), and distilled, yielding 1-cyclohexenyl methyl ketone: bp 58–59° (2.5 mm); $n^{25}D$ 1.4861 (lit.[23] $n^{20}D$ 1.4881); ir 5.8 (C=C) and 6.0 μ (C=C).

The basic, aqueous layer, after acidification with acetic acid–urea–water at 0–5°, was extracted with ethyl ether. The ether extract, after having been washed with 5% sodium bicarbonate and saturated aqueous sodium chloride containing a trace of hydrochloric acid, dried ($MgSO_4$), and distilled, resulted in 1-(1-cyclohexenyl)-1-nitroethane, yield 1.5 g, (15%), bp 75–79° (2.5 mm), identical with initial material.

Reaction of Potassium 9-Fluorenenitronate (26) with Potassium Persulfate.—Potassium persulfate (10.8 g, 0.04 mol), water (250 ml), and a few drops of aqueous 10% potassium hydroxide were added to a stirred, heterogeneous mixture of **26** (5.0 g, 0.02 mol), water (60 ml), benzene (60 ml), and sufficient aqueous potassium hydroxide to bring the pH to *ca.* 9.0. Aqueous potassium hydroxide was added periodically to maintain the pH at 8–9.5 at 20–30°. After 4 hr, the pH of the mixture was raised to pH *ca.* 12.0 by addition of potassium hydroxide and the benzene layer was separated. The aqueous layer was extracted with benzene and ethyl ether. The organic extracts were dried ($MgSO_4$) and concentrated. Addition of benzene and petroleum ether gave 9,9′-dinitro-9,9′-bifluorenyl (**28**), yield 0.55 g (13%), mp 181–182° (from benzene–petroleum ether), no depression by an authentic sample. Concentration of the filtrate and cooling yielded fluorenone, yield 2.6 g (72%), mp 82–83°, no depression by an authentic sample.

Reaction of Sodium 1-Nitropentane-1-nitronate (33) with Ammonium Persulfate.—Ammonium persulfate (98 g, 0.428 mol) in water (144 ml) was added to 1,1-dinitropentane (18.5 g, 0.144 mol) in aqueous 10% sodium hydroxide (63 ml). The mixture was warmed to 30–40° for 8.5 hr, heated to 53–55° (the pH dropped to 5.3), cooled, and acidified with dilute hydrochloric acid to pH *ca.* 1.5.

The aqueous layer was extracted with ethyl ether. The residue obtained, upon evaporation of the organic extracts, was triturated with ethyl ether and Skellysolve F and cooled. Valeramide separated, yield 2.28 g, mp 104–105°, no depression by an authentic sample.

The ethyl ether–Skellysolve F filtrate was evaporated and distilled to give a volatile fraction, yield 4.54 g, bp 75–90° (10 mm), and a residue. Addition of Skellysolve F to the residue precipitated additional valeramide, yield 1.55 g, mp 104–105°; the valeramide produced in this experiment totaled 55%. The distillate exhibited strong infrared absorption at 3.0–3.5 (CO_2H) and 6.3 μ [$C(NO_2)_2$]. An aliquot (10 ml) of the distillate (0.1643 g) in 0.1 *N* sodium hydroxide (100 ml) was diluted to 1000 ml and analyzed at 226 and 386 mμ. The aliquot corresponds to 4.47 g of 1,1-dinitropentane (24.5% recovery) in the distillate. The valeric acid, as determined by difference, totaled 1.07 g (35%).

The aqueous layer was evaporated and the residue was triturated with ethyl ether. The ether extract, on evaporation, yielded a residue which gave strong absorption for a carboxyl group and which, when refluxed with thionyl chloride and then poured into cold ammonia, gave valeramide, mp 104–105°, no depression by an authentic sample.

Reaction of Sodium 2-Propanenitronate with Silver Nitrate.—A series of decompositions of silver 2-propanenitronate were effected (Table III) under differing conditions of temperature and time using dimethyl sulfoxide–water or acetonitrile–water as solvents. All oxidations were conducted as follows.

Sodium hydroxide (5.92 g, 0.148 mol), water (35 ml), and 2-nitropropane (13.4 g, 0.15 mol) were added rapidly to silver nitrate (25.5 g, 0.15 mol) in either dimethyl sulfoxide or acetonitrile and stirred for the time indicated.

After the reaction was complete, the silver was filtered. Water (0.5–1.5 l.) was added to the filtrate and the mixture was cooled to 0–5°. 2,3-Dimethyl-2,3-dinitrobutane (1) was filtered, washed with water, and dried. An aliquot of the filtrate was dissolved in 2,4-dinitrophenylhydrazine reagent. The remaining aqueous filtrate was acidified with acetic acid–water–urea at 0° and extracted with ethyl ether. The ether extract was washed with water, aqueous sodium bicarbonate, and dilute sulfuric acid, dried ($MgSO_4$), and concentrated. The oily residue was dissolved in minimal ethyl ether, a large quantity of Skellysolve F was added, and additional 1 was filtered. The ethereal filtrate was concentrated and the 2-nitropropane recovered was distilled.

Reaction of Potassium Cyclohexanenitronate with Silver Nitrate.—A solution of nitrocyclohexane (12.9 g, 0.1 mol), potassium hydroxide (5.6 g, 0.1 mol), and water (40 ml) was added rapidly to a stirred mixture of silver nitrate (17.0 g, 0.1 mol) in dimethyl sulfoxide (400 ml) at 30°. After 5.5 hr, the silver was filtered and washed with warm chloroform. Water (*ca.* 1.5 l.) was added to the combined filtrate. The filtrate was extracted with chloroform and ethyl ether and analyzed for cyclohexanone *via* precipitation of its 2,4-dinitrophenylhydrazone.

Concentration of the organic extracts *in vacuo* gave a viscous residue and 1,1′-dinitrobicyclohexyl (**2**). Ethyl ether (10 ml) and Skellysolve B (100 ml) were added and **2** (3.50 g) was filtered. The filtrate was washed with water, dried ($MgSO_4$), filtered. and cooled to 0°; additional **2** (1.03 g) precipitated, overall yield 49%, mp 217–221.5°, no depression by authentic **2**.

The various filtrates after separation of **2** were concentrated and analyzed for cyclohexanone as its 2,4-dinitrophenylhydrazone and for regenerated nitrocyclohexane (3.48 g, 27%) by difference. The overall yield of cyclohexanone was 40%.

Reaction of Sodium 1-Phenyl-1-ethanenitronate with Silver Nitrate.—A solution of 1-nitro-1-phenylethane (13.8 g, 0.091 mol) and potassium hydroxide (5.04 g, 0.090 mol) in water (40 ml) was added to silver nitrate (15.6 g, 0.092 mol) in dimethyl sulfoxide (400 ml) at 20–35°. After 4 hr the silver was filtered; water (*ca.* 1 l.) was added to the filtrate. The solution was extracted with chloroform and with ethyl ether at 0°. The silver was washed with warm chloroform. The extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. When ethyl ether and Skellysolve B were added to the residue, the solution was stored at 0°, and the precipitate was filtered, white 2,3-dinitro-2,3-diphenylbutane (3.0 g) was obtained, mp 140–141° (from ethanol–water), ir 6.45 μ (CNO_2).

Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.32. Found: C, 64.34; H, 5.56; N, 9.08.

The ethereal filtrate, on vacuum distillation, gave a mixture of acetophenone and 1-nitro-1-phenylethane, yield 5.53 g, bp 32–58° (*ca.* 0.2 mm), and a residue (3.78 g) which crystallized on addition of ethanol or ethyl ether to give white 2,3-dinitro-2,3-diphenylbutane, mp 150° (from ethanol–water), ir 6.45 μ (CNO_2). The melting point of a mixture of the two isomeric forms of 2,3-dinitro-2,3-diphenylbutane was 100–180°.[24]

Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.32. Found: C, 63.62; H, 5.30; N, 9.17.

An aliquot of the distillation product was added to methanol and the mixture was dissolved in excess 2,4-dinitrophenylhydrazine solution. The acetophenone 2,4-dinitrophenylhydrazone was isolated, mp 250°, no depression by an authentic sample, and corresponds to 2.66 g of acetophenone in the distillate. The remainder of the distillate was 1-nitro-1-phenylethane (2.87 g, 21%). An aliquot of the initial aqueous layer and the aqueous washings gave additional acetophenone 2,4-dinitrophenylhydrazone. The total acetophenone obtained corresponded to 40% conversion of 1-nitro-1-phenylethane.

Reaction of Potassium 9-Fluorenenitronate with Silver Nitrate.—The silver, formed during a 4.5-hr period after addition of potassium 9-fluorenenitronate (10 g, 0.04 mol) in water (45 ml) to silver nitrate (7.7 g, 0.045 mol) in dimethyl sulfoxide (200 ml),

(22) W. H. Linnell and C. C. Shen, *J. Pharm. Pharmacol.*, **2**, 13 (1950).

(23) L. Ruzicka, D. R. Koolhaas, and A. H. Wind, *Helv. Chim. Acta*, **14**, 1157 (1931).

(24) Stereochemical assignments can possibly be made for the isomeric 2,3-dinitro-2,3-diphenylbutanes on the basis of their melting points. Using the generalization (R. Stern, Abstracts, 131st National Meeting of the American Chemical Society, Miami, Fla., Apr 1957, No. 5-0)—of diastereoisomeric compounds containing two identically substituted acyclic centers of asymmetry, the *meso* modification will have the higher melting point than either the racemic or the optically active epimer provided that it is centrosymmetrical—thus the 2,3-dinitro-2,3-diphenylbutane having the melting point of 150° would be assigned as the *meso* isomer.

was filtered and washed with hot benzene. Water (*ca.* 1 l.) was added to the dimethyl sulfoxide–water filtrate and the resulting aqueous solution was extracted with benzene. The combined organic extracts were washed with saturated sodium chloride, dried ($MgSO_4$), and concentrated *in vacuo*. Addition of ethyl ether and petroleum ether to the semisolid and concentration of the mixture gave 9,9′-dinitro-9,9′-bifluorenyl (**28**), yield 5.45 g, mp 181–182°, no depression by authentic **28**. Concentration, cooling, and filtration of the benzene–ethyl ether–petroleum ether filtrate gave fluorenone (**27**), yield 2.38 g (33%), mp 82–83°, no depression by authentic **27**. Reaction of the final filtrate with hydroxylamine hydrochloride resulted in formation of fluorenone oxime, yield 0.23 g (3%), mp 194–195° (from chloroform–petroleum ether), no depression by an authentic sample.

Reaction of Sodium 1-Propanenitronate with Silver Nitrate.—The results of the following experiment are typical of those of a series for silver 1-propanenitronate in dimethyl sulfoxide–water, acetonitrile–water, and water.

A solution of sodium hydroxide (11.9 g, 0.209 mol), water (45 ml), and 1-nitropropane (**20**, 26.7 g, 0.3 mol) was added to silver nitrate (51 g, 0.3 mol) in dimethyl sulfoxide (375 ml)–methanol (45 ml)[25] at 0–5°. After 5 hr the silver was filtered. Water (*ca.* 1.6 l.), ethyl ether, and hydrochloric acid were added to the filtrate (pH *ca.* 1.5) at *ca.* 10° and the mixture was separated. The ether extract was washed with water, dried, and concentrated to give distillate A and residue B. The aqueous extract and washings were acidified.

Residue B was distilled to give (1) highly volatile products; (2) **20**,[26] yield 4.7 g (19%); (3) 1,1-dinitropropane[26] (**37**), yield 5.7 g (17%), bp 58–60° (4–4.5 mm), $n^{20}D$ 1.4360, ir 6.3 μ [$C(NO_2)_2$]; (4) 4-nitro-3-hexanol[26] containing a small amount of 3-nitro-3-hexene, yield 2.6 g (14%), bp 85–88° (4–4.5 mm), $n^{20}D$ 1.4458; and (5) 3,4-dinitrohexanes[26] (**16**), yield 4.0 g (18%), bp *ca.* 106° (4–4.5 mm), $n^{20}D$ 1.4510. The volatile products were combined with distillate A and analyzed for propionaldehyde (**17**) as its 2,4-dinitrophenylhydrazone. The 1-nitropropane converted into **17** amounted to 10%.

(25) The methanol was added to lower the freezing point of the dimethyl sulfoxide.

(26) Identified by comparison with authentic samples.

Registry No.—Sodium phenylcyanomethanenitronate, 12385-04-5; sodium phenylmethanenitronate, 12321-46-9; ammonium persulfate, 7727-54-0; sodium 1-propanenitronate, 12384-98-4; sodium persulfate, 7775-27-1; sodium 1-butanenitronate, 12385-00-1; sodium 2-methyl-1-propanenitronate 12385-01-2; 2,5-dimethyl-4-nitro-3-hexanol, 22482-65-1; 4-acetoxy-2,5-dimethyl-3-nitrohexane, 22482-66-2; 2,5-dimethyl-3-nitro-3-hexene, 22482-67-3; potassium persulfate, 7727-21-1; sodium 2-propanenitronate, 12384-99-5; silver nitrate, 7761-88-8; potassium cyclohexanenitronate 12385-03-4; 2,3-dinitro-2,3-diphenylbutane, 22479-37-4; *meso*-2,3-dinitro-2,3-diphenylbutane, 22486-14-2; **4**, 622-42-4; **16**, 22482-64-0; **21**, 22485-93-4; **22**, 22485-94-5; **23**, 12385-05-6; **24**, 12385-06-7; **26**, 12385-07-8; **33**, 12385-02-3.

Acknowledgment.—We are pleased to acknowledge support of this research by the Office of Naval Research.

Arylation by Aromatic Nitro Compounds at High Temperatures. VIII. Reactions of Nitrobenzene and Nitrobenzene-d_5 with Cyclohexane at 600°

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Received May 27, 1969

Nitrobenzene and cyclohexane at 600° give benzene, biphenyl, phenol, ethylene, propylene, and butadiene as major products. Minor products are ethylbenzene, styrene, β-methylstyrene, allylbenzene, indene, and naphthalene; these are formed by reaction of olefins derived from cyclohexane with phenyl radicals derived from nitrobenzene. Only a small amount of benzene comes from cyclohexane; dehydrogenation is mainly to cyclohexene. Phenyl radical prefers to abstract hydrogen from cyclohexane rather than add to the aromatic ring of benzene by a ratio of 16:1. The products from cycloheptane and cyclooctane are similar to those from cyclohexane; cyclopentane differs mainly in giving almost no products derived from a C_4 fragment.

Nitrobenzene decomposes above 400° to phenyl radical and NO_2.[2] In the presence of aromatic compounds, even of such a completely substituted benzene derivative as hexafluorobenzene, phenyl radical adds to the aromatic system to give biphenyls as the major products.[3] Hydrogen abstraction is a minor process; nitrobenzene with toluene gives mainly methylbiphenyl isomers, rather than benzene and biphenyl.[4]

It was of interest, therefore, to study the behavior of nitrobenzene with compounds that contain only abstractable hydrogens and no carbon–carbon double bonds. This article describes the reactions of nitrobenzene and nitrobenzene-d_5 with cyclohexane, and of nitrobenzene with cyclopentane, cycloheptane, and cyclooctane.

Experimental Section

Reactions were run in a Vycor tube filled with Vycor chips in an electric furnace maintained at 600 ± 1° under pure, dry nitrogen with contact times of 14–22 sec. The vapors were condensed in a flask at 0°; the uncondensed effluent gases were passed through a series of three traps containing bromine in chloroform at 0°. The condensates were distilled to recover unreacted material, and the residues were analyzed by gas chromatography, mass spectrometry, and directly coupled gas chromatography–mass spectrometry.[5] The brominated products were analyzed by gas chromatography.

Gas chromatographic–mass spectral analysis was used not only to identify chromatographically separated components of product mixtures but also to determine the isotopic composition of such components from reactions with nitrobenzene-d_5. For the latter purpose, variation of the isotopic distribution over the

(1) (a) Amoco Chemicals Corp.; (b) American Oil Co.

(2) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 724 (1967).

(3) E. K. Fields and S. Meyerson, *ibid.*, **89**, 3224 (1967); *J. Org. Chem.*, **32**, 3114 (1967).

(4) E. K. Fields and S. Meyerson, *ibid.*, **33**, 2315 (1968).

(5) E. K. Fields and S. Meyerson, *ibid.*, **33**, 4487 (1968).

time span of a chromatographic peak requires repetitive scanning of the molecular-ion region at a preselected reduced ionizing voltage.[6] Intensity corresponding to each isotopic species is then plotted *vs.* time, and the integrated areas under these curves are taken as measures of the concentrations of the various species.[6]

In a typical experiment, a solution of 10.3 ml (0.1 mol) of nitrobenzene in 43.2 ml (0.4 mol) of cyclohexane was passed through a Vycor tube at 600° under a nitrogen flow of 15 ml/min, with a contact time of 20.1 sec. The vapors were condensed in a flask at 0°. The condensate was distilled to give 21.3 g of distillate and 4.7 g of residue. Analysis of the distillate by gas chromatography on a column of 5% Bentone 34 and 5% DC550 on Chromosorb W showed 15.6 g of cyclohexane, 1.2 g of cyclohexene, and 3.9 g of benzene. Analysis of the residue on a column of 10% OV17 on Chromosorb W gave the results shown in Table I. The bromine solutions were reduced with sodium thiosulfate and extracted with chloroform to give 17.5 g of a mixture which was analyzed on a column of 5% SE-30 on Chromosorb W. This analysis provided the data on the olefins shown in Table I.

TABLE I

PRODUCTS FROM NITROBENZENE AND CYCLOHEXANE[a]

Product[b]	Yield, mol %[c]
Ethylene	25.5
Propylene	20.4
Butenes	2.5
Butadiene	13.7
Benzene	54.4
Cyclohexene	15.5
Phenol	1.7
Biphenyl	0.7
Ethylbenzene	1.0
Styrene	2.0
β-Methylstyrene	1.0
Allylbenzene	0.2
Indene	0.7
Naphthalene	1.2

[a] Reaction conditions: 600°, contact time 20.1 sec, 0.1 mol of nitrobenzene, 0.4 mol of cyclohexane. [b] The gaseous olefins were analyzed as bromine addition products. Other gases were methane, ethane, propane, and hydrogen. [c] The yields were determined by gas chromatography and are based on a 94.2% conversion of nitrobenzene.

The reagents and standards for gas chromatography were reagent grade and were used as received.

Results and Discussion

Nitrobenzene with Cyclohexane.—The major products from the reaction of nitrobenzene with cyclohexane are shown in Table I. The alkylaromatic products apparently result from the fragmentation of cyclohexane to C_2, C_3, and C_4 hydrocarbons, which then react with the phenyl radical derived from nitrobenzene. Nitrobenzene alone at 600° gives phenol, biphenyl, and dibenzofuran as major products.[3] The formation of ethylene, propylene, and butadiene from the pyrolysis of cyclohexane is well known.[7] However,

SCHEME I

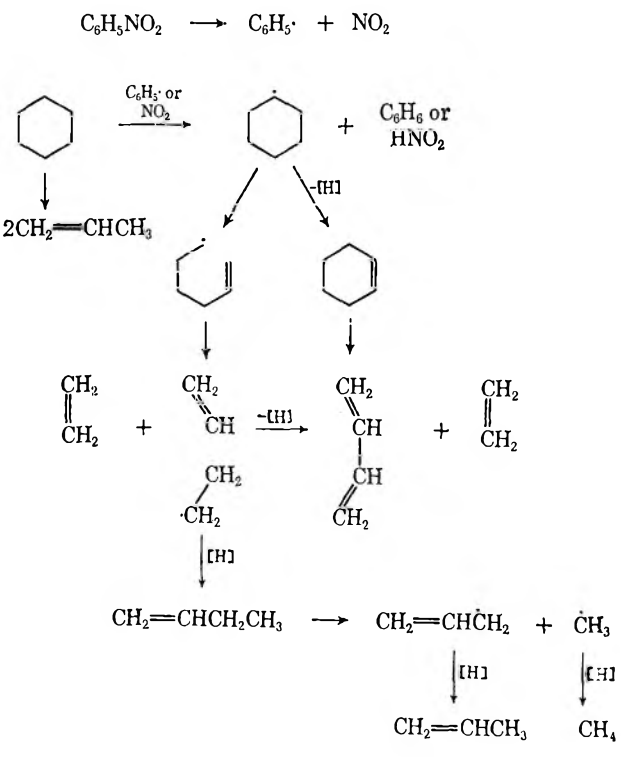


TABLE II

PRODUCTS FROM CYCLOHEXANE[a]

Product	Yield, mol %[b]
Ethylene	0.07
Propylene	0.30
Butenes	0.04
Butadiene	0.23

[a] Reaction conditions: 600°, contact time 21.2 sec, 0.4 mol of cyclohexane. [b] The yields were determined by gas chromatography and are based on a 10% conversion of cyclohexane. The material unaccounted for, which was lost with the nitrogen stream, presumably consisted of additional unreacted cyclohexane, low-boiling saturates, and hydrogen.

as shown in Table II, under the reaction conditions employed in this work, cyclohexane alone underwent but little thermal decomposition. The major product from the pyrolysis of nitrobenzene with cyclohexane is benzene, which can arise either by the dehydrogenation of cyclohexane or by hydrogen abstraction by the phenyl radical derived from nitrobenzene, or by both routes. The dehydrogenation of cyclohexane, as evidenced by the formation of cyclohexene, can also be effected by hydrogen abstraction by nitrogen dioxide.[8] Cyclohexene can then undergo a retro Diels–Alder reaction to give ethylene and butadiene.[7,9] However, this is not the only path by which cyclohexane breaks down. Substantial quantities of propylene also formed. The mechanisms underlying the formation of these olefins from cyclohexane in the presence of added free radicals presumably differ from those of the corresponding re-

(6) L. P. Lindeman and J. L. Annis, *Anal. Chem.*, **32**, 1742 (1960); W. E. Falconer and R. J. Cvetanovic, *ibid.*, **34**, 1064 (1962); R. Bentley, N. C. Saha, and C. C. Sweeley, *ibid.*, **37**, 118 (1965); C. C. Sweeley, W. H. Elliott, I. Fries, and R. Ryhage, *ibid.*, **38**, 1549 (1966); J. A. McCloskey, A. M. Lawson, and F. A. J. M. Leemans, *Chem. Commun.*, 285 (1967); F. A. J. M. Leemans and J. A. McCloskey, *J. Amer. Oil Chem. Soc.*, **44**, 11 (1967).

(7) N. D. Zelinskii, B. M. Mikhaizov, and Y. A. Arbuzov, *J. Gen. Chem. USSR*, **4**, 856 (1934); L. Kuchler, *Trans. Faraday Soc.*, **35**, 874 (1939); V. Haensel and V. N. Ipatiev, *Ind. Eng. Chem.*, **35**, 632 (1943); L. Berg, G. L. Summer, C. W. Montgomery and J. Coull, *ibid.*, **37**, 352 (1945); Imperial Chemical Industries Ltd., British Patents 567,913 (1945) and 568,536 (1945); J. H. Haslam, U. S. Patent 2,418,879 (1947); H. A. Gollman, U. S. Patent 2,575,341 (1951); W. O. Keelig, British Patent 595,879 (1948); S. D. Mekhtiev, Y. G. Kambanov, and A. F. Aliev, *Dokl. Akad. Nauk Azerb. SSR*, **15**, 125 (1959); S. D. Mekhtiev, A. F. Aliev, Y. G. Kambarov, and V. V. Sharov, *Azerb. Khim. Zh.*, **3**, 3 (1959); K. Setivek and V. Bazant, *Collect. Czech. Chem. Commun.*, **26**, 442 (1961); D. L. Fanter, M. A. Grayson, and C. J. Wolf, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, No. B60; Y. M. Paushkin A. G. Liakumovich, S. V. Adel'son, P. A. Nekeforov, and O. V. Lysykh, *Khim. Prom.*, **44**, 811 (1968).

(8) W. L. Fierce, U. S. Patent 3,413,368 (1968).

(9) H. Kwart and K. King, *Chem. Rev.*, **68**, 415 (1968).

TABLE III

REACTION OF NITROBENZENE-d_5 WITH CYCLOHEXANE[a]

	Isotopic distributions[b] of products,[c] %									
Deuterium atoms	Recovered nitrobenzene	Benzene	Styrene	Ethylbenzene	β-Methylstyrene	Allylbenzene	Indene	Naphthalene	Biphenyl	Phenol
0		4	2	13	6		12			1
1							1			
2	1			3		12				1
3	1						8	5		4
4	5	7	11	9	17	12	47	58	1	23
5	93	89	85	74	75	75	14	27	9	68
6			2	1	2		7	3		3
7							8	2	2	
8							3	5	8	
9									53	
10									27	

[a] Reaction conditions: 600°, contact time 14.4 sec, 0.04 mol of nitrobenzene-d_5, 0.16 mol of cyclohexane. The isotopic composition of nitrobenzene was 0.1% d_3, 3.3% d_4, and 96.6% d_5. [b] Determined with a directly coupled gas chromatograph–mass spectrometer by repetitive scanning over the parent-mass region at reduced ionizing voltage, followed by integration of the spectral intensities over the duration of the chromatographic peak. [c] α-Methylstyrene was identified by mass spectrometry; however, it was present at a concentration too low for isotopic analysis.

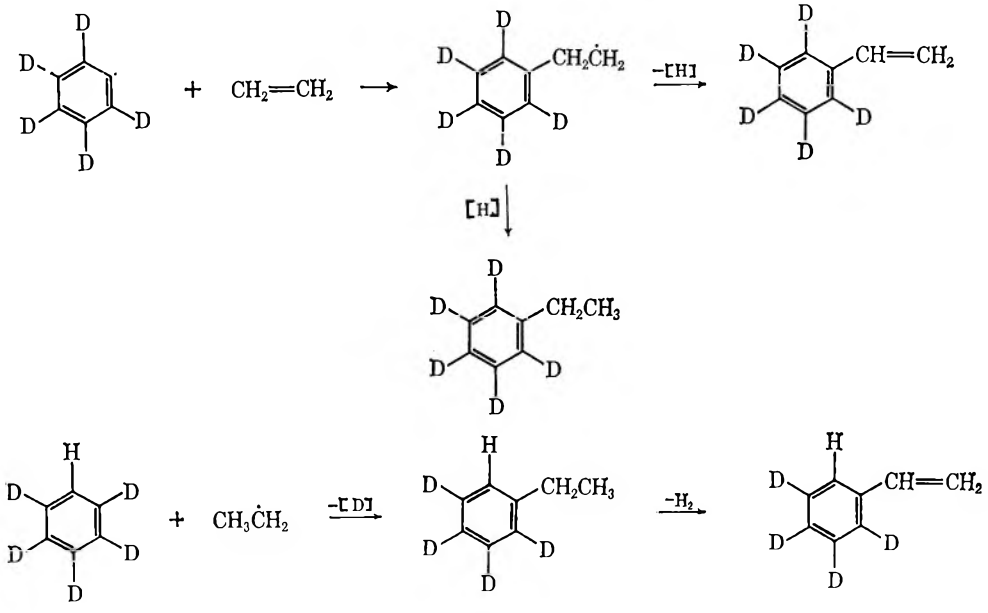
action carried out in their absence, as evidenced by the difference in product distribution of the gases shown in Tables I and II. Possible reaction paths for the radical-induced decomposition of cyclohexane involve β scission of the cyclohexyl radical, ring scission to propylene, and formation of cyclohexene as an intermediate. Propylene and methane also result from 1-butene by homolytic cleavage and hydrogen abstraction.[10] These routes are outlined in Scheme I.

The low yield of phenol suggests that the phenyl radical derived from the decomposition of nitrobenzene prefers to abstract hydrogen rather than react with nitrogen dioxide to form phenol *via* the nitro–nitrite rearrangement.[3] The substantial quantities of unreacted olefins and the low yield of arylation products are additional evidence for predominance of hydrogen abstraction.

Nitrobenzene-d_5 with Cyclohexane.—To gain a better understanding of the dehydrogenation of cyclohexane and the interaction of the phenyl radical with the fragments derived from cyclohexane, we treated nitrobenzene-d_5 with cyclohexane at 600°. The isotopic distribution of the products is shown in Table III. The scrambling of protium and deuterium, as evidenced by the deuterium distribution of the recovered nitrobenzene, was low enough to allow us to draw valid conclusions.

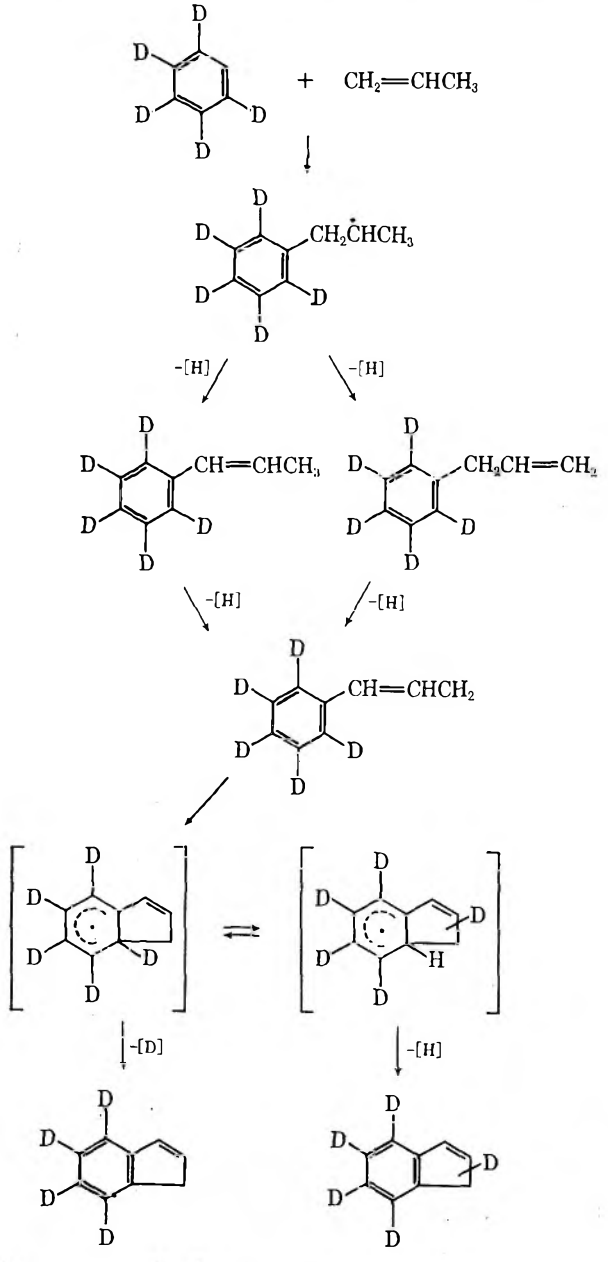
The isotopic distribution of benzene showed that it was formed mainly by hydrogen abstraction by the phenyl-d_5 radical, with only 4% arising by dehydrogenation of cyclohexane. Styrene and ethylbenzene consisted largely of d_4 and d_5 species, with the latter predominating in both instances, from phenylation of ethylene by the phenyl-d_5 radical. The concentrations of the d_4 species relative to benzene-d_4 were somewhat high to have arisen solely from arylation by the phenyl-d_4 radical, and may have formed in part by alkylation of benzene-d_5.

The isotopic composition of β-methylstyrene and allylbenzene shows the arylation of propylene by the phenyl-d_5 radical with subsequent loss of hydrogen. The relatively high concentrations of the d_4 components of these isomers, paralleling those of styrene and



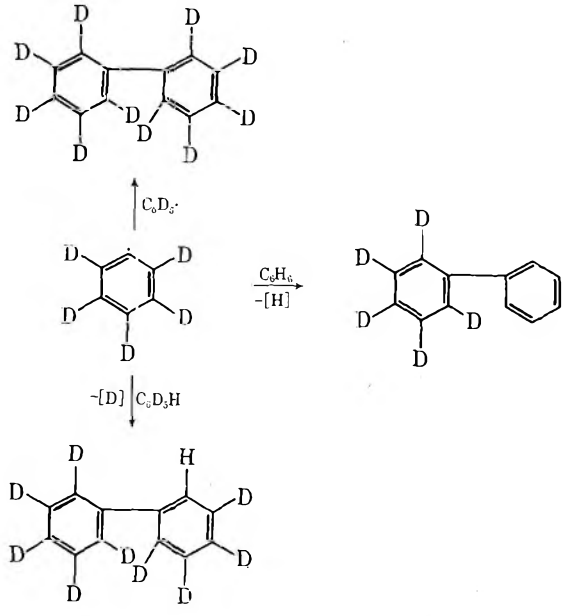
(10) M. Szwarc and A. H. Sehon, *J. Chem. Phys.*, **18**, 237 (1950), and references cited therein; J. A. Kerr, R. Spencer, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 6652 (1965), and references cited therein.

ethylene, indicate the alkylation of benzene-d_5 by the allyl radical or, alternatively, propyl-radical alkylation followed by dehydrogenation. Abstraction of an allylic hydrogen from β-methylstyrene-d_5 and allylbenzene-d_5 gives the same allylic radical, which then cyclizes to form indene-d_4. Indene-d_5 arises from protium–deuterium exchange in the intermediate cyclohexadienyl radical. Alkylation of benzene-d_4 by the propenyl radical followed by loss of hydrogen and cyclization contributes to indene-d_4 and also accounts for the observed indene-d_3. The relatively large amount of unlabeled ethylbenzene and indene must arise solely from cyclohexane. Gas chromatographic–mass spectral analysis of mixtures from reactions with unlabeled nitrobenzene furnished evidence for ethylcyclohexene and propenyl- or allylcyclohexane, and these are likely precursors of such cyclohexane-derived products.



The isotopic distribution of naphthalene is similar to that of indene in that the d_4 and d_5 species predominate. A similar reaction sequence can be invoked in which arylation of butadiene by the phenyl-d_5 radical is followed by cyclization and loss of hydrogen. Again, protium–deuterium exchange in the cyclohexadienyl radical intermediate accounts for naphthalene-d_5.

Biphenyl consisted chiefly of the d_9 and d_{10} species, with a secondary maximum in the isotopic distribution at d_5. Arylation by the phenyl-d_5 radical of undeuterated benzene derived from cyclohexane accounts for the formation of biphenyl-d_5. The more abundant biphenyl species arise by arylation of benzene-d_5 by the phenyl-d_5 radical to give biphenyl-d_9 and a little biphenyl-d_{10}, and by dimerization of the phenyl-d_5 radical to give biphenyl-d_{10}.



Most of the phenol forms *via* a nitro–nitrite rearrangement of nitrobenzene-d_5. Phenol-d_4 forms in two ways:

$$C_6D_5NO_2 \longrightarrow C_6D_5ONO \longrightarrow C_6D_5O\cdot + NO$$
$$\downarrow RH$$
$$C_6D_5OH$$

reaction of phenyl-d_4 with NO_2 followed by nitro–nitrite rearrangement, and protium–deuterium exchange of ring deuteriums from phenol-d_5.

Arylation by the phenyl radical is the preferred reaction when nitrobenzene reacts with benzene at 600°,[3] whereas hydrogen abstraction predominates with cyclohexane. To measure the preference of phenyl radical, we allowed nitrobenzene-d_5 to react with an equimolar mixture of cyclohexane and benzene at 600°. The isotopic distributions and yields of benzene and biphenyl are shown in Table IV. The other products from this reaction exhibited a distribution similar to that shown in Table I. The combined yield of benzene-d_4 and -d_5 (56%) corresponds closely to the yield of benzene (54%) derived from the reaction of nitrobenzene with cyclohexane alone. The yield of biphenyl-d_4 and -d_5, resulting from the arylation of benzene by the phenyl-d_5 radical, is greater than the yield of biphenyl in the absence of added benzene, probably because a fivefold excess of benzene was employed in this reaction. The higher yield of benzene-d_5 over biphenyl-d_5, 16:1, shows the strong preference of the phenyl radical to abstract hydrogen rather than to add to the aromatic system.

To determine whether the reactions of other cycloalkanes parallel those of cyclohexane, we treated cyclo-

TABLE IV

REACTION OF NITROBENZENE-d_5 WITH CYCLOHEXANE AND BENZENE[a]

Product	Isotopic distribution, %[b]	Yield, mol %[c]
Benzene	d_0, 89.0	
	d_1, 1.5	
	d_4, 0.7	4.2
	d_5, 8.6	51.8
	d_6, 0.2	
Biphenyl	d_0, 9.0	
	d_1, 2.3	
	d_2, 0.9	
	d_3, 1.4	
	d_4, 6.8	0.3
	d_5, 64.6	3.3
	d_6, 2.3	
	d_7, 2.7	
	d_8, 1.8	
	d_9, 5.0	
	d_{10}, 3.2	

[a] Reaction conditions: 600°, contact time 17.1 sec, 0.04 mol of nitrobenzene-d_5, 0.2 mol of cyclohexane, 0.2 mol of benzene. The isotopic composition of nitrobenzene was 2.2% d_4 and 97.8% d_5. [b] Calculated from low-voltage (7.5 ionizing eV, uncorrected) mass spectrum. [c] Based on an 82% conversion of nitrobenzene-d_5.

pentane, cycloheptane, and cyclooctane with nitrobenzene under similar conditions. The major products boiling over 140°, together with those from cyclohexane and from nitrobenzene alone for comparison, are listed in Table V. All of the cycloalkanes alone, under the same conditions, were recovered 90% or more unchanged.

Among the products from all four cycloalkanes, the yields of those attributed to the reaction of phenyl radical with C_2 and C_3 fragments, styrene and indene, are roughly the same. Naphthalene, from phenyl radical with a C_4 fragment, is formed in almost identical amounts from cyclohexane, -heptane, and -octane, but much less from cyclopentane. This would be expected because fragmentation of cyclopentane, its radical, or cyclopentene into C_4 and C_1 species would not appear energetically likely. The relative yields of phenol, biphenyl, dibenzofuran, and diphenyl ether from the reaction of nitrobenzene with cyclopentane more nearly resemble those from nitrobenzene alone than do those with the other cycloalkanes. This pattern, again, probably reflects the important role of C_4 intermediates in these systems. Because of its failure to produce such intermediates, cyclopentane contributes substantially less than the larger cycloalkanes to reaction products with nitrobenzene and thus acts, in effect, as a relatively inert diluent. We are presently studying the reactions of nitrobenzene and nitrobenzene-d_5 with cyclic olefins and polyolefins.

TABLE V

PRODUCTS FROM NITROBENZENE[a,b] AND CYCLOALKANES

Product	Cycloalkane: None	C_5	C_6	C_7	C_8
	Relative concentration				
Phenol	100	100	100	100	100
Styrene	...	87	101	77	87
Indene	...	26	22	15	30
Naphthalene	7	31	122	114	118
Biphenyl	73	115	59	24	30
Dibenzofuran	80	55	9	7	15
Diphenyl Ether	35	15	7	5	6

[a] Reaction conditions: 0.1 mol of nitrobenzene, 0.4 mol of cycloalkane, 600°, N_2 flow 20 ml/min, contact time 7–14 sec. [b] The products listed here represent a small part of the reaction mixtures, the bulk of which was distilled off below 140°. This table is intended only to compare product distributions from the various reactants. [c] Relative intensities in the low-voltage (7.5 ionizing eV, uncorrected) mass spectrum normalized to phenol = 100. Sensitivity, *i.e.*, the proportionality factor between parent-peak intensity and concentration, differs from one compound to another. However, closely related compounds have roughly equal sensitivities at the ionizing voltage employed in our work.[4] In any case, the use of relative intensities is perfectly valid for intercomparison of concentration ratios of identical components in separate samples, within the limits of reproducibility of the low-voltage data. See S. Meyerson and E. K. Fields, *Chem. Commun.*, 275 (1966); E. K. Fields and S. Meyerson, *Advan. Phys. Org. Chem.*, **6**, 1 (1968).

Registry No.—Nitrobenzene, 98-95-3; nitrobenzene-d_5, 13657-09-5; cyclohexane, 110-82-7; cyclopentane, 287-92-3; cycloheptane, 291-64-5; cyclooctane, 292-64-8.

Effects of Distant Substituents on Photoinduced Aromatic Substitution Reactions[1,2]

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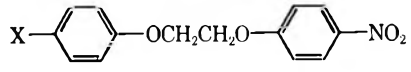
Received June 10, 1969

Electron-donating substituents (X) markedly retard photoinduced nucleophilic attack on compounds in the series $XC_6H_4OC_6H_4NO_2$. The methoxyl group (X = OCH_3) similarly retards photoinduced nucleophilic attack at the nitroaromatic ring in $XC_6H_4OCH_2CH_2OC_6H_4NO_2$. Emission-spectral data and experiments with model compounds suggest that the deactivation results from interaction of the photoexcited nitroaromatic ring with the dialkoxybenzene ring to yield a transient species which is inactive or of very low reactivity in nucleophilic substitution.

The photoinduced reactions of nitroaromatics with nucleophiles such as pyridine, hydroxide, and cyanide are markedly dependent on substituent groups in the aromatic compound.[2,4,5] For example, pyridine in dilute aqueous solution reacts readily with photoexcited 4-nitroanisole but fails to react with excited nitrobenzene or 4-nitrophenol.

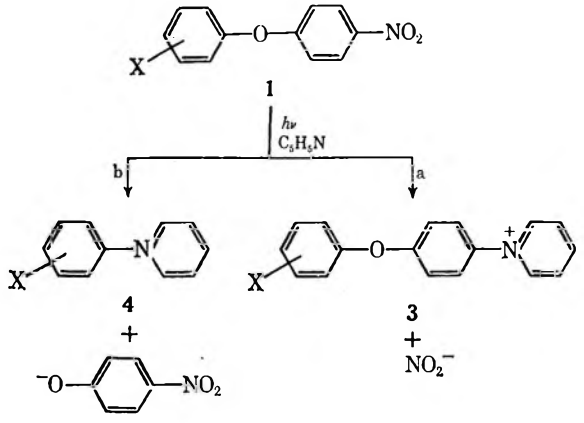
As part of a program aimed at learning more about the effects of substituent groups in such systems, we have examined photoreactions of a series of substituted 4-nitrodiphenyl ethers (**1**) and several 2-aryloxy-1-(4-nitrophenoxy)ethanes (**2**). Several features common to the two series led to this choice. All compounds have an oxygen atom *para* to the nitro group; therefore, the structures are favorable for some type of photoinduced substitution. Since the nitrophenoxy group is the dominant chromophore, the light-absorbing step should be essentially independent of the substituent. These series therefore provide a measure of effects of substituents exerted subsequent to the absorption of light. In addition, steric effects should be negligible, since the substituents are remote from the reactive nitroaromatic function. There are also characteristics unique to each system. Thus the oxygen bridge in **1** permits electronic effects to be transmitted from one ring to the other, whereas the two methylene groups in **2** would severely limit transmission of inductive and resonance effects. An aqueous solution containing a high concentration of pyridine (20% by volume) was selected as the reaction medium for the survey. Subsequently, the major effects were checked with key substrates reacting with ionic nucleophiles at low concentration.



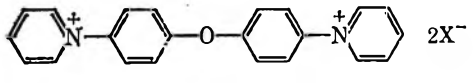
2a, X = H
b, X = CN
c, X = OCH_3

Results

Nitrodiphenyl Ethers (1).—Two types of reaction were observed on photolysis of the 4-nitrodiphenyl ethers in aqueous pyridine: (a) displacement of nitrite by pyridine, and (b) displacement of 4-nitrophenoxide by pyridine. The latter reaction is unusual in that the nucleophile attacks a benzene ring which does not bear a nitro group.[6] The extent of reaction proceeding *via* path a was evaluated by the amount of nitrite ion liberated; that going by path b was determined by the increase in absorbance at 400 mμ owing to 4-nitrophenoxide. Three of the photoreactions were



carried out on a preparative scale and the pyridinium salts were isolated and characterized as picrates. N-[4-(4-Cyanophenoxy)phenyl]pyridinium picrate (cation **3**, X = 4-CN), N-4-(3-cyanophenoxy)phenyl pyridinium picrate (cation **3**, X = 3-CN), and the bis-N-pyridinium picrate **5** were obtained from reactions of the corresponding ethers (**1**, X = 4-CN, 3-CN, and 4-NO_2) in yields of 49, 94, and 56%, respectively.



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Rate and product data for photoreactions of the 4-nitrodiphenyl ethers in an aqueous solution 20% in pyridine and 22% in *t*-butyl alcohol at 25° are assembled in Tables I and II. It may be noted that the absorption spectra of the nitro compounds in the reaction solvent are indeed very similar. Accordingly,

(1) This research was supported in part by a research grant from the National Science Foundation (GP 5715).

(2) Part VIII in the series on photoinduced substitution. For part VII, see R. L. Letsinger and J. H. McCain, *J. Amer. Chem. Soc.*, **91**, 6425 (1969).

(3) Public Health Service Predoctoral Fellow.

(4) R. L. Letsinger and O. B. Ramsay, *J. Amer. Chem. Soc.*, **86**, 1447 (1964); R. L. Letsinger, O. B. Ramsay, and J. H. McCain, *ibid.*, **87**, 2945 (1965).

(5) E. Havinga, R. O. de Jongh, and M. E. Kronenberg, *Helv. Chim. Acta.*, **50**, 2550 (1967), and references cited therein.

(6) This reaction was discovered by Dr. O. B. Ramsay, who characterized the nitrophenol and N-phenylpyridinium salt produced from the photoreaction of 4-nitrodiphenyl ether with pyridine: O. B. Ramsay and R. L. Letsinger, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964.

TABLE I
PHOTOREACTION OF $XC_6H_4OC_6H_4NO_2$ WITH PYRIDINE

Substituent	Registry no.	λ_{max},[a] mμ	$k_{obsd}/k_{obsd}^{parent}$ [b]
Parent		311	1.0
4′-Br	21969-04-0	309	1.6
4′-Cl	1836-74-4	308	2.9
3′-Cl	2303-23-3	307	1.4
4′-CN	17076-68-5	300[c]	1.7
3′-CN	17076-74-3	298[d]	1.7
4′-NO_2	101-63-3	310[e]	1.2
3′-OCH_3	22479-76-1	310	0.07
4′-OCH_3	6337-24-2	313	~0.003
4′-OH	22479-78-3	313	~0
3′-OH	22483-31-4	312	~0
4′-NH_2	6149-33-3	309	~0
3′-NH_2	22528-34-3	312	~0
4′-$NHCOCH_3$	2687-40-3	312	~0
3′-$NHCOCH_3$	22483-34-7	311	~0

[a] Determined in aqueous *t*-butyl alcohol (22%), log ε 4.06 ± 0.02 unless otherwise noted. [b] Reactions in 20% aqueous pyridine under N_2 atmosphere at 25°. [c] Log ε 4.10. [d] Log ε 4.09. [e] Log ε 4.24.

TABLE II
PRODUCTS FROM REACTIONS OF NITRODIPHENYL ETHERS WITH PYRIDINE

Substituent	4-Nitrophenol, %	NO_2^-, phenol, %	Relative electrophoretic mobility at pH 10.8[a] Y	W	P
Parent	56	34	−1.0	+0.81	+1.1
4′-Br	55	43	−1.0	+0.97	+1.2
4′-Cl	60	35	−1.0	+0.98	+1.3
3′-Cl	10	80	−1.0	+0.74	
4′-CN	8	87	−1.0	+0.74	
3′-CN	4	91		+0.78	
4′-NO_2	6	90[b]		+2.0	
3′-OCH_3	10	(28)[c]			

[a] Relative to 4-nitrophenoxide. Y, W, and P refer to products which appear as yellow spots (4-nitrophenoxide) and white (N-pyridinium salt with *p*-oxygen) and purple spots (N-pyridinium salts without *p*-oxygen) on paper under uv light. [b] Based on reaction of both nitro groups; a total of 1.8 mol of NO_2^- was obtained/mol of compound. [c] Low because of long reaction time.

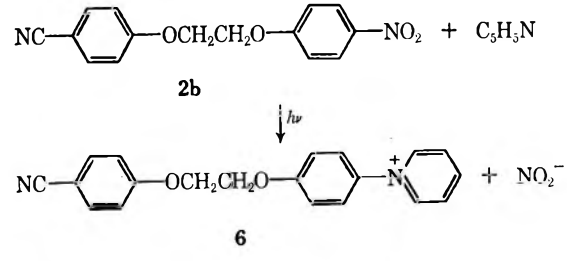
the relative rate constants approximately equal the relative quantum yields.

Three conclusions may be drawn from these results. First, electron-withdrawing groups in the 3′ and 4′ positions have little effect on the overall rate of the photochemical reaction in this system. The parent compound (4-nitrodiphenyl ether) and derivatives with chlorine, bromine, cyano, and nitro substituents at the 3′ or 4′ positions all react at rates within a factor of three of each other. Second, the strong electron-withdrawing substituents, nitro and cyano, and to a lesser extent 3′-chloro, favor reaction by path a (nitrite displacement) relative to path b (nitrophenoxide displacement). The reason for this behavior is not apparent at this time. Third, electron-donating groups such as hydroxyl, methoxyl, amino, and acetamino have a major effect on the photochemical reaction. Hydroxyl, amino, and acetamino substituents at the 3′ or 4′ positions quench the reaction completely. Methoxyl in the 3′ position inhibits the reaction somewhat (k_{obsd} = $^1/_{14}$ that of 4-nitrodiphenyl ether) and methoxyl in the 4′ position inhibits the reaction very strongly (k_{obsd} < $^1/_{300}$ that of 4-nitrodiphenyl ether).

Since interpretation of the effect of substituents possessing O–H and N–H bonds is complicated by possible ionization of the group in the photoexcited molecule,[7] further studies of the deactivating effect of electron-donating groups utilized methoxyl derivatives, for which deactivation by ionization is not possible.

The relative rates of reaction of 4-nitrodiphenyl ether (1×10^{-4} *M*) and 4′-methoxy-4-nitrodiphenyl ether (1×10^{-4} *M*) with sodium hydroxide (0.04 *M*), potassium cyanide (0.008 *M*), and ethylamine (0.1 *M*) in aqueous 22% *t*-butyl alcohol at 25° were determined to see whether the effect of the 4′-methoxyl group was general for nucleophilic substitution reactions. 4-Nitrodiphenyl ether was found to react readily with hydroxide to give 4-nitrophenoxide (91% by uv) and nitrite (5%). Under the same conditions, the reaction of 4′-methoxy-4-nitrodiphenyl ether was extremely slow, about $^1/_{150}$ of the rate for 4-nitrodiphenyl ether. Similar results were obtained with the other nucleophiles. In these cases the reactions were carried out in absorption cells and were followed by scanning the spectrum at appropriate time intervals of irradiation. With ethylamine the relative reactivity of the 4-methoxyphenyl and the phenyl derivatives was *ca.* $^1/_{120}$; with potassium cyanide the corresponding ratio was *ca.* $^1/_{300}$. It is therefore clear that 4′-methoxyl deactivates the excited state of the 4-nitrodiphenyl ether system responsible for nucleophilic substitution. The effect is observed in reactions of both charged and uncharged nucleophiles and at low (0.008 *M*) and very high (20% pyridine) nucleophile concentration.

2-(Aryloxy)ethyl 4-Nitrophenyl Ethers (2).—A preparative-scale reaction was carried out with 2-(4-cyanophenoxy)-1-(4-nitrophenoxy)ethane (**2b**) in aqueous pyridine in the same manner used for the 4-nitrodiphenyl ethers. An N-pyridinium product, **6**, was isolated as the picrate in 92% yield, showing that the reaction is completely analogous in type with that of 4-nitroanisole. Other reactions were carried out with dilute solutions of the ethers (1×10^{-4} *M*). That these also followed the same pathway was shown by analysis of the nitrite liberated and by electrophoresis of the organic products. In each case a single organic product was observed. It migrated as a +1 species and appeared as a white, fluorescent spot when viewed on paper under ultraviolet light.



Information on the rates of reaction of compounds **2a–c** and two related substances with pyridine are presented in Table III. 2-Phenoxy-1-(4-nitrophenoxy)-ethane (**2a**) was found to react at about the same rate as 4-nitroanisole. 2-(4-Cyanophenoxy)-1-(4-nitrophenoxy)ethane (**2b**) reacted a little faster. The big

(7) E. J. Baum, J. K. S. Wan, and J. N. Pitts, Jr., *J. Amer. Chem. Soc.*, **88**, 2652 (1966); G. Porter and P. Suppan, *Trans. Faraday Soc.*, **62**, 3375 (1966); D. Schulte-Frohlinde and C. V. Sonntag, *Z. Phys. Chem.* (Frankfurt am Main), **44**, 314 (1965).

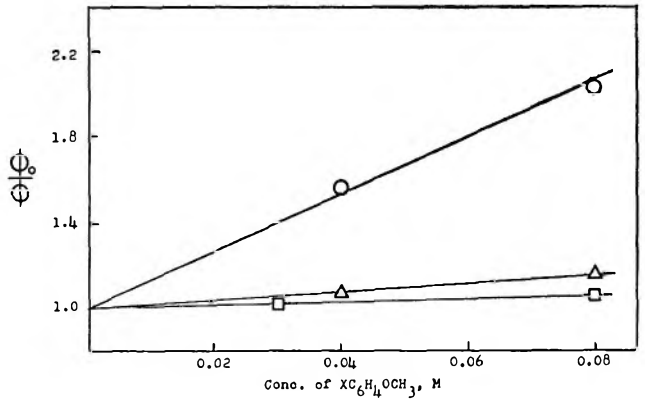


Figure 1.—Stern–Volmer plot for formation of 4-nitrophenoxide (measured by absorbance increase at 400 mμ) on irradiation of 4-nitroanisole and sodium hydroxide (0.008 *M*) in 22% *t*-BuOH at 25° in the presence of substituted anisoles, $XC_6H_4OCH_3$ (○, X = 4-OCH_3; △, X = H; □, X = 4-CN).

effect, as in the nitrodiphenyl ether series, was observed with the methoxy analog (**2c**), for which the rate was only $^1/_{23}$ that of 4-nitroanisole. Reactions of partial models for **2c**—2-methoxyethyl 4-nitrophenyl ether (**7**) and 3-(4-methoxyphenyl)propyl 4-nitrophenyl ether (**8**)—indicate that the low reactivity of **2c** is related to the dialkoxybenzene moiety. Neither the monoalkoxyphenyl substituent in **2a** nor that in **8** had an appreciable effect on the reaction. Also it does not appear reasonable to attribute the relatively low reactivity of **2c** to greater basicity of the oxygen at the 2 position of the ethane, since compound **7**, in which this oxygen should be even more basic than that in **2c**, exhibited no anomalous behavior.

TABLE III
PHOTOREACTIONS OF $XCH_2CH_2OC_6H_4NO_2$ WITH AQUEOUS PYRIDINE AT 25°

Compd	X	$k^X_{obsd}/k^{nitroanisole}_{obsd}$ [a]	NO_2^-, [b] %
2a	$C_6H_5O^-$	0.9	73
2b	p-$NCC_6H_4O^-$	1.8	83
2c	p-$CH_3OC_6H_4O^-$	0.043	(6)
7	CH_3O^-	1.4	85
8	p-$CH_3OC_6H_4CH_2^-$	1.5	

[a] Ratio of k_{obsd} for reaction of substituted ether to k_{obsd} for reaction of 4-nitroanisole under the same conditions. [b] Measured at end of the reaction. From control reactions it was found that the pyridinium salts are stable but nitrite slowly decomposes under the reaction conditions. These values are low as a consequence.

Deactivation by methoxyl was also observed for reactions of compounds **2** with other nucleophiles. As shown in Table IV, compound **2c** reacted considerably more slowly than **2a** and **2b** with hydroxide in aqueous *t*-butyl alcohol and with cyanide in aqueous dimethylacetamide.

Intermolecular Quenching of Nucleophilic Substitution.—The experiments with compounds **1** and **2** indicate that a dialkylbenzene moiety interferes with the photoinduced reaction of a neighboring nitrophenoxy group with nucleophiles. To see whether a similar effect would obtain in an intermolecular system, we examined the reaction of 4-nitroanisole with hydroxide in the presence of anisole, 4-cyanoanisole, and 1,4-dimethoxybenzene. Solutions containing the reactants

TABLE IV
PHOTOREACTIONS OF $XC_6H_4OCH_2CH_2OC_6H_4NO_2$ WITH OH^- AND CN^-

Nucleophile (concn, *M*)	X	k_{obsd} relative to k_{obsd} for 4-nitroanisole
NaOH (0.04)[a]	H	0.2
	CN	0.7
	OCH_3	0.03
KCN (0.004)[b]	H	0.54
	CN	1.7
	OCH_3	0.014

[a] 50% v/v water–*t*-butyl alcohol. [b] 30% v/v dimethylformamide in water.

in absorption cells were irradiated with the 366-mμ band isolated by a Bausch & Lomb monochromator. At this wavelength only 4-nitroanisole in the mixture absorbs. Initial rates were determined by the increase in absorbance at 400 mμ (owing to formation of 4-nitrophenoxide). It is seen from the data in Figure 1 that 1,4-dimethoxybenzene does inhibit the reaction of photoexcited 4-nitroanisole with hydroxide. At a concentration of 0.08 *M* it reduces the initial rate of formation of 4-nitrophenoxide by a factor of 2. Anisole has only a slight effect and 4-cyanoanisole has no measurable effect on the reaction of 4-nitroanisole with hydroxide.

Emission Spectra.—One possible explanation for the slow reaction of **2c** is that excitation energy is transferred from the 4-nitrophenoxy group, the site of chemical attack, to the dialkoxybenzene moiety. Intramolecular energy transfer is a well-established phenomenon in other systems.[8] This possibility was examined by observing emission spectra of compound **2c** and models containing the same chromophores, *i.e.*, dimethoxybenzene, 4-nitroanisole, and a mixture of 1,4-dimethoxybenzene and 4-nitroanisole (Table V).

TABLE V
EMISSION FOR METHOXYBENZENE DERIVATIVES UNDER EXCITING LIGHT AT λ 300 mμ

Compd[a]	Fluorescence[b] intensity[d]	Phosphorescence[c] intensity[d]
p-$CH_3OC_6H_4OCH_3$	52	56
p-$CH_3OC_6H_4NO_2$	0	0
p-$CH_3OC_6H_4OCH_3$ + p-$CH_3OC_6H_4NO_2$	41	29
p-$CH_3OC_6H_4OCH_2$-$CH_2OC_6H_4NO_2$-p	0	0

[a] Concentration of 1.0×10^{-5} *M* each for fluorescence measurement; 3.6×10^{-4} *M* each for phosphorescence measurements. [b] Solvent, 50% aqueous *t*-BuOH; temperature, 25°; λ_{max} observed, 336 mμ. [c] Solvent, EPA; temperature, liquid N_2; λ_{max} observed, 416 mμ. The intensity units for phosphorescence differ from those for fluorescence. [d] In arbitrary units.

On excitation at 300 mμ, 1,4-dimethoxybenzene both fluoresces in 50% aqueous *t*-butyl alcohol at room temperature (λ_{max} 336 mμ) and phosphoresces in EPA (ether–pentane–alcohol) at liquid nitrogen temperature (λ_{max} 416 mμ). Under the same conditions

(8) O. Schnapp and M. Levy, *J. Amer. Chem. Soc.*, **84**, 172 (1962); P. A. Leermakers, G. W. Byers, A. A. Lamola, and G. S. Hammond, *ibid.*, **85**, 2670 (1963); **87**, 2322 (1965); S. Shifrin, *Biochem. Biophys. Acta*, **81**, 205 (1964); S. A. Latt, H. T. Cheung, and E. R. Blout, *J. Amer. Chem. Soc.*, **87**, 995 (1965); R. A. Keller, *ibid.*, **90**, 1140 (1968); R. D. Rauh, T. R. Evans, and P. A. Leermakers, *ibid.*, **90**, 6897 (1968); J. R. DeMember and N. Filipescu, *ibid.*, **90**, 6425 (1968).

no emission was observed from 4-nitroanisole or compound **2c**. Fluorescence and phosphorescence from 1,4-dimethoxybenzene in solution with an equivalent amount of 4-nitroanisole was observed, but the intensity was considerably reduced.

Fluorescence from the mixture of 1,4-dimethoxybenzene and 4-nitroanisole shows that 1,4-dimethoxybenzene is excited in the presence of the 4-nitrophenoxy chromophore. Absence of fluorescence from compound **2c** therefore indicates that, if singlet excitation energy transfer is involved, the transfer is from the dialkoxybenzene ring to the 4-nitrophenoxy group rather than in the reverse sense. Intramolecular energy transfer therefore cannot account for the low reactivity of compound **2c** if the reaction is one in which the nucleophile attacks a singlet excited state.

If the triplet state of **2c** is the intermediate in the substitution reaction, the energy-transfer explanation requires that triplet excitation energy be transferred from the nitrophenoxy group to the dialkoxybenzene ring. In this case, phosphorescence from **2c** similar to that from 1,4-dimethoxybenzene should be observed. Since no phosphorescence from **2c** was detectable, although phosphorescence from a mixture of 1,4-dimethoxybenzene and 4-nitroanisole at the same concentration was easily measured, the energy-transfer mechanism can also be ruled out as an explanation for the low reactivity of **2c** if the intermediate is a triplet state.

Since transfer of electronic excitation energy can be ruled out for both singlet and triplet intermediates, the most plausible explanation for the deactivating effect of $CH_3OC_6H_4OR$, either intramolecularly or intermolecularly, is that this moiety forms a complex with electronically excited $R'OC_6H_4NO_2$ and that the complex is itself inactive toward nucleophiles and on dissociation affords $R'OC_6H_4NO_2$ which is likewise inactive (probably ground-state nitroaromatic). Considerable evidence from other systems supports the view that excited aromatic species indeed form complexes (*e.g.*, an "exciplex") with substances in the ground state.[9]

Experimental Section

Ultraviolet spectra were recorded on a Cary Model 11 spectrophotometer and nmr spectra were obtained with a Varian Model A-60 spectrometer. Chemical shifts are reported as parts per million downfield from tetramethylsilane. Emission spectra were measured with an Aminco–Bowman spectrophotofluorometer (SPF 4-8106), equipped with an Amino–Keirs phosphoroscope (C27-62140) attachment for phosphorescence measurements. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

A Savant flat plate apparatus was used for separation of ions by electrophoresis. Separations were carried out on 55 × 15 cm Whatman 3-mm paper strips saturated with buffer solution. An applied potential of 2000 V was employed. Fluorescent products were detected by illumination of the dried paper with a Mineral Lamp.

Solvents for fluorometry were Fisher Spectroanalyzed Reagent methanol, Spectroquality Reagent hexane (Matheson Coleman and Bell), and 50% v/v *t*-butyl alcohol–water, prepared from freshly distilled samples.

Preparation of Substituted 4′-Nitrodiphenyl Ethers.—3′-Methoxy-4-nitrodiphenyl ether, mp 86–87° (lit.[10] mp 86.5–87°), 4′-methoxy-4-nitrodiphenyl ether, mp 109° (lit.[11] mp 110–111°), 3′-acetamino-4-nitrodiphenyl ether, mp 135–135.5° (lit.[10] mp 138–139°), and 4′-acetamino-4-diphenyl ether, mp 154–155° (lit.[10,12] mp 153°), were prepared by condensation of 4-bromonitrobenzene with the appropriate potassium phenoxide over copper–bronze by the general procedure of Stohr.[11] 3′-Hydroxy-4-nitrodiphenyl ether, mp 98–99° (lit.[10] mp 101–101°), and 4′-hydroxy-4-nitrodiphenyl ether were obtained by cleaving the methyl ethers with aluminum chloride in nitrobenzene at 0° as reported by Ito.[13] 3′-Amino-4-nitrodiphenyl ether, mp 79° (lit.[10] mp 80–81°), and 4′-amino-4-nitrodiphenyl ether, mp 134–135° (lit.[11] mp 134–135°), were made by hydrolyzing the corresponding acetamino derivatives with hydrochloric acid in refluxing ethanol.[12] 4-Amino-4-nitrodiphenyl ether was also synthesized by partial reduction of 4,4′-dinitrodiphenyl ether with hydrogen sulfide and ammonium hydroxide.[14] The compound prepared in this manner was identical with that prepared by hydrolysis of the 4′-acetamido derivative. 4′-Bromo-4-nitrodiphenyl ether, mp 60° (lit.[15] mp 61°), was made by bromination[16] of 4-nitrodiphenyl ether, and 3′-chloro-4-nitrodiphenyl ether, mp 57° (lit.[17] mp 59.5–60.4°), 3′-cyano-4-nitrodiphenyl ether, and 4′-cyano-4-nitrodiphenyl ether were synthesized by Sandmeyer reactions. Further details are provided for the cyano derivatives, since thay are new compounds.

A cold, aqueous solution of sodium nitrite (0.28 g, 0.004 mol) was added to an aqueous solution containing concentrated hydrochloric acid (4 ml) and 4′-amino-4-nitrodiphenyl ether (0.92 g, 0.004 mol) cooled in an ice bath. The mixture was stirred for 10 min, neutralized with sodium carbonate, and filtered. It was then added slowly to a cold, well-stirred mixture of cuprous cyanide solution (50 ml, 0.027 mol)[18] and benzene (50 ml). The mixture was stirred vigorously, allowed to warm to room temperature, and filtered. The yellow, flocculant precipitate was isolated by filtration and heated in water to decompose the complex. Extraction with benzene, evaporation of the solvent, and recrystallization of the residue from benzene and from ethanol gave 4′-cyano-4-nitrodiphenyl ether, yield 0.27 g (28%), mp 162–163°, ir 4.45 μ (CN).

Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.64. Found: C, 65.49; H, 3.61; N, 11.40.

By the same procedure, **3′-cyano-4-nitrodiphenyl ether**, yield 0.35 g (38%), mp 106–106.5°, ir 4.45 μ (CN), was obtained from 3′-amino-4-nitrodiphenyl ether.

Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.64. Found: C, 64.81; H, 3.48; N, 11.69.

Since 4′-methoxy-4′-nitrodiphenyl ether plays a key role in the photochemical experiments, it was further characterized by the nmr spectrum and by elemental analysis, even though it has been previously described.[11]

Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.69; H, 4.45; N, 5.88.

2-(4-Nitrophenoxy)ethyl Tosylate.—Sodium 4-nitrophenoxide (39.6 g, 0.20 mol) was added to a solution of 2-bromoethanol (24.8 g, 0.20 mol) in anhydrous dimethylformamide (100 ml). The solution was refluxed overnight and poured onto ice. Recrystallization of the solid from benzene gave 2-(4-nitrophenoxy)-ethanol, yield 35.2 g (95%), mp 85–86°.

A solution of this alcohol (14.65 g, 0.08 mol) in a minimal amount of anhydrous pyridine was cooled and added to a cold solution of *p*-toluenesulfonyl chloride (15.3 g, 0.08 mol) in pyridine (20 ml). The solution was refrigerated overnight and then poured onto ice. Recrystallization of the solid from benzene–hexane afforded 25.2 g (93%) of the title compound, mp 122–123°.

Anal. Calcd for $C_{15}H_{15}NO_6S$: C, 53.49; H, 4.49; N, 4.15. Found: C, 53.83; H, 4.66; N, 4.17.

Substituted 1-(Phenoxy)-2-(4-nitrophenoxy)ethanes.—The three compounds were prepared in the same manner, typified by the synthesis of the methoxy derivative.

(9) See, *e.g.*, S. L. Murov, R. S. Cole, and G. S. Hammond, *J. Amer. Chem. Soc.*, **90**, 2957 (1968); R. S. Cook and G. S. Hammond, *ibid.*, **90**, 2958 (1968); J. B. Birks and L. G. Christophorou, *Nature*, **196**, 33 (1962).

(10) G. Modena, *Boll. Sci. Fac. Chim. Ind. Bologna*, **17**, 45 (1959).

(11) R. Stohr, *Z. Physiol. Chem.*, **201**, 142 (1931).

(12) F. F. Ray and L. Soffer, *J. Org. Chem.*, **14**, 1037 (1950).

(13) G. Ito, *Pharm. Bull.* (Tokyo), **5**, 397 (1957); *Chem. Abstr.*, **52**, 9006 (1958).

(14) Reduction procedure of A. Cerniani, R. Passerini, and G. Righi, *Boll. Sci. Fac. Chim. Ind. Bologna*, **12**, 114 (1954).

(15) H. A. Scarborough, *J. Chem. Soc.*, 2361 (1929).

(16) C. M. Suter, *J. Amer. Chem. Soc.*, **51**, 2581 (1929).

(17) M. Rolla and M. Sanesi, *Ric. Sci.*, A[2], **1**, 289 (1961).

(18) H. T. Clarke and R. R. Read, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1946, p 514.

To a solution of the sodium salt of 4-methoxyphenol (1.46 g, 0.01 mol) in anhydrous dimethylformamide (10 ml) was added 2-(4-nitrophenoxy)ethyl tosylate (1.62 g, 0.0048 mol). The solution was heated at 75° with stirring for 6 hr and at 40–50° for 2 days; then it was poured into ice–water. The solid was collected and recrystallized from benzene–hexane to yield **1-(4-methoxyphenoxy)-2-(4-nitrophenoxy)ethane**: yield 1.31 g (94%); mp 115–116°; nmr ($CDCl_3$) 3.84 (3, methyl H), 4.45 (4, methylene H), 7.01–7.10, 7.23, and 7.42 (6, aromatic H), and 8.31 and 8.47 ppm (2, aromatic H). The ultraviolet spectrum was determined in aqueous solution 20% in pyridine and 22% in *t*-butyl alcohol, since this was the solution used in the photochemical reactions, uv λ_{max} 315 mμ (ϵ 1.22 × 10^4).

Anal. Calcd for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84. Found: C, 62.22; H, 5.27; N, 4.98.

1-Phenoxy-2-(4-nitrophenoxy)ethane was similarly prepared from sodium phenoxide (3.84 g) and 2-(4-nitrophenoxy)ethyl tosylate (3.38 g) by reaction for 24 hr at 65° and pouring the product into water: yield 2.35 g (91%); mp 86–87°; λ_{max} (aqueous 20% pyridine–22% *t*-butyl alcohol) 315 mμ (ϵ 1.09 × 10^4); nmr ($CDCl_3$) 4.47 (4, methylene H), 7.01–7.26 and 7.37–7.53 (7, aromatic H), and 8.31 and 8.47 ppm (2, aromatic H).

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.94; H, 5.00; N, 5.39.

1-(4-Cyanophenoxy)-2-(4-nitrophenoxy)ethane was synthesized by heating sodium 4-cyanophenoxide, which was prepared from 3.57 g of 4-cyanophenol, with the tosylate in DMF for 20 hr at 120°: yield 2.61 g (92%); mp 139°; λ_{max} (aqueous 20% pyridine–22% *t*-butyl alcohol) 313 mμ (ϵ 1.09 × 10^4); nmr ($CDCl_3$) 4.53 (4, methylene H), 7.09, 7.24, and 7.43 (4, aromatic H), and 7.69 and 7.85 ppm (2, aromatic H).

Anal. Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.50; H, 4.32; N, 9.90.

3-(4-Methoxyphenyl)-1-(4-nitrophenoxy)propane.—3-(4-Methoxyphenyl)propionic acid (Aldrich reagent grade, 9.0 g, 0.05 mol) in ether (50 ml) was added during 1 hr to lithium aluminum hydride (4.0 g, 0.1 mol) in dry ether (50 ml). The mixture was refluxed for 3 hr, 3% aqueous sodium hydroxide solution was added with stirring, and the precipitated salts were removed by filtration. The ether layer was separated, dried, and evaporated to give 8.12 g of 3-(4-methoxyphenyl)propanol. To a portion of this material (6.0 g) in carbon tetrachloride at 60° was added phosphorus tribromide (4.88 g) in carbon tetrachloride (5 ml). After 20 min at reflux the mixture was hydrolyzed and the organic layer was collected, dried, and evaporated to yield 1-bromo-3-(4-methoxyphenyl)propane (6.60 g). A portion of this product (5.80 g) was stirred with excess sodium 4-nitrophenoxide (12.1 g) in anhydrous dimethylformamide (25 ml) for 13 hr at 115°, and the mixture was poured onto ice. Recrystallization of the product from aqueous ethanol gave 3-(4-methoxyphenyl)-1-(4-nitrophenoxy)propane: yield 5.91 g (66% from the propionic acid); mp 87.5–88.5°; λ_{max} (aqueous 20% pyridine–22% *t*-butyl alcohol) 316 mμ (ϵ 1.18 × 10^4); nmr (CCl_4) 1.95–2.85 (4, methylene H), 3.87–4.07 (2, methylene H), 3.71 (3, methyl H), 6.61–7.07 (6, aromatic H), and 7.98 and 8.13 (2, aromatic H *ortho* to nitro).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.89. Found: C, 67.11; H, 5.98; N, 4.91.

Kinetic Studies.—Monochromatic light for the series of reactions with 4-nitroanisole irradiated at 366 ± 5 mμ was obtained from a Bausch & Lomb high-intensity monochromator utilizing an L-33-86-35-01 super-pressure 200-W mercury source. Standard silica absorption cells (10.0-mm path) fitted with ground-glass stoppers served as the reaction vessels. The cell containing reactant solution was placed in a thermostated metal holder 2 cm from the monochromator exit slit. Efficient stirring was provided by a micro Teflon-coated magnetic stirring bar.

In other kinetic studies a GE 1200-W photochemical lamp (UA-11) cooled by a Vycor water condenser was employed.[3] A typical reaction with pyridine was carried out by pipeting a solution (1.0 ml) of the nitrophenyl ether (5.00 × 10^{-1} *M*) in *t*-butyl alcohol, pyridine (10.0 ml), and *t*-butyl alcohol (10.0 ml) into a volumetric flask and diluting to 50 ml with water. The solution was added to the reaction vessel (a low cylindrical vessel with an outside jacket for circulation of ethylene glycol at constant temperature) and covered with a large, flat Pyrex top equipped with a standard taper joint for joining to the reaction vessel and ports for admitting nitrogen and removing aliquots of solution. Prepurified nitrogen was bubbled through the solution for 30 min, then the exit port was closed, and a positive pressure of nitrogen was maintained within the vessel. The solution was placed under the photochemical lamp at zero time and the progress of reaction was followed by periodically removing samples for measuring the absorbance at the λ_{max} value of the compound being studied. After *ca.* 10 half-lives, a final reading was taken. Plots of log $(A - A_\infty)/(A_0 - A_\infty)$ were linear through 60–70% conversion of the nitroaromatic compound. Data are therefore presented in the form of relative pseudo-first-order rate constants.

Reactions with aqueous sodium hydroxide were followed by the decrease in absorbance at the λ_{max} of the aromatic and by the increase in absorbance at 400 mμ owing to 4-nitrophenoxide. Solutions in these cases were prepared by mixing a 5.00 × 10^{-3} *M* solution (0.5 ml) of the aromatic compound in *t*-butyl alcohol, 0.50 *M* aqueous sodium hydroxide (2.0 ml), and *t*-butyl alcohol (5.0 ml) and diluting the mixture to 25 ml. Reactions of the 2-aryloxy-1-(4-nitrophenoxy)ethanes with sodium hydroxide were followed by periodically determining the amount of nitrite ion liberated. Reactions with cyanide ion and with ethylamine were carried out in glass-stoppered absorbing cells (10.0-mm light path), irradiated by the GE lamp. The progress was followed by scanning the spectrum from 240 to 400 mμ at appropriate intervals. The concentration of nitrite liberated in the photochemical reactions was determined by the method of Rider and Mellon.[19]

General Procedure for Preparative-Scale Reactions.—Unless otherwise specified, the reaction mixtures were placed in a cylindrical, jacketed vessel (12.5-cm i.d.) maintained at 25° by flowing water. The top was covered by a Pyrex cover and the solution was irradiated with light from the GE lamp. After irradiation, the solution was evaporated *in vacuo* and the residue was taken up in a minimum amount of ethanol. On cooling and mixing with a saturated solution of picric acid in ethanol, the product precipitated as a picrate salt. It was collected by filtration and recrystallized from aqueous ethanol.

The **4,4′-bis-N-pyridinium picrate derivative** of diphenyl ether **5** was prepared by irradiating bis(4-nitrophenyl) ether (0.26 g) in pyridine (200 ml) and water (400 ml) for 6 hr and treating the product with picric acid. After two recrystallizations from aqueous ethanol, the product was obtained: yield 0.44 g (56%), mp 143–145°.

Anal. Calcd for $C_{34}H_{22}N_8O_{15}\cdot{}^1/_2H_2O$: C, 51.59; H, 2.92; N, 14.16. Found: C, 51.53; H, 2.87; N, 14.16.

N-[4-(4-Cyanophenoxy)phenyl]pyridinium picrate (3, X = 4-CN), yield 0.031 g (49%), mp 193–194°, was obtained from photolysis for 3 hr of 4′-cyano-4-nitrodiphenyl ether (0.030 g) in a solution prepared by diluting a mixture of *t*-butyl alcohol (66 ml) and pyridine (6 ml) to 300 ml with water.

Anal. Calcd for $C_{24}H_{15}N_5O_8\cdot H_2O$: C, 55.49; H, 3.29. Found: C, 55.32; H, 3.27.

The photoreaction of 2-(4-cyanophenoxy)-1-(4-nitrophenoxy)-ethane (0.142 g) was carried out by irradiating a solution in pyridine (200 ml) and water (400 ml) for 8 hr. After two recrystallizations from aqueous ethanol, the **N-4-[2-(4-cyanophenoxy)ethoxy]phenyl pyridinium (6) picrate** was obtained, yield 0.223 g (82%), mp 162–163°. The white fluorescent spot due to the cation had a mobility of +1.4 relative to the yellow spot due to picrate (−1.0) on electrophoresis at pH 7.9.

Anal. Calcd for $C_{16}H_{19}N_5O_9$: C, 57.25; H, 3.51; N, 12.83. Found: C, 57.36; H, 3.34; N, 12.77.

In the case of 3′-cyano-4-nitrodiphenyl ether, a solution containing the ether (0.046 g) in pyridine (23 ml) and *t*-butyl alcohol (46 ml) was diluted to 230 ml with water and irradiated in a narrow, cylindrical vessel with a Hanovia 450-W immersion lamp for 2 hr. The light was filtered by a Pyrex sleeve around the lamp. A stream of nitrogen was bubbled through the solution throughout the irradiation and the temperature was maintained below 25° by a stream of cold water around the immersion well. The optical density at 400 mμ showed that the 4-nitrophenol was formed in the reaction in no more than 3% yield. Precipitation with picric acid yielded 0.089 g (94%) of N-[4-(3-cyanophenoxy)phenyl]pyridinium picrate, mp 135–138°. The analytical sample, yield 0.064 g (67%), mp 137–138°, was obtained by three recrystallizations from aqueous ethanol.

Anal. Calcd for $C_{24}H_{15}N_5O_8$: C, 57.50; H, 3.07; N, 13.94. Found: C, 57.61; H, 3.20; N, 13.88.

(19) B. F. Rider and M. G. Mellon, *Anal. Chem.*, **18**, 96 (1946).

Registry No.—2a, 22483-35-8; 2b, 22483-36-9; 2c, 22483-37-0; 3 (X = 4-CN), 22483-38-1; 5 (X = picrate), 22483-39-2; 6, 22483-42-7; 7, 22483-40-5; 8, 22483-41-6; N-[4-(3-cyanophenoxy)phenyl]pyridinium picrate, 22483-43-8; 2-(4-nitrophenoxy)ethyl tosylate, 22483-44-9.

Stable Carbonium Ions. LXXXII.[1] Protonation and Cleavage of N-Alkoxycarbonyl-Substituted Amino Acids in Strong Acid Solution

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Received May 5, 1969

Protonation and cleavage of N-alkoxycarbonyl-substituted amino acids have been studied in SbF_5–FSO_3H–SO_2 solution. Complete alkyl–oxygen cleavage at −76° was observed for all the benzyloxycarbonyl and *t*-butyloxycarbonyl derivatives studied, to give dications having both protonated carboxylic and protonated carbamic functions. In the latter case, the trimethylcarbonium ion was observed. N-*n*-Butyloxycarbonyl DL-alanine did not cleave at −20°; N-*sec*-butyloxycarbonyl cleaved slowly at −50°; and N-vinyloxycarbonyl glycine and N-allyloxycarbonyl DL-alanine underwent complex change in the strong acid solution. The spectrum of di-O-protonated N-formylglycine was observed.

The benzyloxycarbonyl group is an important protecting group for the amino function in amino acids and peptides owing to its stability under amino acid coupling conditions, as well as the many methods available for its removal.[3] On removal, the free amino group is obtained, carbon dioxide is liberated, and a benzyl compound is formed. The *t*-butyloxycarbonyl group is

$$PhCH_2OCONHCHRCO_2H + 2HX \longrightarrow PhCH_2X + CO_2 + HXNH_2CHRCO_2H$$

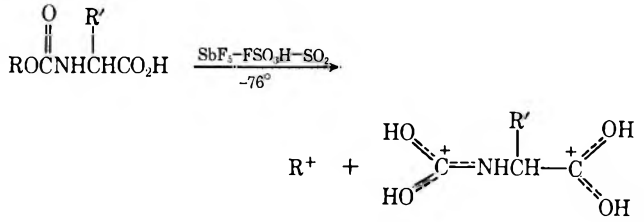
also widely used in peptide synthesis as an amino function protecting group. It is similarly removed under nonhydrolytic mild acid conditions to yield the free amino group, although, as is not the case for the benzyloxycarbonyl group, it is resistant to catalytic hydrogenation and treatment with sodium in liquid ammonia.

The following is the order of ease of removal of some amino-protecting groups for amino acids and peptides under nonhydrolytic acid conditions with evolution of carbon dioxide: *t*-butyloxycarbonyl > benzyloxycarbonyl > allyloxycarbonyl > *sec*-butyloxycarbonyl.[4,5]

Protonated carboxylic acids[6] and protonated alkyl carbamates and carbamic acids[7] have been investigated in our previous studies by nmr spectroscopy in the strong acid system SbF_5–FSO_3H–SO_2. It was of interest to extend these studies to the behavior of N-alkoxycarbonyl-substituted amino acids in SbF_5–FSO_3H–SO_2 solution and to investigate, over a range of temperature, their cleavage reactions.

Results and Discussion

N-Benzyloxycarbonyl and N-*t*-Butyloxycarbonyl Amino Acids.—When solutions of N-benzyloxycarbonyl and N-*t*-butyloxycarbonyl amino acids were prepared in SbF_5–FSO_3H–SO_2 solution at −70°, only at the products of alkyl–oxygen cleavage were observed. In the case of the N-*t*-butyloxycarbonyl amino acids, the cleaved trimethylcarbonium ion was observed as a singlet absorption at δ 4. In the case of the N-benzyloxycarbonyl amino acids, very broad, weak absorptions were observed at δ 7–10, probably corresponding to polymeric products of the cleaved benzyl cation.



I

R = *t*-butyl or benzyl (R′ was not observed for R = benzyl)

For the general species I, the protonated carboxylic function was observed as a singlet at *ca.* δ 13.1. The carboxylic protons are deshielded by *ca.* δ 0.9 compared with the carboxylic protons of protonated aliphatic carboxylic acids[6] owing to the protonated carbamic group on the α-carbon atom. Compared with the carboxylic protons of the simple diprotonated α-amino acids $RCH(NH_3^+)C^+(OH)_2$,[8] they are shielded by δ 0.9.

Only carbonyl oxygen protonation was observed for the carbamic group of I. The proton on nitrogen was observed as a broad absorption at *ca.* δ 7.7. Two resonances were seen for the two protons on the carbamic oxygen atoms. This is most likely a result of hindered rotation about the C_α–N bond and relatively free rotation about the C_α–O bonds. Both resonances appear in the region δ 10.5–11.0, and there is allylic coupling between the lower field resonance and the hydrogen atom on nitrogen. For the proton on the hydroxyl group *trans* to the proton on nitrogen with respect to the C–N bond, there is the possibility of a favorable planar W coupling path with the protons on nitrogen.[9] Consequently, the coupled lower field resonance is assigned to

(1) Part LXXXI: G. A. Olah and M. B. Comisarow, *J. Amer. Chem. Soc.*, **91**, 2955 (1969).

(2) National Institutes of Health Postdoctoral Research Investigator, 1967–1968.

(3) See, *e.g.*, M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience Publishers, Inc., John Wiley & Sons, Inc., New York, N. Y., p 25.

(4) R. A. Boissonnas and G. Preitner, *Helv. Chim. Acta*, **36**, 875 (1953).

(5) J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol. 2, John Wiley & Sons, Inc., New York, N. Y., 1961, pp 887–901 and 1187–1257.

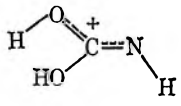
(6) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 3591, 4752, 7072 (1967).

(7) G. A. Olah and M. Calin, *ibid.*, **90**, 401 (1968).

(8) G. A. Olah, D. L. Brydon, and R. D. Porter, *J. Org. Chem.*, **35**, 317 (1970)

(9) S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

the *trans* carbamyl oxygen proton. The following N-alkoxycarbonyl derivatives were studied in SbF_5–



FSO_3H–SO_2 solution: N-benzyloxycarbonyl and N-*t*-butyloxycarbonyl glycine, L-alanine, L-valine, L-leucine, and L-proline; N-benzyloxycarbonyl L-aspartic acid; N,N′-dibenzyloxycarbonyl L-lysine; and ϵ-N-benzyloxycarbonyl L-lysine. The nmr parameters at −60° of the protonated carbamic–carboxylic species I, obtained by alkyl–oxygen cleavage, are summarized in Table I.

After the temperature was raised to −20° and then relowered to −60°, the original spectra of I could be observed unchanged. When the temperature was raised from −60° it was observed that the carboxylic protons exchanged more rapidly than the protons on the carbamic oxygen atoms, which were unaffected by exchange processes at −20°.

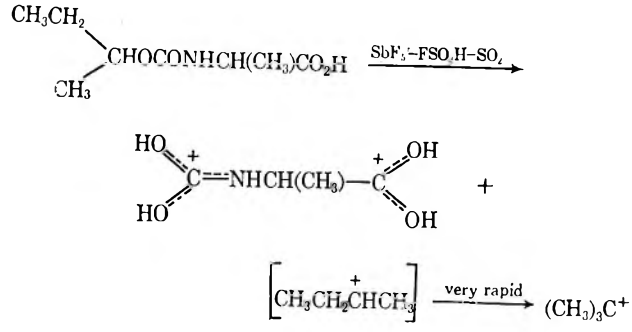
The diprotonated N-carboxy amino acids II–V derived from the N-benzyloxycarbonyl and N-*t*-butyloxycarbonyl derivatives of glycine, L-alanine, L-valine, and L-leucine, can be exemplified by that obtained from L-alanine. The carboxylic protons (2 H) appear as a singlet at δ 13.69 while the two carbamic OH groups appear at δ 10.70 (1 H) and 11.10 (1 H, J_{OH-NH} = 3 Hz). The NH hydrogen (1 H) gives rise to a broad doublet at δ 7.77. This chemical shift reflects the partial positive charge carried by the nitrogen atom. The methyl resonance (3 H) is a doublet at δ 2.23 (J_{CH_3-CH} = 7 Hz), while the methine proton, being vicinal to both a nitrogen and a carbon atom carrying some positive charge, appears as a multiplet at δ 5.66.

The triprotonated species VI resulting from the cleavage of N-benzyloxycarbonyl aspartic acid has to be cooled to −80° to lower the exchange rates before the resonances of both protonated carboxylic groups at δ 13.93 (2 H) and 14.57 (2 H) can be observed. The lower field resonance is assigned to the protons on the carboxylic group on the tertiary carbon atom. Both the CH (1 H) and NH (1 H) protons, at δ 6.27 and 8.00, respectively, are shifted downfield compared with their counterparts in the species derived from L-alanine. Also the carbamic OH resonances are at lower field [δ 11.13 (1 H) and 11.72 (1 H)] with the latter resonance broadened but not quite resolved as a doublet.

The nitrogen atom in the diprotonated carbamic derivatives VII of proline carried no hydrogen atoms. The carbamic OH resonances appear as two singlets, with a lower separation and a higher field than usual, at δ 10.43 (1 H) and 10.57 (1 H).

The triprotonated species IX, possessing two O-protonated carbamic functions, produced from N,N′-dibenzyloxycarbonyl lysine, demonstrates the fact that the alkoxycarbonyl group need not necessarily be linked to an amino group on the α atom of a carboxylic acid for alkyl–oxygen cleavage, with the production of a protonated carbamic group, to occur. The OH protons of the protonated carbamic group adjacent to the protonated carboxylic group are assigned to the two resonances at δ 10.77 (1 H) and 11.17 (1 H), while the NH proton (1 H) of this group appears at δ 7.7. For the other carbamic function, the OH protons appear at δ 9.63 (1 H) and 9.87 (1 H), with the NH proton (1 H) at δ 7.17. These assignments are based on comparison with the nmr parameters of the triprotonated species VIII obtained from the cleavage of ϵ-N-benzyloxycarbonyl lysine. In this case, the carbamic OH protons are seen at δ 9.70 (1 H) and 9.93 (1 H), while the NH proton and NH_3^+ protons appear as a broad peak at δ 7.17 (4 H). No cleavage reaction was observed even when a solution of N-*n*-butyloxycarbonyl DL-alanine in SbF_5–FSO_3H–SO_2 was maintained at −20° for 1 hr. The di-O-protonated N-*n*-butyloxycarbonyl DL-alanine (X) was observed with the carboxylic protons (2 H) appearing as two resonances, δ 13.47 and 13.52, at −60°. The proton on the carbonyl oxygen appeared as a singlet at δ 10.60 and as a doublet at δ 10.66 (J_{OH-NH} = 3 Hz). As before, there is assumed to be a greater energy barrier to rotation about the C–N bond than about the C–O bond. The singlet corresponds to the isomer in which the OH group is *cis* to the proton on nitrogen with respect to the C–N bond, and the doublet to the *trans* isomer.[9]

It was observed that N-*sec*-butyloxycarbonyl DL-alanine had undergone slight cleavage (as evidenced by the trimethyl carbonium ion at δ 4) after the solution in SbF_5–FSO_3H–SO_2 had been prepared at −78°. When the temperature is raised to between −60 and −35°, alkyl–oxygen cleavage takes place in the following manner.



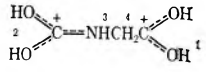
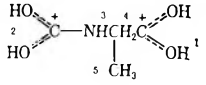
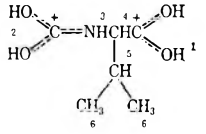
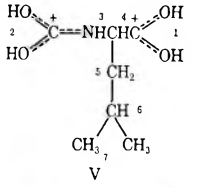
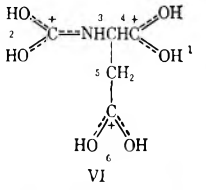
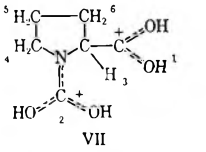
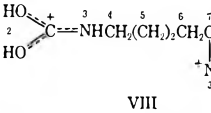
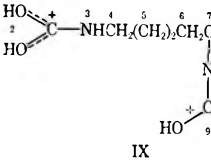
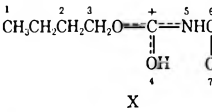
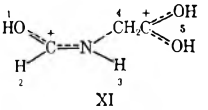
However, when the temperature is raised to −20°, secondary reactions occur; and, after the solution had been kept at −20° for 1 hr, the trimethyl carbonium ion absorption disappears.

The stability of the three isomeric N-butyloxycarbonyl alanines in the superacid system is inversely related to stabilities of the respective butyl cations initially formed by alkyl–oxygen cleavage. The *n*-butyl isomer is not cleaving at −20°, while the *t*-butyl isomer cleaves rapidly and completely at −78°. The *sec*-butyl isomer behaves in an intermediate fashion, cleaving in the range −60 to −35°.

N-Allyloxycarbonyl DL-alanine, when dissolved in SbF_5–FSO_3H–SO_2 at −76°, underwent a reaction, as evidenced by the two high-field doublets at δ 1.83 and 2.20. The nmr spectrum at −60° and below is consistent with an intramolecular cyclization having taken place between the carbonyl oxygen and the secondary carbon atom of the allyl group. When the temperature is raised from −60°, the spectrum becomes more complex, but at no time, even after the solution was left at room temperature for 2 hr, was the diprotonated N-carboxy alanine (III) expected from alkyl–oxygen

TABLE I[a]

NMR CHEMICAL SHIFTS (PARTS PER MILLION) AND COUPLING CONSTANTS (HERTZ)[b] OF PROTONATED CARBAMIC-CARBOXYLIC ACIDS (PRODUCED BY CLEAVAGE OF N-ALKOXYCARBONYL PRECURSORS) AND PROTONATED *n*-BUTYLOXYCARBONYL DL-ALANINE AND N-FORMYLGLYCINE AT −60° IN FSO_3H–SbF_5–SO_2 SOLUTION

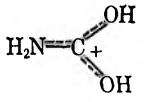
Species	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9
 II	13.66	10.66 11.06 d ($J_{2,3}$ = 3)	7.7 br	5.23 d ($J_{3,4}$ = 6)					
 III	13.69	10.70	7.7 br	5.66 m	2.23 d ($J_{4,5}$ = 7)				
 IV	13.8	10.47 11.06 d ($J_{2,3}$ = 3)	7.8 br	5.4 br	2.90 br	1.43 br			
	13.66	10.43 11.00 d ($J_{2,3}$ = 3)	7.8 br	5.37 d ($J_{3,4}$ = 5) ($J_{4,5}$ = 8)	2.90 m	1.52 d ($J_{5,6}$ = 6.5) 1.43 d ($J_{5,6}$ = 6.5)			
 V	13.66	10.70 11.10 ($J_{2,3}$ = 3)	7.63 br	5.47 m	2.10 m	2.10 m	1.16 m		
 VI	14.57[c]	11.13 11.72	8.0 br	6.27 br	4.47 br	13.93			
 VII	13.7	10.43 10.57	5.60 dd	4.23 t	2.8 m	2.8 m			
 VIII	14.53[c]	9.70 9.93	7.17 br	3.87 br	2.07 br	2.66 br	5.23 br		
 IX	13.80	9.63 9.87	7.17 br	3.73 br	1.97 br	2.47 br	5.47 br	7.7 br	10.77 11.17
 X	1.07[d] m	1.7[d] m	4.9[d] m	10.60[d] 10.66 d ($J_{4,5}$ = 3)	7.43[d] m	5.50[d] m	2.10[d] d ($J_{6,7}$ = 8) 2.17 d ($J_{6,7}$ = 8)	13.47 13.52	
 XI	11.95[d] dd ($J_{1,2}$ = 5) ($J_{1,3}$ = 2.25)	9.23[d] ($J_{1,2}$ = 5) ($J_{2,3}$ = 5)	9.53[d] br	5.68[d] d ($J_{3,4}$ = 6)	13.93				

[a] Spectra of compounds in this table may be obtained by ordering document no. 00602 from ASIS National Auxiliary Publications Service, % CCM Information Services, Inc., 22 W. 34 Street, New York, N. Y. 10001, remitting $1.00 for microfiche or $3.00 for photocopies. [b] Coupling constants are in parentheses. Multiplicity is indicated as follows: d, doublet; t, triplet; m, multiplet; br, broad. [c] At −80°. [d] At −20°.

cleavage observed. Complex changes were observed when N-vinyloxycarbonyl glycine was dissolved in the strong acid solution at −76° and the temperature was raised. However, after the solution had been maintained at 55° for 1 hr, a small amount of diprotonated N-carboxy glycine (II) was observed in the nmr spectrum when the solution was cooled back to −40°.

The behavior of vinyl carbamate in SbF_5–FSO_3H–SO_2 was also investigated. The nmr spectrum of the solution prepared at −76° was complex, but resonances

corresponding to the alkyl–oxygen cleavage product, protonated carbamic acid[7]



were observed. The OH protons (2 H) were observed at δ 10 and the NH protons (2 H) at δ 7.47 as broad singlets. After the solution was heated to 60°, complex spectral changes took place, but, when the solution was cooled back to below −60°, the resonances attributed to protonated carbamic acid were observable.

Diprotonated N-formylglycine (XI) is an aldehydic analog of the diprotonated N-carboxy amino acids of type I and is therefore an interesting model compound. N-Formylglycine was di-O-protonated in SbF_5–FSO_3H–SO_2 solution, and no decomposition was observed to occur at −20°. At −60° the carboxylic protons (2 H) appear at δ 13.93 as a singlet, and at −20° they exchange too rapidly to be seen. The methylene protons (2 H) are seen as a doublet (J_{CH_2-NH} = 6 Hz) at δ 5.68 and the proton on nitrogen (1 H) appears as a broad peak at δ 9.53, which is comparable with the chemical shift of the proton on nitrogen in protonated imines.[10] The proton on the aldehydic oxygen (1 H) appears at δ 11.95 and is the same δ 3 upfield compared with the proton on oxygen in aliphatic aldehydes,[11] while the proton on the aldehydic carbon atoms appears at δ 9.23. These spectral observations might suggest that the positive charge attributable to aldehydic O-protonation is delocalized over the oxygen, carbon, and adjacent nitrogen atoms. Also, as in protonated, carbamic acids,[7] there is hindered rotation about the C–N bond and relatively free rotation about the C–O bond. Only one isomer is observed and that observed CH–NH coupling is 5 Hz, suggesting that the CH and NH protons bear a cisoid relationship, as depicted in Table I. The CH resonance (1 H) is observed as a triplet (J_{CH-NH} = Hz, J_{CH-OH} = 5 Hz), and the proton on the aldehydic oxygen atom is seen as a doublet of doublets due to a 5-Hz coupling with the proton on the vicinal carbon and an allylic-type coupling (J_{OH-NH} = 2.25 Hz) with the proton on nitrogen. Analogously with the protonated carbamic acid cases, the coupled NH and OH protons can assume a planar W coupling path and the hydroxyl group and the NH proton bear a *trans* relationship with respect to the C–N bond. However, in the case of protonated formylglycine, the long-range coupling is 0.55–0.75 Hz less than in the case of the protonated carbamic groups.

(10) G. A. Olah and P. Kreinbühl, *J. Amer. Chem. Soc.*, **89**, 4756 (1967).
(11) G. A. Olah, D. H. O'Brien, and M. Calin, *ibid.*, **89**, 3582 (1967).

Experimental Section

Materials.—N-Benzyloxycarbonyl and N-*t*-butyloxycarbonyl α-amino acids were commercially available and were obtained as pure compounds from Schwarz Bioresearch, Inc., and Nutritional Biochemicals Corp.

N-Formylglycine was prepared by slowly adding acetic anhydride to a cooled solution of glycine in formic acid (90%). The product was recrystallized from water,[12] mp 148–150° (lit. mp 153–154°).

N-*n*-butyloxycarbonyl and N-allyloxycarbonyl DL-alanine were prepared from DL-alanine and the appropriate chloroformates according to the general procedure of Stevens and Matanabe.[13] Both compounds were recrystallized from benzene–pentane, and the latter compound had a melting point of 61.9–62.3° (lit. mp 60–61°). N-*n*-butyloxycarbonyl DL-alanine was obtained in 53% yield, mp 67.7–68°.

Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.91; N, 7.40. Found: C, 50.89; H, 7.72; N, 7.38.

N-*sec*-Butyloxycarbonyl DL-alanine, mp 55° (lit. mp 59°), was prepared from DL-alanine and *sec*-butyl chloroformate,[4] after the chloroformate was first prepared from phosgene and *sec*-butyl alcohol.[13]

Nmr Spectra.—A Varian Associates Model A-56/60A nmr spectrometer equipped with a variable-temperature probe was used for all spectra. Coupling constants are believed accurate to ±0.1 Hz. The reference standard used was capillary TMS.

Preparation of Superacid Solution.—Solutions were usually in the following molar proportions: amino acid derivative (1); sulfur dioxide (15); 1:1 *M* antimony pentafluoride–fluorosulfonic acid (6).

The amino acid derivative was dissolved in sulfur dioxide and added slowly at −76° with vigorous agitation to the 1:1 SbF_5–FSO_3H solution diluted with sulfur dioxide. The few amino acid derivatives which did not dissolve in sulfur dioxide were added slowly to the SbF_5–FSO_3H–SO_2 solution with vigorous agitation.

There was usually a large peak at *ca.* δ 11 owing to excess acid. All the solutions were either colorless or faintly colored except for the benzyloxycarbonyl solutions, which were yellow at −76° and darkened rapidly with rise in temperature.

Registry No.—II, 22483-22-3; III, 22486-00-6; IV, 22486-01-7; V, 22486-02-8; VI, 22486-03-9; VII, 22486-04-0; VIII, 22493-24-9; IX, 22486-05-1; X, 22486-06-2; XI, 22483-23-4.

Acknowledgment.—Professor M. Bodanszky is thanked for stimulating discussions and the arousal of our interest in this study. The research was made possible through a grant of the National Institutes of Health. Professor R. A. Olofson is thanked for samples of N-vinyloxycarbonyl glycine and vinyl carbamate.

(12) Reference 5, p 921.
(13) C. M. Stevens and R. Matanabe, *J. Amer. Chem. Soc.*, **72**, 725 (1950).

Stable Carbonium Ions. LXXXIII.[1] Protonation of Amino Acids, Simple Peptides, and Insulin in Superacid Solutions

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Received May 5, 1969

The protonation of α-, β-, γ-, and δ-amino acids, protein-occurring α-amino acids, some simple peptides, and porcine insulin has been studied by nmr spectroscopy in FSO_3H–SbF_5–SO_2 and FSO_3H–SbF_5 solution. For comparison, protonation of some lactones was also studied in the same solvent systems. In the case of the amino acids, protonation of the amino and carboxyl groups, as well as of other available basic sites, was observed. No dehydration of the protonated α- and β-amino acids to oxocarbonium ions was observed, but some cleavage of protonated γ- and almost complete cleavage of δ-amino acids took place. Protonation on carboxyl oxygen of peptides was observed, besides protonation of other basic sites.

Earlier papers in this series have reported the nmr observation of the protonation of carboxylic and dicarboxylic acids and their subsequent dehydration to the respective oxocarbonium ions in the strong acid system FSO_3H–SbF_5.[3] The nmr spectra of amino acids and peptides have been investigated in basic, acidic, and neutral solvent systems.[4-7] Recently, the spectra of 20 amino acids in CF_3CO_2H and CF_3CO_2D solutions have been obtained at 220 MHz and used in an investigation of protein structure.[8] The conformation of polypeptides has been investigated by nmr and optical methods.[9]

Protonation of the carboxyl group in amino acids is not observed in trifluoroacetic acid, but Thomas and Niemann[10] interpreted their cryoscopic studies of L-leucine in 100% sulfuric acid in terms of the presence of small amounts of L-leucine protonated on both the amino and carboxyl groups. Subsequent cryoscopic studies in 100% sulfuric acid[11] indicated that, as the amino group is further removed from the carboxyl group in amino acids, the carboxyl group is protonated to a greater extent (i = 2.3 for L-leucine, i = 2.7 for β-alanine, and i = 3.0 for aminocaproic acid).

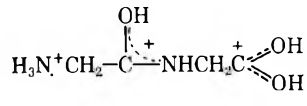
In our continued studies, the protonation and thermal stability of protein-occurring α-amino acids and of a range of α-, β-, γ-, and δ-amino acids in the strong acid system FSO_3H–SbF_5 was investigated by nmr spectroscopy. In the same acid system, the protonation of some simple peptides and lactams was investigated, as well as that of porcine insulin.

Results and Discussion

All the α-amino acids naturally occurring in proteins,[12] as well as δ-aminovaleric acid, α-, β-, and γ-aminobutyric acids, some simple peptides, and insulin, were dissolved in the strong acid system FSO_3H–SbF_5–SO_2 at −76°, and the nmr spectra of the solutions were examined over a range of temperatures from −90 to −20°. Generally, protonation of the amino function was observed (3 H) as a broad resonance at *ca.* δ 7.0 with the protonated carboxyl group (2 H) appearing at *ca.* δ 14.5. The protonated amino group could usually be observed over the whole range of temperatures studied, while the protons of the carboxylic group generally exchanged too rapidly to be observed at temperatures higher than −40°. The additional deshielding of the protonated carboxylic group by the protonated amino group on the α-carbon atom is illustrated by the fact that the protons of the protonated carboxylic groups of aliphatic carboxylic acids are observed at *ca.* δ 12.6.[3] To study the possible cleavage of protonated amino acids, representative samples of the α-amino acids, glycine, L-alanine, L-valine, L-phenylalanine, L-proline, L-lysine, and L-glutamic acid were heated for 2 hr at −40° in the FSO_3H–SbF_5 solution. Apart from L-phenylalanine, whose aromatic group reacted with the acid system at temperatures above −30°, the diprotonated amino acids were observed to be stable at this temperature. There was no dehydration to the corresponding oxocarbonium ion, as is the case with the protonated aliphatic carboxylic acids.[3]

$$RCO_2H_2^+ \xrightarrow[0 \text{ to } -30^\circ]{FSO_3H\text{–}SbF_5\text{–}SO_2} RCO^+ + H_3O^+$$

At temperatures below −20° in FSO_3H–SbF_5–SO_2 solution, the simple peptides examined were observed to be chemically stable, and to be protonated on the terminal amino and carboxyl groups and on the carbonyl oxygen of the peptide bonds.



Diprotonated α- and β-aminobutanoic acids in FSO_3H–SBF_5 solution underwent no decomposition after being maintained at 45° for 4 hr. γ-Aminobutanoic acid underwent some side reactions but was observed to undergo about 50% dehydration. Diprotonated δ-aminovaleric acid dehydrated slowly at −20°, and after 4 hr at 45°, 97% dehydration had occurred to yield the oxocarbonium ion $H_3N^+(CH_2)_3CO^+$. The facility with which diprotonated amino carboxylic acids dehydrated in the acid system studied increased with the separation of the protonated amino group from

(1) Part LXXXII: G. A. Olah and D. L. Brydon, *J. Org. Chem.*, **35**, 313 (1970).

(2) (a) National Institutes of Health Postdoctoral Research Investigator, 1967–1968; (b) National Institutes of Health Predoctoral Research Investigator, 1968–1969.

(3) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 3591, 4752, 7072 (1967).

(4) M. Takeda and O. Jardetzky *J. Chem. Phys.*, **26**, 1346 (1956).

(5) O. Jardetzky and C. D. Jardetzky, *J. Biol. Chem.*, **233**, 383 (1958).

(6) F. A. Bovey and G. V. D. Tiers, *J. Amer. Chem. Soc.*, **81**, 2870 (1958).

(7) S. Fujiwara and Y. Arata, *Bull. Chem. Soc. Jap.*, **36**, 578 (1963); **37**, 344 (1964).

(8) B. Bak, C. Dambmann, F. Nicolaisen, and E. J. Pedersen, *J. Mol. Spectrosc.*, **26**, 78 (1968).

(9) F. A. Bovey, *Pure Appl. Chem.*, **16**, 417 (1968).

(10) D. W. Thomas and C. Niemann, *J. Biol Chem.*, **175**, 241 (1948).

(11) J. L. O'Brien and C. Niemann, *J. Amer. Chem. Soc.*, **73**, 4264 (1951).

(12) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, John Wiley & Sons, Inc., New York, N. Y., 1961, p 3.

TABLE I

NMR CHEMICAL SHIFTS (PARTS PER MILLION) AND COUPLING CONSTANTS[a] (HERTZ) OF PROTONATED MONOAMINO MONOCARBOXYLIC ALIPHATIC ACIDS AT −60° IN FSO_3H–SbF_5–SO_2 SOLUTION

Species	Registry no.	H_1	H_2	H_3	H_4	H_5	H_6	H_7
$CH_2(\overset{+}{N}H_3)CO_2H$[b]	22493-25-0	14.43 ... 14.2[d] 14.43[d]	7.13 br	5.25[c] q ($J_{2,3}$ = 6)				
$CH_3CH(\overset{+}{N}H_3)CO_2H$[b]	22493-26-1	14.37	7.00 br	5.40[c] m	2.30[c] d ($J_{3,4}$ = 7.5) 2.40[c] d ($J_{3,4}$ = 7.5)			
$(CH_3)_2CHCH(\overset{+}{N}H_3)CO_2H$[b]	22493-27-2	14.45	7.03 br	5.13[c] m	3.07[c] m	1.50[c] d ($J_{4,5}$ = 6.8) 1.54[c] d ($J_{4,5}$ = 6.8) 1.60[c] d ($J_{4,5}$ = 6.8)		
$(CH_3)_2CHCH_2CH(\overset{+}{N}H_3)CO_2H$	22493-28-3	14.40 (14.50)	7.03 br (7.00)	5.20 m (5.20)	2.43[c] m (2.37)	2.43[c] m (2.37)	1.43[c] d ($J_{5,6}$ = 5) (1.40)	
$CH_3CH_2CH(CH_3)CH(\overset{+}{N}H_3)CO_2H$	22493-29-4	14.50	7.03 br	5.20[c] m	1.45[c] d ($J_{4,5}$ = 6)	2.8[c] m	1.90[c] m	1.62[c] d ($J_{6,7}$ = 7)
$[-SCH_2CH(\overset{+}{N}H_3)CO_2H]_2$	22493-30-7	14.93[e]	7.27[c] br	5.17[c] m	3.93[c] m			
$CH_3\overset{+}{S}(H)CH_2CH_2CH(\overset{+}{N}H_3)CO_2H$	22493-31-8	15.17[e]	7.20 br	5.30 m	3.23 m	3.93 m	6.93 m	3.3 d ($J_{6,7}$ = 8)

[a] Coupling constant are in parenthesis. Multiplicity is indicated as follows: d, doublet; q, quartet; m, multiplet; br, broad. [b] Spectra may be obtained from ASIS National Auxiliary Publications Service, % CCM Information Corp., 909 3rd Ave., New York, N. Y. 10022. Order Document No. 00602. [c] At −20°. [d] At −90°. [e] At −80°.

the protonated carboxyl group. This is most probably due to an electrostatic repulsion, since there is a greater positive charge on the carboxylic carbon atom in the protonated carboxylic acid than on the oxocarbonium carbon atom in the respective oxocarbonium ion (as evidenced by the comparative deshielding of the α-hydrogen atoms by *ca.* δ 1.0 in the case of δ-amino-valeric acid). Similarly, it has been found that the ease with which diprotonated dicarboxylic acids can be dehydrated increases with the increasing separation of the acid functions.[3]

Monoamino Monocarboxylic Aliphatic Acids.—The nmr spectral data of the diprotonated species obtained by dissolving glycine, L-alanine, L-valine, L-leucine, and L-isoleucine in FSO_3H–SbF_5–SO_2 are summarized in Table I, as are the data for protonated L-cystine and L-methionine (Figure 1).

The simplest amino acid studied was glycine, in which, at $-60°$, the protons on nitrogen (3 H) were observed as a broad peak at δ 7.13, while the carboxylic protons (2 H) appeared as a sharp singlet at δ 14.43 and as two lines at δ 14.2 and 14.43 at $-90°$. At $-20°$, the methylene protons (2 H) were resolved into a quartet at δ 5.25 (J_{CH-NH} = 6 Hz).

The methyl resonances of diprotonated L-alanine and L-valine are interesting in that, with alanine, a very low intensity doublet at δ 2.30 was observed as well as the strong doublet at δ 2.40, while with valine, two intense doublets were observed at δ 1.60 and 1.54 and a very low intensity doublet was discernible at δ 1.50.

L-serine and L-threonine underwent chemical change in the strong acid system, as evidenced by the absence of low-field resonance absorptions. A singlet at δ 5.77 and a broader singlet of equal area at δ 7.50 was observed from -20 to $-80°$ in the case of serine. With threonine, a doublet (3 H) appeared at δ 2.35 (J = 6 Hz), a broad singlet (3 H) at δ 7.47, and broad multiplets at δ 5.57 (1 H) and 6.17 (1 H). The reaction of serine and threonine in trifluoroacetic acid solution has been discussed previously.[6,8]

The carboxylic protons of L-cystine appear as a broad exchanging resonance at δ 14.93. Even at $-80°$, no protonation of the disulfide system was detected and the chemical shifts of the protonated amino group at δ 7.27 (3 H), the methine proton at δ 5.17 (1 H), and the methylene protons at δ 3.93 (2 H) in FSO_3H–SbF_5–SO_2 are similar to the chemical shifts of δ 7.75, 4.80, and 3.61, respectively, determined in trifluoroacetic acid.[6] L-Cysteine underwent chemical reaction in the strong acid system in contrast to its behavior in trifluoroacetic acid.[6,8] Broad peaks were observed at δ 7.33 (NH_3) and 5.43 (CH), no low-field resonances were seen, and after a few hours a white precipitate was deposited.

A very characteristic spectrum was obtained with L-methionine (Figure 1). The terminal group (3 H) appeared at δ 3.3 as an extremely sharp doublet (J_{CH_3-SH} = 8 Hz) as a result of the sulfur protonation. These values compare with protonated dimethyl sulfide, where the methyl protons appear as a doublet at δ 3.08 and the proton on sulfur as a septuplet at δ 6.52 (J_{CH_3-SH} = 8 Hz).[13] Again, the carboxyl protons

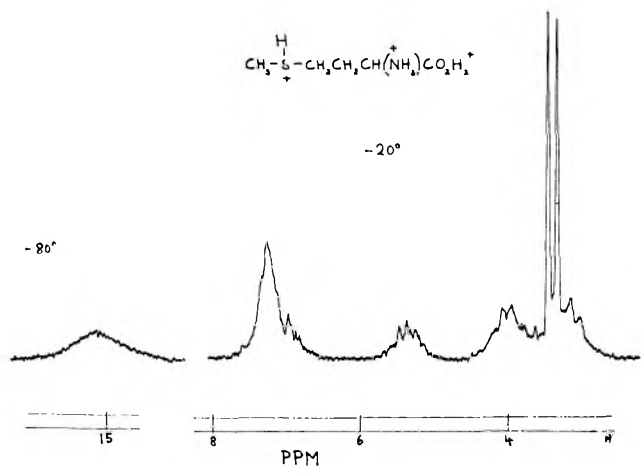


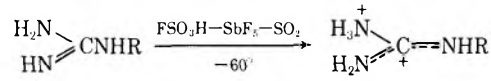
Figure 1.—60-MHz nmr spectrum of L-methionine in $HFSO_3$–SbF_5–SO_2.

could only be observed at $-80°$, and then as a broad exchanging resonance at δ 15.17.

Diamino Monocarboxylic and Monoamino Dicarboxylic Aliphatic Acids.—The nmr parameters obtained upon protonation of diamino monocarboxylic and amino dicarboxylic acids in FSO_3H–SbF_5–SO_2 solutions are summarized in Table II. L-Lysine was observed to be triprotonated, with the α-amino protons (3 H) and the amino protons (3 H) appearing at δ 7.06 and 6.03, respectively. All the methylene and methine protons appeared as broad peaks at $-20°$, and only at $-80°$ are the carboxylic protons observed as a sharp singlet at δ 14.53.

With δ-hydroxy lysine, poorly resolved spectra were obtained. Only at -80 and $-90°$ could the protons of the carboxylic group be observed as a very broad resonance at δ 14.8, and no resonances could be observed for the hydroxy group. It is conceivable that the δ-hydroxy lysine underwent ring closure to form a lactone. If this were the case, the observed species might have been either the protonated lactone or an equilibrium mixture of protonated acid and protonated lactone.

Arginine and its nonprotein-occurring homolog, homoarginine, are basic α-amino acids which possess a guanidine end group. Olah and White[14] have shown that guanidines are diprotonated in FSO_3H–SbF_5–SO_2 in the following manner.



The α-amino group (3 H) in arginine appeared at δ 7.07, the protonated amino function (3 H) of the guanidine group appeared at δ 8.9 as a sharper peak than that owing to the protonated amino group (2 H), and the substituted amino group (1 H) appeared at δ 8.13. Homoarginine exhibited a very similar spectrum to arginine at $-60°$, with the difference that in the case of arginine the carboxylic protons exchanged too rapidly to be seen, while in the case of homoarginine the carboxylic protons (2 H) were observed as a sharp singlet.

Aspartic acid is triprotonated in the strong acid solution. The carboxylic protons (4 H) were observed

(13) G. A. Olah, D. H. O'Brien, and C. U. Pittman, *J. Amer. Chem. Soc.*, **89**, 2996 (1967).

(14) G. A. Olah and A. M. White, *ibid.*, **90**, 6087 (1968).

TABLE II

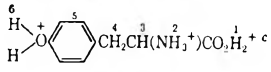
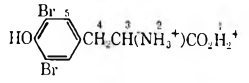
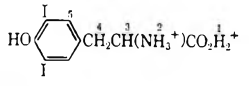
NMR CHEMICAL SHIFTS (PARTS PER MILLION) AND COUPLING CONSTANTS[a] (HERTZ) OF PROTONATED DIAMINO MONOCARBOXYLIC AND MONOAMINO DICARBOXYLIC ALIPHATIC ACIDS AT −60° IN FSO_3H–SbF_5–SO_2 SOLUTION

Species	Registry no.	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8
$CH_2(NH_3^+)(CH_2)_2CH_2CH(NH_3^+)CO_2H_2^+$[b]	22493-32-9	14.53[c]	7.06 br	5.2 br	2.63 br	2.06 br	6.08 br	3.57 br	
$CH_2(NH_3^+)CH(OH)(CH_2)_2CH(NH_3^+)CO_2H_2^+$	22533-99-9	14.8[c]	7.23[d] br	5.33 br	2.87 br	5.60 br	6.70 br	4.17 br	
$(NH_3^+)(NH_2)C{=}NHCH_2(CH_2)_2CH(NH_3^+)CO_2H_2^+$	22493-33-0	14.87[c] br	7.07 br	5.2 m	2.6 br	4.06 br	8.13	8.13	8.9
$(NH_3^+)(NH_2)C{=}NHCH_2(CH_2)_3CH(NH_3^+)CO_2H_2^+$[b]	22493-34-1	14.53	7.10 br	5.23 m	2.20 br 2.60 br	4.0 br	8.10	8.10	8.87
$H_2O_2CCH_2CH(NH_3^+)CO_2H_2^+$[b]	22493-35-2	14.40[c] m	7.50[d] br	5.93[d] m	4.60[d] d ($J_{3,4}$ = 5)	14.40[c] m			
$^+H_2O_2CCH_2CH_2CH(NH_3^+)CO_2H_2^+$[b]	22493-36-3	15.07[c] br	7.27 br m	5.37[d] m	3.23[d] m	3.97[d] t ($J_{4,5}$ = 6)	13.38		
$HO(H_2N)C{=}^+CCH_2CH(NH_3^+)CO_2H_2^+$	22493-37-4	15.48[c]	7.43[d] br	5.8[d] m	4.30[d] br	8.87[d] 9.23[d]	11.53		
$HO(H_2N)C{=}^+CCH_2CH_2CH(NH_3^+)CO_2H_2^+$[b]	22493-38-5	15.06[c] br	7.2[d] br	5.30[d] m	3.17[d] m	3.53[d] m	10.63 d (J = 3)	8.43 8.80	

[a] Coupling constants are in parenthesis. Multiplicity is indicated as follows: d, doublet; t, triplet; m, multiplet; br, broad. [b] See footnote *b*, Table I. [c] At −80°. [d] At −20°. [e] At −90°.

TABLE III

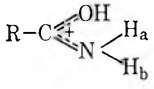
NMR PARAMETERS[a] (δ, PARTS PER MILLION) OF PROTONATED AROMATIC AMINO ACIDS AT $-60°$ IN FSO_3H–SbF_5–SO_2[b] SOLUTION

Species	Registry no.	H_1	H_2	H_3	H_4	H_5	H_6
$C_6H_5CH_2CH(NH_3^+)CO_2H_2^+$[c]	22493-39-6	14.47 br	6.83 br	5.30 br	3.87 br	7.77 br	
 [c]	22493-40-9	14.77[d]	7.03 br	5.43 br	4.07 br	7.97	13.0
	22493-41-0	14.73[d] br	7.00 br	5.33 br	3.87 br	8.03	
	22493-42-1	14.73[e]	6.96[e] br	5.33[e] br	3.8[e] br	8.23[e]	

[a] Multiplicity is indicated as follows: br, broad. [b] Phenylalanine in 9:1 FSO_3H–SbF_5. [c] See footnote *b*, Table I. [d] At $-80°$. [e] At $-90°$.

at $-80°$ as a broad peak at δ 14.40. The methylene group (2 H) appeared at δ 4.60 and resolved at $-20°$ into a doublet (J_{CH_2OH} = 5 Hz). In the spectrum of glutamic acid, the carboxylic proton resonances are observed at δ 13.38 and 15.07 (the latter only at $-80°$). The methylene (2 H) group furthest from the amino group appears at $-20°$ as a poorly resolved triplet at δ 3.97 ($J_{CH_2-CH_2}$ = 6 Hz). Compared with the spectra of diprotonated dicarboxylic acids,[3] a considerable deshielding effect is observed owing to the protonated amino group.

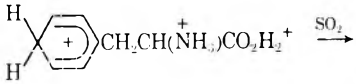
In the spectra of asparagine and glutamine, the carboxylic protons can only be observed as broad peaks at δ 15.48 ($-90°$) and 15.06 ($-80°$), respectively. O-Protonation of the amide group is observed in both cases. With asparagine, the proton is observed as a singlet at δ 11.53 and the amide protons (2 H) on nitrogen as two resonances at δ 8.87 and 9.23. With glutamine, the proton on amide oxygen appears as a doublet (J = 3 Hz) at δ 10.63 and the amide protons (2 H) on nitrogen appear at δ 8.43 and 8.80. The amide protons on nitrogen are nonequivalent owing to the partial double-bond character of the C–N bond. The protonation of amides has



been discussed by Katritzky and Jones[15] and, in the case of fluorosulfuric acid, by Gillespie and Birchall.[16] For protonated acetamide ($-80°$), the latter workers observed the proton on oxygen at δ 10.72 and the protons on nitrogen at δ 8.24 and 8.36.

Aromatic Amino Acids.—The nmr data obtained for protonated aromatic amino acids in FSO_3H–SbF_5 are summarized in Table III.

When L-phenylalanine was dissolved in the usual manner with a sixfold excess of 1:1 FSO_3H–SbF_5 and diluted with sulfur dioxide (15 *M*), sulfonylation occurred[17] to give a mixture of diprotonated phenylalanines. The *para*-protonated sulfinic acid of diprotonated phenylalanine was formed by ring protonation and reaction with sulfur dioxide.



The presence of the sulfinic acid derivative was evidenced by the appearance of an AA'BB' quartet at δ 8.2 ($J_{A\text{-}B(A'\text{-}B')}$ = 8 Hz) and a resonance attributable to the protonated sulfinic group at δ 9.83. When the temperature of the solution was raised to $-30°$, an irreversible reaction of the aromatic nucleus with the acid system took place. When FSO_3H alone was used as the solvent, protonation of only the amino group was observed. With 1:1 FSO_3H–SbF_5 diluted with sulfuryl chloride fluoride, the solution was bright red, and a reaction was observed with the aromatic nucleus. Similarly, 12.5:1 HF–SbF_5 reacted with the phenylalanine, and after 1 hr at $-60°$ a yellow oil separated. However, 9:1 FSO_3H–SbF_5 was found to be the best strong acid system, and a spectrum of diprotonated phenylalanine [$C_6H_5CH_2CH(NH_3^+)CO_2H_2^+$] could be obtained at temperatures below $-50°$. At temperatures above $-50°$, the acid system reacted with the aromatic nucleus. At $-60°$, the carboxylic protons (2 H) appeared as a broad singlet at δ 14.47, the aromatic protons (5 H) and the ammonium protons (3 H) as broad singlets at δ 7.77 and 6.83, respectively, and the methylene (2 H) and methine (1 H) protons as broad resonances at δ 3.87 and 5.30.

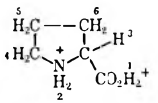
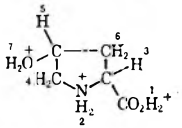
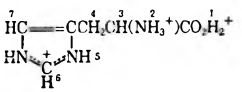
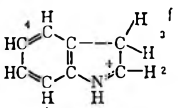
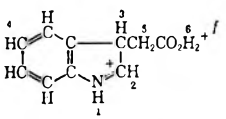
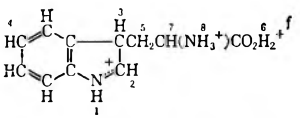
L-Tyrosine underwent no chemical transformation in 1:1 FSO_3H–SbF_5 diluted with SO_2, even at $-20°$; consequently, this strong acid system was used to study its protonation. The aromatic protons (4 H) appeared as a sharp singlet at δ 7.97, and at $-60°$ a broad singlet was observed at δ 13.0. This latter resonance is assigned to the two protons on phenolic oxygen, resulting from its protonation. The fact that the aromatic resonance appeared as a singlet indicates that the positive charge from this protonation resided on the phenolic oxygen and was not delocalized to any appreciable extent over the aromatic ring. The carboxylic protons appeared as a broad peak at $-60°$, and at $-70°$ as a singlet (2 H) at δ 14.77.

Spectral parameters were obtained for L-3,5-dibromotyrosine at -60 and $-80°$, where the strong acid solution was of pale brown color. However, when the temperature of the solution was raised, the color rapidly darkened, and diffuse spectra were observed indicating an irreversible process. An exchanging resonance absorption was observed for the carboxylic protons (1.5 H) at -80 and $-90°$ and, at these temperatures

(15) A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), **722** (1961).
(16) R. J. Gillespie and T. Birchall, *Can. J. Chem.*, **41**, 148 (1962).
(17) G. A. Olah and T. E. Kiovsky, *J. Amer. Chem. Soc.*, **89**, 5692 (1967).

TABLE IV

NMR CHEMICAL SHIFTS (PARTS PER MILLION) AND COUPLING CONSTANTS[a] (HERTZ) OF PROTONATED HETEROCYCLIC AMINO ACIDS AND RELATED COMPOUNDS AT −60° IN FSO_3H–SbF_5–SO_2 SOLUTION

Species	Registry no.	H_1	H_2	H_3	H_4	H_5	H_6	H_7
	22493-43-2	14.30 14.30[b] 14.50[b]	7.30 br	5.73 m	4.07 m	2.80 br m	2.80 br m	
	22493-44-3	15.30[c] br	8.17[d] br	5.97[d] br	4.87[d] br	6.5[d]	3.83[d] br m	11.51[d] br
	22534-00-5	15.4[b] br	7.27 br	5.53 m	4.23 br m	11.33 11.43	9.07	8.03
	22493-45-4	7.97 m	9.48 d ($J_{2,3}$ = 6)	4.73	7.97 m			
	22493-46-5	8.10[e] m	9.58[e] d ($J_{1,2}$ = 6)	5.22[e] t ($J_{3,5}$ = 7)	8.10[e] m	4.40[e] 4 lines	13.15[c] 13.50[c]	
	22493-47-6		9.53[e] d ($J_{1,2}$ = 5.6) 9.63 d ($J_{1,2}$ = 5.6)	5.30[e] br m	8.15[e] m	3.50[e] br m (width = 100 Hz)	15.3[b] br	5.10[e] m (H_8, 7.3 br)

[a] Coupling constants are in parenthesis. Multiplicity is indicated as follows: d, doublet; t, triplet; m, multiplet; br, broad. [b] At −90°. [c] At −70°. [d] At −35°. [e] At −20°. [f] See footnote *b*, Table I.

and at −60°, although the aromatic resonance was quite sharp, the other resonances appeared as broad peaks. Only at −90° could a spectrum of diprotonated L-3,5-diiodotyrosine be obtained. With rise of temperature, chemical reaction was observed, giving a deeply colored solution at −50°. No resonance attributable to phenolic protons was observed with either the dibromo or diiodo tyrosines.

Spectra of protonated L-3,5,3′-triiodotyrosine and L-thyroxine could not be obtained in solutions of 1:1 FSO_3H–SbF_5 and SO_2 or 9:1 FSO_3H–SbF_5.

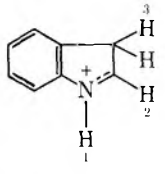
Heterocyclic Amino Acids.—The nmr data obtained in FSO_3H–SbF_5–SO_2 for protonated heterocyclic amino acids as well as related protonated model compounds such as indole and indoleacetic acid are summarized in Table IV.

L-Proline (Figure 2) is diprotonated and chemically stable at −40°. At −90°, the protons on oxygen split into two peaks at δ 14.30 and 14.50. In the case of L-hydroxyproline, triprotonation occurs. The carboxyl protons only appear at −80° as a broad resonance at δ 15.30, while the protons on nitrogen (2 H) appear at δ 8.17 (δ 0.87 deshielded compared to the corresponding protons in diprotonated proline), and the hydroxyl protons appear at δ 11.51 as an unresolved peak adjacent to the solvent peak at −35°.

L-Histidine (Figure 3) is triprotonated. The temperature of the solution had to be lowered to −90° to slow the rate of exchange of the carboxyl protons before they could be observed at δ 15.4. The protons on the nitrogen atoms of the imidazole ring were observed at δ 11.33 and 11.43 as shoulders of the solvent peak at −60°. The other aromatic protons, at positions 2 and 5 of the imidazole ring, appeared at −60° as singlets at δ 9.07 and 8.03. The protons on the imidazole nitrogen atoms are better resolved from the solvent peak in 9:1 FSO_3H–SbF_5 and appear (−20°) as a broad singlet at δ 11.3.

Indole and indoleacetic acid were used as model compounds to study the protonation of tryptophan.

Indole was found to protonate on the carbon atom of the pyrrole ring β to the nitrogen atom, with consequent formation of a methylene group and delocalization of the positive charge over the appropriate C–N system, giving the C–N bond some ethylenic character.



The methylene group was not coupled to the vicinal proton because of their angular relationship, but this latter proton exhibited a cisoid coupling to the proton on nitrogen. Thus the methylene protons appeared as a singlet (2 H) at δ 4.73, the proton 2 appeared as a sharp doublet (1 H) at δ 9.48 (J_{CH-NH} = 6 Hz), and the proton on nitrogen (1 H) was under the aromatic resonance (4 H) at δ 7.97.

The indole system of indoleacetic acid was protonated similarly to indole itself, in that protonation occurred at the 3 position. The carboxylic group was also found to protonate, and at −80° two peaks appeared at δ 13.15 and 13.50 (2 H). The aromatic protons (4 H)

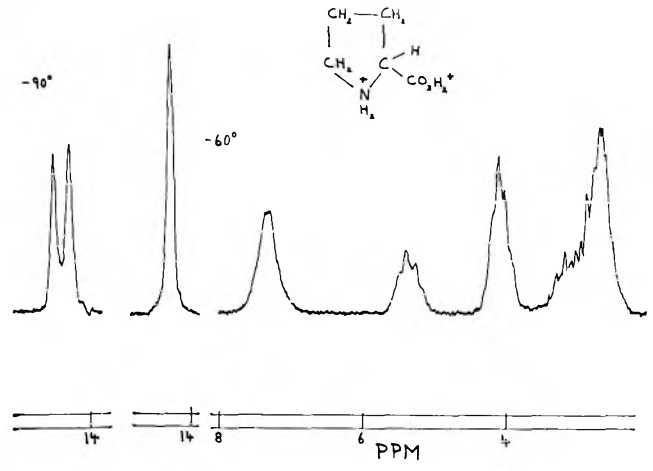


Figure 2.—60-MHz nmr spectrum of L-proline in $HFSO_3$–SbF_5–SO_2.

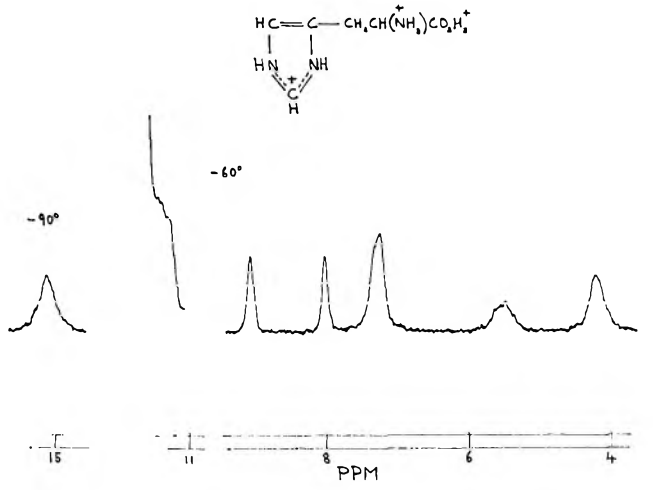


Figure 3.—60-MHz nmr spectrum of L-histidine in $HFSO_3$–SbF_5–SO_2.

and the proton on nitrogen (1 H) appeared at δ 8.10 as an intense multiplet, while the proton adjacent to nitrogen in position 2 of the indole system appeared as a doublet (J_{CH-NH} = 6 Hz) at δ 9.58 (1 H). As before, this multiplicity was due to a cisoid coupling with the proton on nitrogen and absence of coupling with the proton in the 3 position. The proton in the 3 position (1 H) appeared as a triplet (J_{CH-CH_2} = 5.7 Hz) at δ 5.22 and the adjacent methylene group appeared at δ 4.40 (2 H) as an asymmetric resonance of four lines. An artifact appeared (0.4 H) at δ 4.9.

As in the cases of indole and indoleacetic acid, L-tryptophan was protonated at the 3 position of indole and, also, the δ-amino group and the carboxylic group were observed to be protonated. The indole nitrogen proton could not be observed, and was probably masked by either the aromatic or ammonium peaks. The proton at the 2 position of the indole residue appeared as two overlapping doublets (1 H) at δ 9.53 and 9.63 (J_{CH-NH} = 5.6 Hz), probably owing to the existence of two conformers with different magnetic environments at the 2 position. It is unlikely that there was coupling

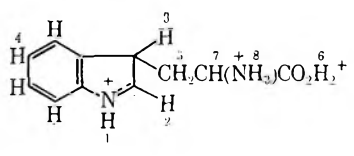
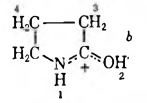
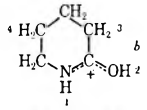
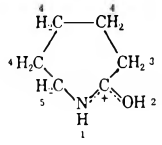


TABLE V

NMR PARAMETERS[a] (δ, PARTS PER MILLION) OF PROTONATED LACTAMS AT −60° IN FSO_3H–SbF_5–SO_2 SOLUTION

Species	Registry no.	H_1	H_2	H_3	H_4	H_5
	22483-24-5	8.55[c]	10.00[c]	3.37 t	2.77 m	4.20 t
	22483-25-6	8.70[c]	9.43[c] br	3.07 m	2.17 m	3.90 m
	22483-26-7	8.77[c]	9.60[c] m	3.20 m	2.13	3.95 m

[a] Multiplicity is indicated as follows: t, triplet; m, multiplet; br, broad. [b] See footnote *b*, Table I. [c] At −90°.

TABLE VI

NMR CHEMICAL SHIFTS (PARTS PER MILLION) AND COUPLING CONSTANTS[a] (HERTZ) OF PROTONATED α-, β-, γ-, AND δ-MONOAMINO MONOCARBOXYLIC ALIPHATIC ACIDS AND δ-AMINO *n*-BUTYLOXOCARBONIUM ION AT −60° IN FSO_3H–SbF_5–SO_2 SOLUTION

Species	Registry no.	H_1	H_2	H_3	H_4	H_5	H_6
$CH_3CH_2CH(NH_3^+)CO_2H_2^+$	22493-48-7	14.37	7.0 br	5.2[b] m 6 lines	2.70[b] m 5 lines	1.57[b] t ($J_{4,5}$ = 7.5)	
$CH_3CH(NH_3^+)CH_2CO_2H_2^+$	22493-49-8	13.57	6.43 br	3.95[b] d ($J_{3,4}$ = 6.0)	4.66[b] m	2.03[b] d ($J_{4,5}$ = 6.5)	
$CH_2(NH_3^+)CH_2CH_2CO_2H_2^+$	22493-50-1	12.80 12.97	6.17	3.57[b] t ($J_{3,4}$ = 7.0)	2.66[b] m	4.0[b] m	
$CH_2(NH_3^+)CH_2CH_2CH_2CO_2H_2^+$[c]	22493-51-2	12.57 12.80	6.07 br	3.63[b] m	2.37[b] m	2.37[b] m	3.63[b] m
$CH_2(NH_3^+)CH_2CH_2CH_2C{=}O^+$[c]	22493-52-3		6.13 br	4.63[b] t ($J_{3,4}$ = 7.0)	2.60[b] m	2.60[b] m	3.73[b] m

[a] Coupling constants are in parenthesis. Multiplicity is indicated as follows: d, doublet; t, triplet; m, multiplet; br, broad. [b] At −20°. [c] See footnote *b*, Table I.

between the protons at position 2 and position 3, since this was not observed for protonated indole or protonated indoleacetic acid. Protons 3 and 7 appeared as overlapping multiplets (2 H) centered at δ 5.30 and 5.10, while the methylene protons (5) were a broad multiplet (width = 100 Hz) centered at δ 3.50. The carboxylic protons could only be observed as a broad exchanging resonance at δ 15.3.

Lactams.—For comparison, nmr data were also obtained for protonated 2-pyrrolidinone, δ-valerolactam, and ε-caprolactam in FSO_3H–SbF_5–SO_2. These are summarized in Table V.

All three lactams were O-protonated and were quite stable even when maintained at 40° for 4 hr.

The OH and NH protons are best observed at −90°. Even at −60°, they appear as broad exchanging peaks. The assignment of the methylene groups is based on the assumption that most of the positive charge resides on the nitrogen atom.

2-Pyrrolidinone gave a particularly well-resolved spectrum. No coupling of the OH and NH protons was observed and the methylene resonance resolved into a complex pattern at 20°.

α-, β-, γ-, and δ-Amino Acids.—The nmr data for the behavior of solutions of α-, β-, and γ-aminobutyric acids and δ-valeric acid in FSO_3H–SbF_5–SO_2 are summarized in Table VI.

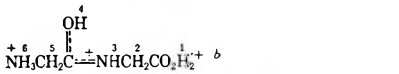
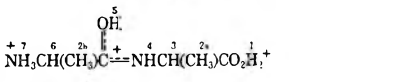
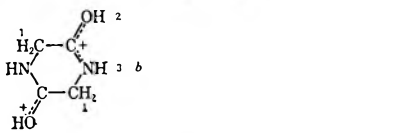
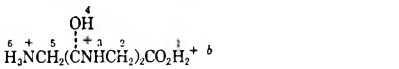
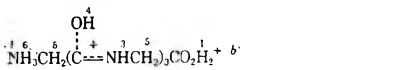
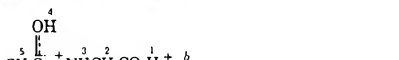
No changes were observed in the spectra of diprotonated α- and β-aminobutyric acids after they had been maintained for 4 hr at 45° and then left at room temperature for 12 hr. A complex spectrum was obtained with γ-aminobutyric acid. Apart from the assigned peaks given in Table VI, unassigned peaks were observed at δ 5.5, 7.2, 8.0, and 9.0. At −20°, a weak triplet was observed (J = 7.0 Hz) at δ 4.62. When the solution was left at −20° for several hours, this peak grew in intensity, and after the solution had been maintained at 45° for 4 hr, this triplet and the triplet at δ 3.57 were of about equal intensity. This, coupled with the decrease in intensity of the carboxyl resonance and the appearance of a new multiplet at *ca.* δ 0.5 downfield from the multiplet at δ 2.66 is interpreted in terms of dehydration of the protonated acid[3] to the extent of about 50% to yield the γ-aminopropyloxocarbonium ion.

$$H_3N^+(CH_2)_3CO_2H_2 \xrightarrow{-H_2O} H_3\overset{+}{N}(CH_2)_3CO^+$$

Diprotonated δ-aminovaleric acid formed the δ-aminobutyloxocarbonium ion slowly at −20° ($t_{1/2} \cong$ 1.5

TABLE VII

NMR CHEMICAL SHIFTS (PARTS PER MILLION) AND COUPLING CONSTANTS[a] (HERTZ) OF PROTONATED PEPTIDES AND N-ACETYLGLYCINE AT −60° IN FSO_3H–SbF_5–SO_2 SOLUTION

Species	Registry no.	H_1	H_2	H_3	H_4	H_5	H_6	H_7
	22493-53-4	14.33	5.71[c] d ($J_{2,3}$ = 5.5)	9.82[c] t ($J_{2,3}$ = 5.5)	12.90	5.15[c] q ($J_{5,6}$ = 6.0)	7.15[c] br	
	22493-54-5	14.40[d]	2.32[c] d 2.38[c] d ($J_{2a,3}$ = $J_{2b,6}$ = 7)	5.90[c] m	9.73[c] d ($J_{3,4}$ = 8)	12.83	5.23[c] m	7.07 br
	22479-35-2	5.43[c]	11.27[c]	9.47[c]				
		14.18	5.73[c] br	9.77[c] br	12.80[c] br 13.47[c] br	5.2[c] q ($J_{5,6}$ = 6)	7.23[c] br	
	22493-55-6	14.17	5.75[c] br	9.77[c] br	12.70[c] br 13.27[c] br 13.43[c] br	5.25[c] q ($J_{5,6}$ = 6)	7.27[c] br	
	22479-36-3	13.66[c]	5.45[c] d ($J_{2,3}$ = 6)	8.97[c] br	11.4[c] d ($J_{3,4}$ = 2.5)	3.07[c]		

[a] Coupling constants are in parenthesis. Multiplicity is indicated as follows: d, doublet; t, triplet; q, quadruplet; m, multiplet; br, broad. [b] See footnote *b*, Table I. [c] At −20°. [d] At −80°. [e] At −70°.

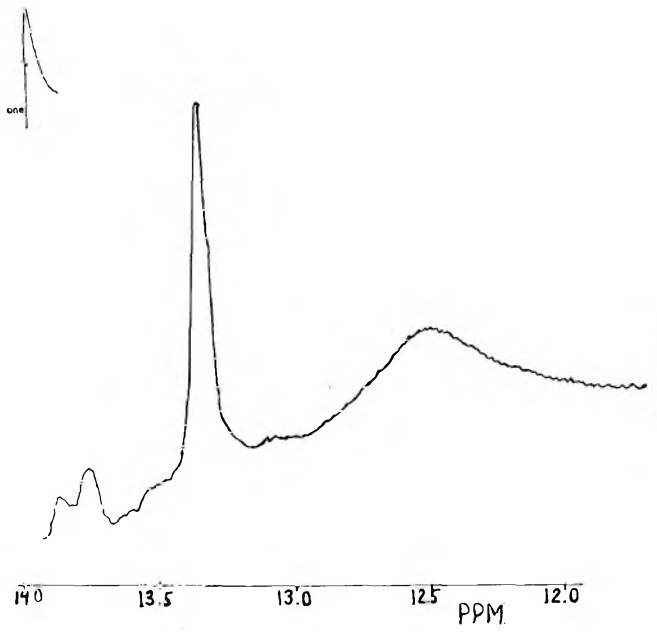


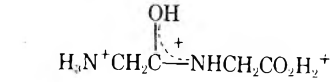
Figure 4.—Low-field portion of time-averaged 100-MHz nmr spectrum of porcine insulin in $HFSO_3$–SbF_5–SO_2 at −80°.

hr), and, after 4 hr at 45°, 97% formation of the oxocarbonium ion had taken place.

$$H_3N^+(CH_2)_4CO_2H_2^+ \xrightarrow[-H_2O]{FSO_3H-SbF_5} H_3N^+(CH_2)_4CO^+$$

In the δ-amino-*n*-butyloxocarbonium ion, there is a downfield shift of δ 1 for the methylene protons α to the oxocarbonium center, and a downfield shift of *ca.* δ 0.5 for the β-methylene protons compared with the corresponding protons in the protonated acid. These shifts are very similar to the shifts found in the dehydration of aliphatic mono- and dicarboxylic acids to oxocarbonium and dioxocarbonium ions.[3] Also, the ease of dehydration increased with increasing separation of the positively charged centers, for both of the diprotonated amino acids and the dicarboxylic acids. In none of the amino acids studied in FSO_3H–SbF_5 was there any evidence of dehydration to form the appropriate protonated lactam.

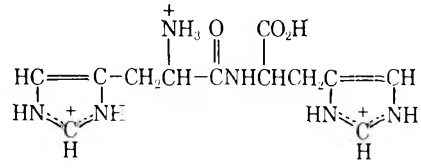
Simple Peptides.—The nmr data, obtained from solutions of N-acetylglycine and the simple peptides diglycine, triglycine, tetraglycine, dialanine, and diketopiperazine in FSO_3H–SbF_5–SO_2, are summarized in Table VII. At temperatures below −20°, diglycine was observed to exist in the strong acid solution as a stable triprotonated species. The peptide linkage was



O-protonated, the proton on oxygen at −60° appears at δ 12.90 as a sharp singlet (1 H), and at −20° the proton on nitrogen (1 H) appears at δ 9.82 as a poorly resolved triplet coupled to the adjacent methylene group. No allylic NH–OH coupling is observed. The terminal protonated amino and carboxyl (2 H) groups appear at the commonly observed amino acid shifts of δ 7.15 and 14.33. At −90°, the carboxylic resonance is a broad doublet. The methylene protons were coupled to the protons on adjacent nitrogen atoms and at −20° resolve into a doublet and a quartet, respectively. After the acid solution was heated at 40° for 2 hr, the peptide was seen to have undergone chemical change, since at −60° only peaks at δ 5.30 (4 H), 7.1 (3 H), and 10.57 (*ca.* 1 H) had been observed.

The cyclic dipeptide diketopiperazine was di-O-protonated, and at −20° the protons on oxygen (2 H) appear as a sharp singlet at δ 11.27, the protons on nitrogen (2 H) as a broad singlet at δ 9.47, and the methylene protons as a sharp singlet at δ 5.43. No allylic OH–NH coupling or vicinal NH–CH coupling are observed because of the dihedral relationship of the protons. A solution of diketopiperazine in FSO_3H–SbF_5 was not affected on being maintained for 2 hr at 40°.

The imidazole rings in histidylhistidine were observed to be protonated as in histidine itself, but, over the temperature range −20 to −90°, protonated carboxyl group, protonated peptide linkage (OH and NH), and imidazole ring NH protons could not be detected, probably because of their rapid chemical exchange.



At −60° broad lines were observed at δ 4.00 (4 H) for the methylene protons, δ 5.37 (1 H) and 5.9 (1 H) for the aliphatic methine protons, δ 7.20 (3 H) for the ammonium group, and δ 7.97 (2 H) and 9:00 (2 H) for the imidazole ring CH protons.

Triglycine was tetraprotonated. The carboxylic protons could be observed at −60°, but the two peptide linkage OH protons were best observed at −70°, when they appear at δ 12.80 and 13.47. The resonance at δ 13.47 broadened more rapidly than that at δ 12.80 with temperature rise.

Tetraglycine behaved similarly to triglycine. Pentaprotonation was observed, with the carboxyl protons being observed as a sharp peak at −60°, and the three peptide OH protons being observed at −70° as three broad exchanging peaks.

As in diglycine and triglycine, the methylene group protons adjacent to the terminal ammonium group were observed as a quartet at higher field (*ca.* δ 0.5) than the other methylene protons.

The data obtained from diprotonated N-acetylglycine provide an interesting comparison with the data from the simple peptides. At somewhat higher field than for the corresponding protons in peptides, the carboxylic protons (2 H) and the NH proton (1 H) appear at −20°, at δ 13.66 and 8.97, respectively. As in the case of the peptide linkage, O-protonation occurs and the proton on oxygen appears at −20° as a doublet as a result of allylic coupling with the NH proton (J_{OH-NH} = 2.5 Hz). The methylene protons (2 H) appear at δ 5.45 as a doublet (J_{CH_2-NH} = 6 Hz), and the methyl protons as a singlet at δ 3.07. As in the case of protonated carbamates and carbamic acids[18] and protonated formylglycine, restricted rotation about the C–N bond is assumed and the spectrum of protonated N-acetylglycine is explained on the basis of the observation of one geometrical isomer.

(18) G. A. Olah and M. Calin, *J. Amer. Chem. Soc.*, **90**, 401 (1968).

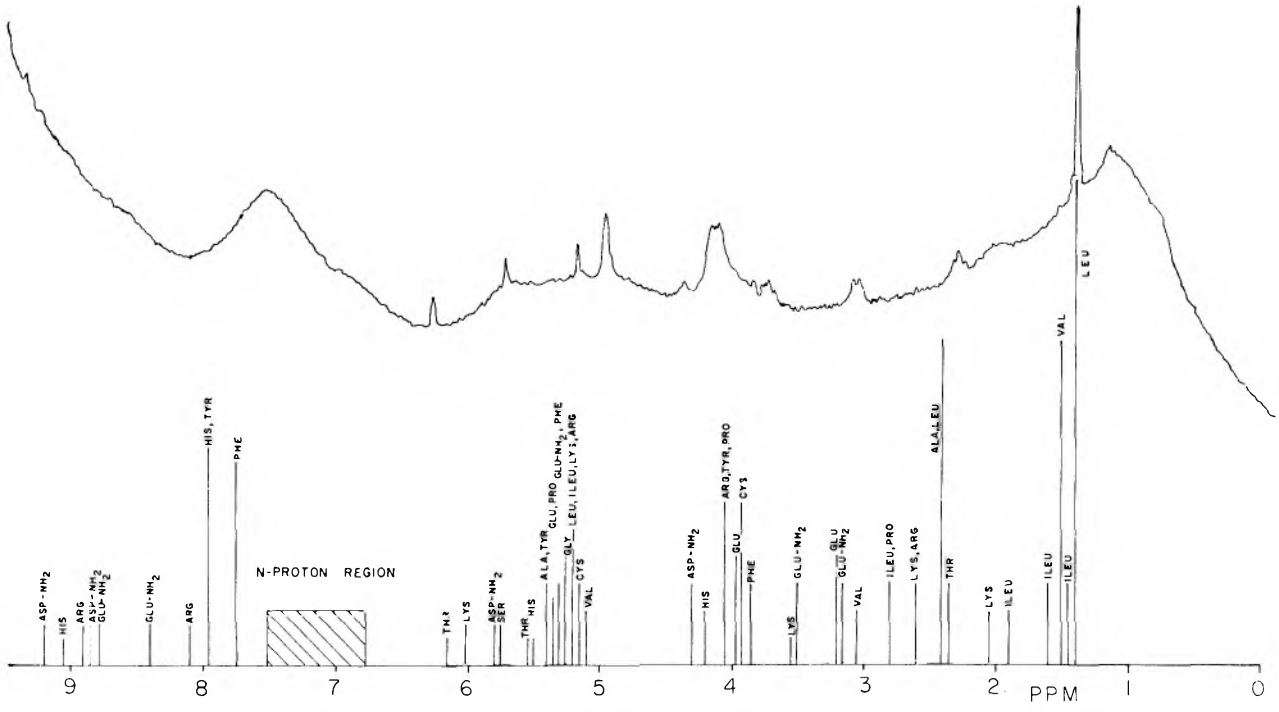


Figure 5.—100-MHz spectrum of porcine insulin in $HFSO_3$–SbF_5–SO_2 time averaged from δ 0 to 10 at −70°.

After having been maintained at 40° for 4 hr, a solution of N-acetylglycine in FSO_3H–SbF_5 was observed to have undergone some chemical change, as evidenced by the appearance of new peaks at δ 5.17 and 10.13.[19]

Porcine insulin was examined in FSO_3H–SbF_5–SO_2 solution at 100 MHz. The low-field portion (δ 11.20–16.20) of the spectrum obtained in low concentration at −80° (Figure 4) was enhanced by computer averaging (525 passes). No improvement was seen using a necessarily more dilute solution at −96.5°. The heavy absorption at δ 13.33 is assigned to the carboxylic acid protons of glutamic acid moieties and protonated hydroxyl groups of tyrosine. These resonances are at δ 13.37 and 13.00, respectively, in the corresponding amino acids in this solvent system. The two peaks at δ 13.76 and 13.87 can be assigned to the terminal carboxylic acid groups for the A and B chains. As amino acids in this medium, asparagine and alanine show absorptions at δ 15.4 and 14.37. In this case it is reasonable to expect a relative shielding effect to be observed, because of the obviously smaller charge density in this region in the protonated peptide than in the protonated amino acid. The broad signal at δ 12.50 is due to O-protonation of various peptide linkages.

The higher field portion of the spectrum (Figure 5) was time averaged at −70° for 185 passes. Figure 5 also shows schematically the absorption signals observed for the protonated amino acids in the proportions in which they comprise porcine insulin. Assignments cannot be made unequivocally by simple comparison with absorptions of the related protonated amino acids. Certain major characteristics, however, can be derived. The broad shielded absorptions as well as the sharp peak at δ 1.38 are mainly due to methyl proton absorptions of leucine, isoleucine, and valine, which comprise 72 of the 294 nonexchanging protons. The broad absorption observed at δ 5–6, is due to the respective methine protons, and that at δ 7.50 to N–H and overlapping aromatic protons.

We had hoped that extensive protonation, not only on nitrogen but also on carbonyl oxygen, would cause sufficiently varying deshielding effects in the superacid media to allow more rigorous characterization of high molecular weight peptides. Work is now in progress on some lower molecular weight peptides to determine characteristics of protonation of the peptide bond and the effect of a wide range of neighboring amino acids.

(19) As our paper was submitted for publication, a brief communication [J. L. Sudmeier and K. E. Schwartz, *Chem. Commun.*, 1646 (1968)] indicated that, in FSO_3H–SbF_5–SO_2 solution at −90°, di-, tri-, and tetraglycines, as well as L-alanylglycine, showed two low-field absorptions for the nonequivalent terminal carboxylic acid protons. Freezing out the C–O bond rotations involved in protonated carboxylic acids was known from previous work. In the present work, carried out generally at −60°, temperatures were not low enough to observe the two isomers of the protonated acids. The nonequivalencies of the carboxylic acid protons were observed only in glycine and proline. In serine, threonine, and cysteine, exchange at the temperatures studied was so rapid that no carboxylic acid proton absorption was observed.

Experimental Section

Materials.—All the compounds used were commercially available in high purity. All asymmetric compounds were of the L configuration apart from DL-glutamic acid, δ-DL-(+)-allohydroxylysine, α- and β-aminobutanoic acid, D-thyroxine, DL-histidyl-DL-histidine, and DL-alanyl-DL-alanine. The monohydrochloride of L-lysine and the monohydrochloride monohydrate of L-homoarginine, L-cysteine, and L-histidine were used.

Nmr Spectra.—A Varian Associates Model A-56/60A nmr spectrometer with a variable-temperature probe was used for all spectra except those for porcine insulin. Coupling constants are believed accurate to ±0.1 Hz. The reference standard used was capillary TMS.

The porcine insulin was examined in a Varian Associates Model HA-100 nmr spectrometer. Signal enhancement was accomplished with a Varian Model C-1024 time-averaging computer. As internal lock, the main acid peak was used, the chemical shift of which was subsequently determined relative to capillary TMS. Owing to limited space, all spectra cannot be published with this article. Spectra, however, may be obtained by ordering from ASIS National Auxiliary Publications Service, % CCM Information Corp., 909 3rd Ave., New York, N. Y. 10022, remitting $1.00 for microfiche or $3.00 for photocopies, Document No. 00602.

Preparation of Strong Acid Solutions.—Solutions were made up with at least 3 mol of 1:1 FSO_3H–SbF_5 for each site available for protonation in the solute, and the solutions were further diluted with *ca.* 3 mol of sulfur dioxide for each mol of 1:1 FSO_3H–SbF_5. The aromatic amino acids were diluted in a solution of 9:1 FSO_3H–SbF_5.

Few of the starting compounds investigated dissolved in sulfur dioxide, and the solutions were made up slowly, at low temperature, by vigorous agitation of the suspensions with the acid solusolutions, resulting in homogeneous solutions of the protonated substrates.

The presence of a large excess of acid was ensured by observing the characteristic acid peak at *ca.* δ 11.

Registry No.—Protonated histidylhistidine, 22493-22-7; protonated triglycine, 22493-23-8.

Acknowledgment.—Professor M. Bodansky is thanked for samples of porcine insulin and stimulating discussions. The research was possible through a grant from the National Institutes of Health.

Stable Carbonium Ions. LXXXIV.[1] Diprotonation of Dialkyl Hydrazodiformates and Their Cleavage to Diprotonated Hydrazodiformic Acid and Alkylcarbonium Ions

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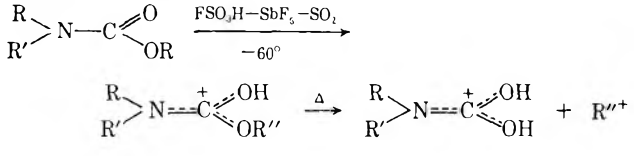
Received May 5, 1969

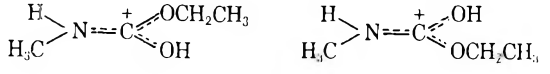
A series of dialkyl hydrazodiformates [$(RO_2CNH)_2$] has been investigated in FSO_3H–SbF_5–SO_2 and/or HF–SbF_5–SO_2 solution. Carbonyl oxygen protonation was observed in all cases, regardless of substituents, by means of low-temperature pmr spectroscopy. With certain of the diprotonated dialkyl hydrazodiformates, cleavage occurred in the extremely strong acid systems at higher temperatures to give stable alkylcarbonium ions and diprotonated hydrazodiformic acid [$(NHCO_2H_2^+)_2$]. Diprotonation of the related azodicarbonamide in strong acid media was also observed by low-temperature pmr spectroscopy.

In an earlier study we reported the observation of protonated alkyl carbamates.[3]



R, R′ = alkyl or hydrogen; R″ = alkyl

For example, in the pmr spectrum of protonated ethyl N-methyl carbamate, the proton on oxygen appears at δ 9.71 as an overlapping doublet on top of a singlet. The OH proton is expected to show two absorptions owing to *cis* and *trans* isomers (**1** and **2**) if on



1 **2**

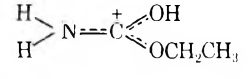
the pmr time scale rotation about the C–N bond is slow. That one of the OH resonances is a doublet (J = 2.8 Hz) is presumably due to long-range coupling in **1** with the NH proton.

Olah and Calin[3] observed that at temperatures as low as −60° protonated alkyl carbamates undergo alkyl–oxygen cleavage to give carbonium ions and protonated carbamic acids and that the rate of cleavage is tertiary alkyl carbamates > secondary > primary > methyl.

Dialkyl hydrazodiformates are bisalkyl carbamates. In an extension of our studies of protonation of weak organic bases, we investigated the chemistry of these compounds in superacid media. Protonation of the following dialkyl hydrazodiformates was examined in FSO_3H(HF)–SbF_5–SO_2 solution: dimethyl, diethyl, di-*n*-propyl, di-*n*-butyl, and di-isobutyl hydrazodiformate.

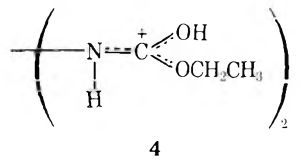
As in the case with alkyl carbamates,[3] imides,[4] amides,[5] and simple dipeptides,[6] protonation in the extremely strong acid media is observed exclusively at the carbonyl oxygen atoms for all dialkyl hydrazodiformates studied. The protonated species give well-resolved low-temperature pmr spectra in the superacid media. The spectral parameters for the diprotonated dialkyl hydrazodiformates are summarized in Table I.

As a representative case, the pmr spectrum of diprotonated diethyl hydrazodiformate (Figure 1) can be compared with that of protonated ethyl carbamate.[3] The OH proton of protonated ethyl carbamate (**3**)



3

shows a doublet (J = 2 Hz) at δ 9.86 caused by coupling to the protons on nitrogen, which show two broad singlets at δ 7.40 and 7.33. The methyl protons show a triplet at δ 1.60 and the methylene protons show a quartet at δ 4.86. In the case of diprotonated diethyl hydrazodiformate (**4**), the chemical shifts of both the



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NH and OH protons are deshielded by about 1 ppm from those in the carbamate, as would be expected for a doubly charged species such as **4**. On closer inspection the spectrum very clearly shows the presence of two virtually identical (Δ *ca.* 2 Hz) ethyl groups. Second-order splitting is ruled out, as Δ is the same for

(1) Part LXXXIII: G. A. Olah, D. L. Brydon, and R. D. Porter, *J. Org. Chem.*, **35**, 317 (1970).
(2) Postdoctoral Research Investigator, 1968–1969.
(3) G. A. Olah and M. Calin, *J. Amer. Chem. Soc.*, **90**, 401 (1968).
(4) G. A. Olah and R. H. Schlosberg, *ibid.*, **90**, 6464 (1968).
(5) T. Birchall and R. J. Gillespie, *Can. J. Chem.*, **41**, 148 (1963).
(6) G. A. Olah, D. L. Brydon, and R. D. Porter, *J. Org. Chem.*, in press.

TABLE I

NMR PARAMETERS OF DIPROTONATED DIALKYL HYDRAZODIFORMATES

R	Registry no.	Temp, °C	δ, ppm[a]						
			CH_3	α CH_2	β CH_2	γ CH_2	CH	NH	OH
Methyl	22479-47-6	−20	4.05 (s)[b] 4.02 (s)					8.25 (br, 3 NH) 8.48 (br, 1 NH)	10.80 11.20
Ethyl	22479-48-7	−30	1.42 (t, J = 7 Hz) 1.45 (t, J = 7 Hz)	4.90 (q, J = 7 Hz) 4.93 (q, J = 7 Hz)				8.62 (br, 3 NH) 8.87 (br, 1 NH)	10.90 (s, 3 OH) 11.02 (d, J = 2 Hz 1 OH)
n-Propyl	22479-49-8	−20	0.72 (t, J = 7 Hz)	4.67 (m)	1.70 (m)			8.48 (br) 8.73 (br)	11.01 11.30
Isopropyl	22479-50-1	−60	1.12 (d, J = 7 Hz)				5.30 (m)	8.32 (br, 3 NH) 8.55 (br, 1 NH)	11.08 (s) 11.37 (s)
n-Butyl	22479-51-2	−50	0.67 (t, J = 6 Hz)	4.67 (m)	1.57	1.17 (m)		8.60 (br) 8.85 (br)	11.00 (s) 11.13 (s) 11.25 (s) 11.40 (s)
Isobutyl	22479-52-3	−60	0.73 (d, J = 6 Hz)	4.47 (m)			1.97 (m)	8.72 (br) 8.93 (br)	11.09 (s) 11.33 (s) 11.43 (s) 11.58 (s)
t-Butyl[c]	22479-53-4	−60	3.68 [s, $(Me_3C)^+$]					8.90 (br)	11.47 (d, J = 3 Hz)
Azodicarbonamide	22479-54-5	−80 −20						10.62 (br)	11.75 (br) 11.63 (d, J = 3 Hz)

[a] From external capillary of tetramethylsilane. [b] Letters in parenthesis represent multiplicity of peaks: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. [c] Even at the lowest temperature studied, only the cleavage products were observed.

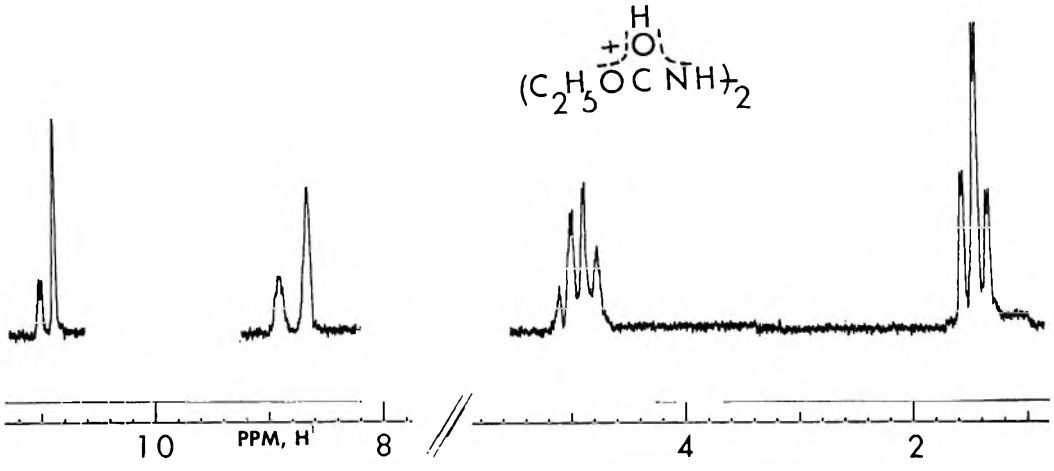
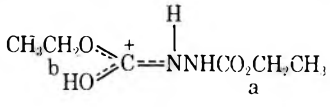


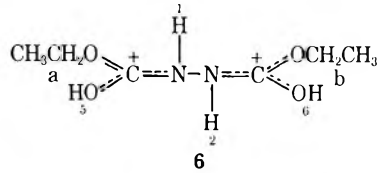
Figure 1.—Pmr spectrum of diprotonated diethyl hydrazodiformate.

both the methyl and methylene groups. Another possibility would be the presence of both di- (**4**) and monoprotonated (**5**) species in the solution. We

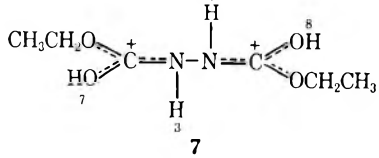


5

feel that this alternative can be disregarded, one would expect $\delta(CH_{2_a}) - \delta(CH_{2_b})$ to be much greater than the 2-Hz difference observed. The explanation favored is that partial multiple bond formation between carbon and nitrogen in the diprotonated species **4** leads to rotation about the C–N σ bond sufficiently hindered on the nmr time scale at low temperature to permit the observation of *cis* and *trans* isomers, **6** and **7**. From the structural formulas, it can be seen that, if the rotational conformers **6** and **7** can be frozen out at low temperature, then in the *ci* sconformer (**6**) CH_{2_a} is magnetically nonequivalent with CH_{2_b}. The methylene group labeled CH_{2_b} is *cis* to the NH proton, H_1, whereas CH_{2_b} is *trans* to H_2.



6

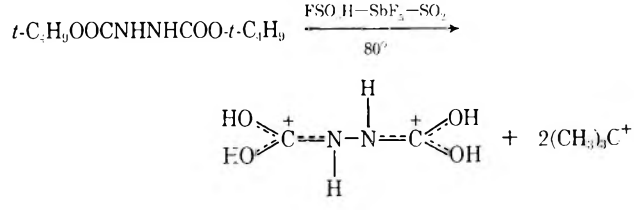


7

If the diprotonated species exists equally as conformers **6** and **7**, then three separate NH resonances should be expected, since $H_1 \neq H_2 \neq H_3 = H_4$. In fact only NH absorptions are found at δ 8.62 and 8.87 in the area ratio 3:1. This is a reasonable result, since the difference between H_2 and H_3 and/or H_4 is only in the relationship with the oxygen substituents on the carbon at the other end of the molecule. The peak at δ 8.87 (H_1) is somewhat broadened.

As is the case with the NH resonances, there should be three OH resonances ($H_5 \neq H_6 \neq H_7 = H_8$), but the magnetic environment of H_6 is very little different from those of H_7 and H_8. Indeed a sharp singlet at δ 10.90 (H_6, H_7, and H_8) and a doublet (J = 2 Hz) at δ 11.02 (H_5) are observed. The doublet presumably arises from coupling of H_5 with H_1 (*i.e.*, HN=$\overset{+}{C}$OH long-range coupling). Table I summarizes the pmr parameters of the diprotonated dialkyl hydrazodiformates investigated.

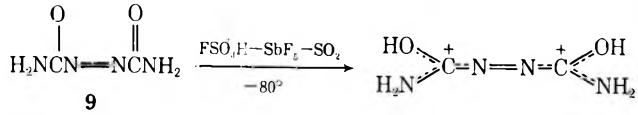
Di-*t*-butyl hydrazodiformate, when treated in "magic acid" solution, cleaves even at the lowest temperatures attainable to give the *t*-butyl cation and diprotonated hydrazodiformic acid [($^+H_2O_2CNH)_2$, **8**]. The observed enhanced deshielding of the NH and OH protons in **8** compared with those in protonated carbamic acid[3] (H_2N—$CO_2H_2^+$) reflects the dipositive ion nature of **8**.



8

When the di-*n*-butyl- and *sec*-butyl hydrazodiformates were treated with FSO_3H–SbF_5 solution and then warmed to 20°, they cleaved to give the *t*-butyl cation and diprotonated hydrazodiformic acid. The di-*n*-propyl and diisopropyl derivatives cleave very slowly at 20°, while the diprotonated dimethyl and diethyl hydrazodiformates were stable at 20°. These cleavage results are in good general agreement with the result cited above for the cleavage of protonated alkyl carbamates.

When azodicarbamate **9** was treated in FSO_3H–(HF)–SbF_5–SO_2 solution at −78° a clear, brilliant



9 **10**

orange solution was obtained. At −80°, in addition to absorptions attributable to the solvent, only two peaks are seen in the pmr spectrum, a singlet at δ 11.75 (OH) and a broad singlet at δ 10.62 (NH_2). At

−20° the upfield peak is completely submerged into one of the acid peaks, while the downfield peak has become resolved into a doublet with a 3-Hz coupling constant. The diprotonated species **10** may be inferred from the data.

Experimental Section

Dialkyl hydrazodiformates were prepared from hydrazine hydrate and the appropriate alkyl chloroformates according to the methods of Diels and Paquin[7] and Dox.[8] Di-*t*-butyl hydrazodiformate and azodicarbamate were obtained from Aldrich Chemical Co.

Nmr Spectra.—All spectra were obtained using a Varian Associates Model A-56/60A nmr spectrometer equipped with a variable-temperture probe and using external TMS as reference.

Generation of the Diprotonated Species and Their Cleavage.—Samples of the diprotonated species were prepared by dissolving 1.5 ml of FSO_3H–(HF)–SbF_5 (1:1 *M* solution) in an equal volume of sulfur dioxide at −78°. The diester (0.3 g) was dissolved in sulfur dioxide at −78° and this solution was added to the acid solution. Cleavage was attempted by warming the diprotonated species until no further reaction occurred.

Acknowledgment.—Support of the work by a grant from the National Institutes of Health is gratefully acknowledged.

(7) O. Diels and M. Paquin, *Ber. Bunsenges, Phys. Chem.* **46**, 2007 (1913).

(8) A. W. Dox, *J. Amer. Chem. Soc.*, **48**, 1951 (1926).

Stable Carbonium Ions. XCIII.[1] Protonated Thion Esters and Dithio Esters and Their Cleavage in Fluorosulfuric Acid–Antimony Pentafluoride Solution

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Received May 5, 1969

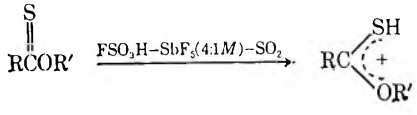
A series of protonated thion esters and dithio esters have been studied in HSO_3F–SbF_5–SO_2 solution. Thiocarbonyl sulfur protonation was observed in both cases at −60° by nmr spectroscopy. Two isomeric species were found for protonated methyl and ethyl thionacetate and protonated methyl dithioacetate at low temperature. Protonated thion esters are quite stable except for isopropyl thionacetate, which cleaved even at −70°. A mechanism for the cleavage reaction is proposed. Protonated *t*-butyl dithio esters underwent alkyl–sulfur cleavage to give protonated dithio acids and *t*-butyl cation.

No investigation of the protonation of thion esters and dithio esters in acid systems was reported so far in the literature. In continuation of previous work relating to the observation of protonated thio carboxylic acids and thio esters,[3] we considered it of interest to extend our investigation to the protonation of thion esters and dithio esters in the strong acid system 4:1 *M* FSO_3H–SbF_5 solution diluted with SO_2 at low temperature.

Results and Discussion

Protonated Thion Esters.—The following thion esters were protonated in FSO_3H–SbF_5 solution diluted with SO_2 at −60°: methyl, ethyl, and isopropyl[4] thionacetate; methyl and ethyl thionpropionate; and methyl thionbenzoate.

All the thion esters studied were protonated on thiocarbonyl sulfur atom in 4:1 *M* FSO_3H–SbF_5 solution diluted with SO_2 and gave well-resolved nmr spectra. As an example, Figure 1 shows the nmr



spectrum of protonated methyl thionacetate. Assignments of the nmr chemical shifts and coupling constants of the thion esters studied are summarized in Table I.

Protonated Thionacetates.—The proton on sulfur of protonated thionacetates (Figure 1, Table I) appeared as a singlet at δ 6.86–7.15, which is at a lower field than in protonated aliphatic thiols and sulfides.[5] In the SH region, another small quartet appeared at δ 7.00 and 6.76 for protonated methyl and ethyl thionacetate, respectively. Double-irradiation experiments indicated that this SH proton is coupled with the thioacetyl protons. The small doublets for the thioacetyl protons of this minor isomer of both protonated methyl and ethyl thionacetate were also observed (Table I). Such a long-range coupling was also observed in protonated thioacetic acid.[3] This indicates that two isomeric species (95:5) are present in both protonated methyl and ethyl thionacetate. Protonated isopropyl thionacetate gave only an SH singlet at δ 6.86.

Protonated Thionpropionates.—Protonated methyl and ethyl thionpropionate (Table I) show the proton on sulfur as a singlet at δ 7.00 and 6.86, respectively. No coupling of this proton with the thioacetyl methyl hydrogens or with the α protons of the alkyl groups was observed.

Protonated Methyl Thionbenzoate.—The proton on sulfur in protonated methyl thionbenzoate appears as a singlet at δ 7.13. Chemical shifts are summarized in Table I.

The Structure of Protonated Thion Esters.—Both protonated methyl and ethyl thionacetate show not only a strong, intense singlet for the SH proton but also give a small quartet in the SH region owing to another

(1) Part XCII: G. A. Olah, C. L. Jeuell, and A. M. White, *J. Amer. Chem. Soc.*, **91**, 3961 (1969).

(2) National Institutes of Health Predoctoral Research Investigator.

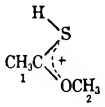
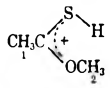
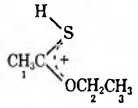
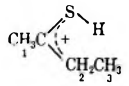
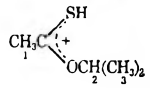
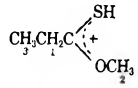
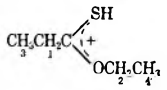
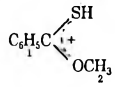
(3) G. A. Olah, A. T. Ku, and A. M. White, *J. Org. Chem.*, **34**, 1827 (1969).

(4) Protonated isopropyl thionacetate could be observed only below −80°.

(5) G. A. Olah, D. H. O'Brien, and C. U. Pittman, Jr. *J. Amer. Chem. Soc.*, **89**, 2996 (1967).

TABLE I

NMR SPECTRAL PARAMETERS FOR PROTONATED THION ESTERS IN 4:1 *M* FSO_3H–SbF_5 DILUTED WITH SO_2 AT −60° [a]

Compd	Registry no.	SH	H_1	H_2	H_3	H_4
	22479-55-6	7.15	3.33	4.73		
	22479-55-6	7.00 (q, 1)	3.16 (d, 1)	4.73		
	22479-56-7	6.85	3.13	4.95 (q, 7.0)	1.73 (t, 7.0)	
	22479-56-7	6.76 (q, 1)	2.96 (d, 1)	4.95 (q, 7.0)	1.73 (t, 7.0)	
	22479-57-8	6.86[b]	3.21[b]	5.63[b] (m)	1.78[b] (d, 7.5)	
	22479-58-9	7.00	3.60 (q, 7.0)	4.86	1.40 (t, 7.0)	
	22479-59-0	6.86	3.55 (q, 7.5)	5.05 (q, 7.5)	1.45 (t)	1.83 (t)
	22479-60-3	7.13	7.76–8.43	5.00		

[a] Chemical shifts are in parts per million from external TMS. Multiplicity is indicated as follows: d, doublet; t, triplet; q, quartet; m, mutiplet. The coupling constants are indicated in hertz next to the multiplicity. [b] At −80°.

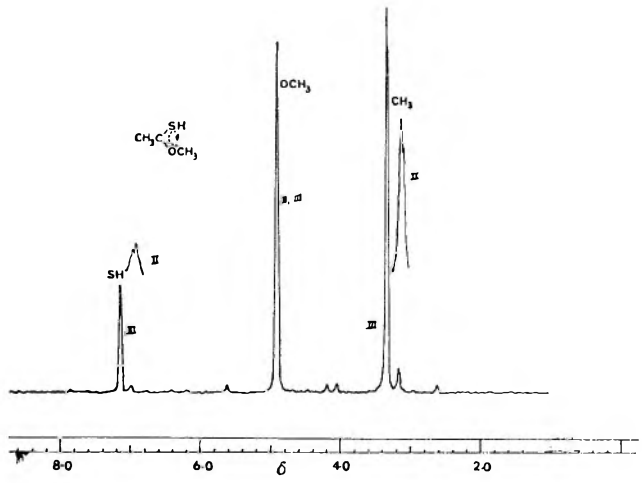
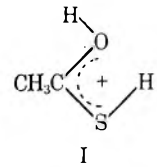


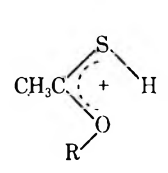
Figure 1.—The nmr spectrum of protonated methyl thionacetate.

isomeric species amounting to about 5%. In this minor isomer the SH proton is coupled with the thioacetyl protons, which appear as doublets at δ 3.16 and 2.96 for protonated methyl and ethyl thionacetate, respectively. Such long-range coupling was also observed in one of the isomers of protonated thioacetic acid in which the SH proton was *trans* to the thio-

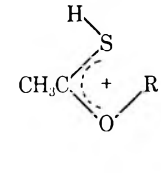


I

acetyl protons (I). The reason for this assignment was given in our previous paper on protonated thio acids.[3] In accordance with the assignment of the structure of protonated thioacetic acid, the SH proton in the minor isomer of both protonated methyl and ethyl thionacetate should have a *trans* relationship with the thioacetyl protons (II, R = CH_3, C_2H_5).



II

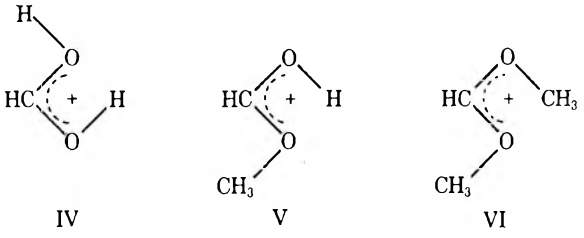


III

The SH proton of the major isomer of protonated thionacetates consequently should be *cis* to the thioacetyl protons and have structure III.

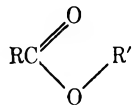
The orientation of the R group cannot be decided on the basis of the available data. However, it has been

shown[6] that protonated methyl formates of simple carboxylic acid have two isomeric forms (IV and V), in which the OH proton, the methine proton, and the methyl group are in a *cis,trans* relationship. In addition, the isomer observed for dimethoxy carbonium ion also has the *cis,trans* structure VI.[7] On the basis



IV V VI

of these observations, the orientation of the group R in protonated thionacetates is suggested to be as shown in II and III. This structural assignment is consistent with the fact that the preferred conformation of esters[8] is the one in which the alkyl group is coplanar and "*cis*" to the carbonyl oxygen (VII), thus minimizing the interaction between the lone pairs on oxygen.[9]



VII

Cleavage of Thion Esters.—We have reported previously[3] the cleavagere action of protonated thiolacetates in strong acid media in which acyl–sulfur cleavage was observed for primary and secondary thiol acetates and alkyl–sulfur cleavage was observed for *t*-butyl thiolacetates. Protonated thion esters are, however, quite stable. With the exception of protonated isopropyl thionacetate, all the protonated thion esters studied gave no significant change[10] in FSO_3H–SbF_5 solution between −60 and 15°. Protonated isopropyl thionacetate, on the other hand, could be observed only below −80° and cleavage occurred even at −75°. At −70° the nmr spectrum (Figure 2) showed the resonances of protonated isopropyl thiolacetate, protonated isopropanethiol, and methyloxocarbonium ion (acetyl cation, $CH_3C^+{=}O$). We have reported previously[3] that protonated isopropyl thiolacetate is stable in FSO_3H–SbF_5–SO_2 solution at −70°. Thus the methyloxocarbonium ion and protonated isopropanethiol formed from protonated isopropyl thionacetate at −70° cannot be due to the cleavage of intermediately formed protonated isopropyl thiolacetate.

A possible mechanism which accounts for the formation of the products in the cleavage reaction involves a

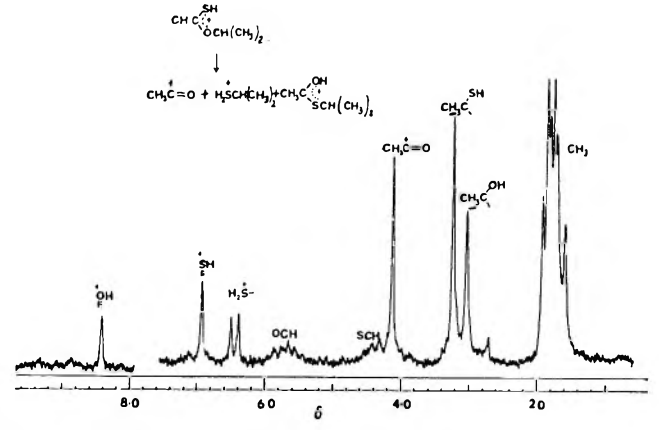
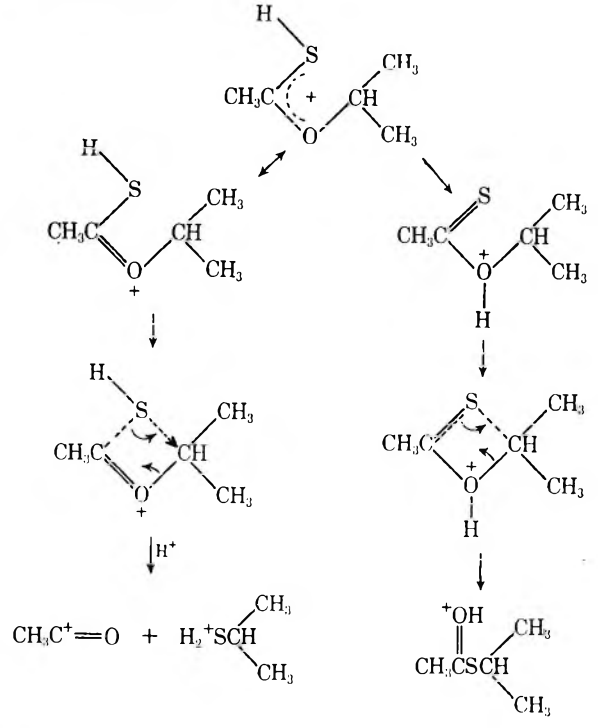
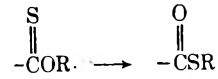


Figure 2.—The nmr spectrum of the cleavage reaction of protonated isopropyl thionacetate.

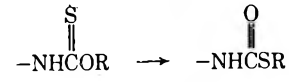
four-membered cyclic transition state formed by nucleophilic attack of the sulfur atom on the α carbon of the alkyl group.



A number of examples of rearrangement reactions of this type are known, which are formally similar to the Schönberg rearrangement[11] involving the migration of a group from oxygen to sulfur in the system



These are best known in the thionocarbamate system, the so called Newman–Kwart rearrangement,[12] and involve a change of the type



(6) G. A. Olah, D. H. O'Brien, and A. M. White, *J. Amer. Chem. Soc.*, **89**, 5694 (1967).

(7) A. M. White and G. A. Olah, *ibid.*, **91**, 2943 (1969); R. F. Borsch, *ibid.*, **90**, 5303 (1968).

(8) G. J. Karabatsos, N. Hsi, and C. E. Orzch, Jr., *Tetrahedron Lett.*, **38**, 4639 (1966), and references cited therein.

(9) N. L. Owen and N. Sheppard, *Proc. Chem. Soc.* (London), 264 (1963).

(10) This reflects the stability of $RC^+{=}O$ relative to $RC^+{=}S$, the latter being the expected result of thioacyl–oxygen cleavage if this were to occur. We have had no evidence for the formation of this ion so far.

(11) H. R. Al-Kazimi D. S. Tarbell, and D. H. Plant, *J. Amer. Chem. Soc.* **77**, 2479 (1955); D. H. Powers and D. S. Tarbell *ibid.*, **78**, 5363 (1956).

(12) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966); H. Kwart and E. R. Evans, *ibid.*, **31**, 410 (1966); H. M. Rells and G. Pezzolato, *ibid.*, **33**, 2249 (1968); K. Miyazaki, *Tetrahedron Lett.*, 2793 (1968).

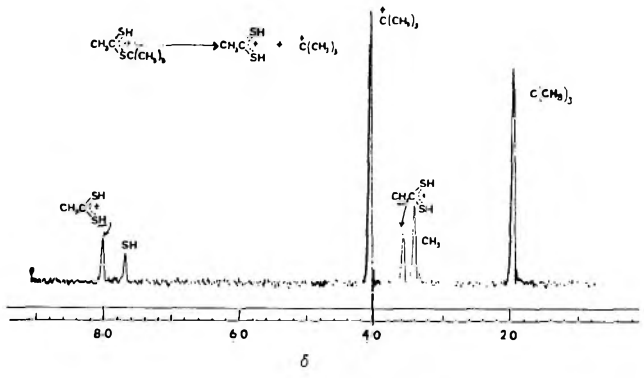
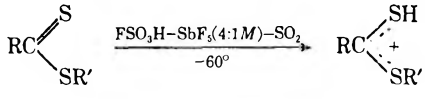
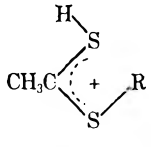


Figure 3.—The nmr spectrum of the cleavage reaction of protonated *t*-butyl dithioacetate.

Protonated Dithio Esters.—The following dithio esters were protonated in 4:1 *M* FSO_3H–SbF_5 solution diluted with SO_2 at −60°: methyl, ethyl, *n*-propyl, isobutyl, and *t*-butyl dithioacetate; *t*-butyl dithiopropionate; and methyl and isopropyl dithiobenzoate. All the dithio esters studied were protonated on the thiocarbonyl sulfur atom and gave well-resolved nmr spectra. The chemical shifts and coupling constants are summarized in Table II.

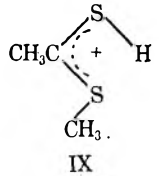


Protonated dithioacetates (Table II) show the proton on sulfur as a singlet at δ 7.38–7.65. No coupling of this proton with the thioacetyl protons or with the α protons of the alkyl groups was observed. As in the case of protonated thion esters, this SH proton is assigned *cis* to the thioacetyl group. Thus the structure of protonated dithio acetates is VIII.



VIII

The reasons for the proposed orientation of the alkyl group are the same as those already discussed in the case of protonated thion esters. At lower temperature, −90°, protonated methyl dithioacetate shows another small quartet due to the SH proton at δ 6.80 with a coupling constant of *ca.* 1 Hz. This indicates the existence of another isomeric species of protonated methyl dithioacetate, in which the SH proton and the thioacetyl group are *trans* to one another. The structure of this second isomer, present in *ca.* 5% amount, probably is as shown in IX.



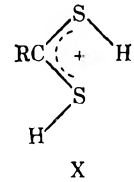
IX

Protonated methyl and isopropyl dithiobenzoate show the proton on sulfur as a singlet (Table II) at δ 7.36 and 7.60, slightly shielded when compared with the proton on sulfur in the corresponding protonated dithioacetates.

Cleavage of Protonated Dithio Esters.—Protonated primary and secondary dithio acetates are very stable. No indication of cleavage was observed even when the solutions were heated up to 100°. Protonated *t*-butyl dithioacetate and dithiopropionate, however, undergo alkyl–sulfur cleavage at −30 to −20° in 4:1 *M* FSO_3H–SbF_5 solution diluted with SO_2 to give *t*-butyl cation and the corresponding protonated dithio carboxylic acids. As an example, the nmr spectrum of the cleavage reaction of protonated *t*-butyl dithioacetate is shown in Figure 3.

Protonated methyl and isopropyl dithiobenzoate underwent cleavage reaction slowly at room temperature and −20°, respectively, to give as yet unidentified products.

Protonated Dithio Carboxylic Acids.—The nmr chemical shifts of protonated dithioacetic and dithiopropionic acid generated by the cleavage of protonated *t*-butyl dithioacetate and dithiopropionate in 4:1 *M* FSO_3H–SbF_5 solution diluted with SO_2 are given in Table III. The nmr spectrum of protonated dithioacetic acid (Figure 3) showed only one singlet at δ 8.03 for the SH protons even when the temperature was lowered as low as −100°. Integration of the peaks indicated two protons on sulfur. Protonated dithiopropionate, however, as in the case of the protonated simple carboxylic acids,[13] showed two singlets at the SH region at δ 7.90 and 7.94. This indicates, as in the case of protonated aliphatic carboxylic acids, that the two protons have nonequivalent environments and is interpreted as a consequence of structure X



X

being the predominant species. In the case of protonated dithioacetic acid, the two SH protons are probably incidently having the same chemical shift, only one singlet was observed for the SH protons.

Experimental Section

Materials.—The thion esters were prepared by the method described by Renson and Bidaine.[14] The imido ester hydrochlorides were first prepared by the reaction of the appropriate nitriles and alcohols with anhydrous hydrogen chloride in dry hexane as solvent at ice-bath temperature. The imido ester hydrochloride was then treated with hydrogen sulfide in quinoline at 0° to give the corresponding thion ester.

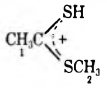
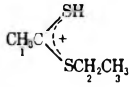
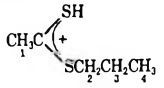
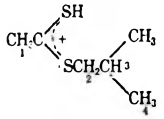
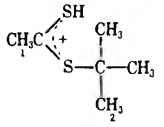
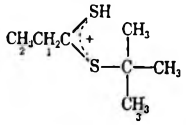
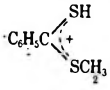
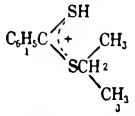
Dithio esters were prepared by the reaction of hydrogen sulfide with thio imido ester hydrochlorides in pyridine. The thio

(13) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **89**, 3591 (1967).

(14) M. Renson and J. Bidaine, *Bull. Soc. Chim. Belges.*, **70**, 519 (1961).

TABLE II

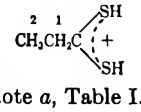
NMR SPECTRAL PARAMETERS FOR PROTONATED DITHIO ESTERS IN 4:1 *M* FSO_3H–SbF_5 SOLUTION DILUTED WITH SO_2 AT −60° [a]

Compd	Registry no.	SH	H_1	H_2	H_3	H_4
	22479-61-4	7.38	3.10	3.30		
	22479-62-5	7.40	3.35	3.66 (q, 7.5)	1.73 (t, 7.5)	
	22479-63-6	7.65	3.50	3.75 (t, 7.5)	2.21 (m)	1.33 (t, 7.5)
	22528-33-2	7.58	3.43	3.58 (d, 7.0)	2.71 (m)	1.31 (d, 7.0)
	22479-64-7	7.70	3.40	1.96		
	22479-65-8	7.62	3.65 (q, 7.5)	1.63 (t)	1.93	
	22479-66-9	7.36	7.76–8.10	3.33		
	22479-67-0	7.60	8.00–8.33	4.55 (m, 7.0)	1.93 (d, 7.0)	

[a] See footnote *a*, Table I.

TABLE III

NMR SPECTRAL PARAMETERS FOR PROTONATED DITHIO CARBOXYLIC ACIDS IN 4:1 *M* FSO_3H–SbF_5 SOLUTION DILUTED WITH SO_2 AT −60° [a]

Compd	Registry no.	SH	H_1	H_2
	22479-68-1	8.03	3.57	
	22479-69-2	7.90 7.94	3.83 (q, 7.5)	1.78 (tq, 7.5)

[a] See footnote *a*, Table I.

imido ester hydrochlorides were prepared by the reaction of the appropriate nitrile and mercaptan and anhydrous hydrogen chloride in petroleum ether.[15]

Nmr Spectra.—Varian Associates Model A-56/60A and HA 100 spectrometers with variable-temperature probes were used for all spectra. Chemical shifts are reported in δ (parts per million) from external (capillary) tetramethylsilane.

Preparation of Solutions.—The procedure used for the preparation of solutions of the protonated thion esters and dithio esters was identical with that described previously.[6]

Acknowledgment.—Support of this work by a grant from the National Institutes of Health is gratefully acknowledged.

(15) (a) C. S. Marvel, P. DeRadzitzky, and J. J. Brader, *J. Amer. Chem. Soc.*, **77**, 5997 (1955). (b) In the preparation of methyl and isopropyl dithiobenzoate, anhydrous ether was used as solvent.

Reactions of *t*-Butyl Peroxy Esters. X. Preparation of Dialkyl *t*-Butyl Phosphates from Dialkyl *t*-Butylperoxy Phosphates, Dialkyl Phosphorochloridates, and Dialkyl Phosphorochloridites[1]

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Received June 6, 1969

Dialkyl *t*-butyl phosphates (**1**, R = Me, Et, *i*-Pr) are produced in low yield by the reaction of the corresponding dialkyl *t*-butylperoxy phosphates (**2**) with triphenylphosphine (**4**), and by the reaction of the corresponding dialkyl phosphorochloridites (**8**) with *t*-butyl hydroperoxide (**7**) in the presence of pyridine. Esters **1** (R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, Ph, $PhCH_2$) are produced in high yield by the reaction of the corresponding dialkyl phosphorochloridates (**6**) with potassium *t*-butoxide at 8–10° under anhydrous conditions.

Although alkoxy derivatives of phosphorus are, in general, quite stable, *t*-butoxy derivatives are usually unstable and their preparation has often presented difficulty.[2] A survey of the literature reveals that the majority of the work reported on *t*-butoxy derivatives of phosphorus deals with di- and tri-*t*-butoxy phosphorus compounds.[2f-h,3]

As part of another investigation, it was of interest to develop a general method for the preparation of dialkyl *t*-butyl phosphates (**1**, R = alkyl). The literature survey showed that only two compounds of this type (**1**, R = Me, Et) have been prepared,[4] the rest of the

$$\underset{\mathbf{1}}{(RO)_2P(O)OCMe_3}$$

reported mono-*t*-butoxy phosphorus compounds being either derivatives of trivalent phosphorus[3i,5] or other derivatives of pentavalent phosphorus.[3h-k,4a,6]

During our investigation of the decomposition of di-*n*-butyl *t*-butylperoxy phosphate (**2**, R = *n*-Bu), a product was suggested to be **1** (R = *n*-Bu).[7] It was of interest, therefore, to synthesize this compound for verification of its structure.

$$\underset{\mathbf{2}}{(RO)_2P(O)OOCMe_3}$$

The reduction of peroxy esters of carboxylic acids (**3**) to the corresponding esters by triphenylphosphine (**4**) has been described.[8]

$$\underset{\mathbf{3}}{RC(O)OOCR'_3} + \underset{\mathbf{4}}{Ph_3P} \longrightarrow RC(O)OCR'_3 + \underset{\mathbf{5}}{Ph_3P(O)}$$

R = alkyl, aryl, aralkyl; R′ = alkyl

As part of a general investigation of the chemistry of **2**, an attempt was made to prepare **1** (R = *n*-Bu) by the reaction of the corresponding peroxy phosphate (**2**, R = *n*-Bu) with **4**. However, since our previous experience had shown that, in homologous series of dialkyl phosphorochloridates, dialkyl phosphates, tetraalkyl pyrophosphates, and dialkyl *t*-butylperoxy phosphates, the di-*n*-butyl member of the series is usually the most difficult to handle, the investigation was commenced on other peroxy phosphates which had proved to be more stable. Thus, the reaction of **2** (R = Me, Et, *i*-Pr) with an ethereal solution of **4** gives **5** and the corresponding dialkyl *t*-butyl phosphate **1** in 9 to 36% yields.

$$\underset{\mathbf{2}}{(RO)_2P(O)OOCMe_3} + \mathbf{4} \longrightarrow \underset{\mathbf{1}}{(RO)_2P(O)OCMe_3} + \mathbf{5}$$

R = Me, Et, *i*-Pr

Removal of **5** and unreacted **4** from the reaction mixture presents difficulty. Filtration and column chromatography on neutral alumina remove only a portion of **4** and **5**. In the cases of **1** (R = Me, Et, *i*-Pr) the esters are stable enough so that distillation in the presence of **4** and **5** is possible. When esters **1** (R = *n*-Bu, *i*-Bu) are distilled in the presence of **4** and **5** the esters decompose and intractable residues are obtained. Thus, it appears that although **1** (R = Me, Et, *i*-Pr) can be prepared in low yield by the reduction of the corresponding **2** with **4**, esters **1** (R = *n*-Bu, *i*-Bu) cannot be prepared by this method.

(1) (a) This investigation was supported in part by a grant from the Public Health Service. U. S. Department of Health, Education, and Welfare (GM 14932-01), and in part by a grant from the Graduate School of the University of Wisconsin. One of us (K. D. S.) was supported by a National Science Foundation Undergraduate Research Participation Grant (GY-4399) during the summer of 1968. (b) The results were presented in part in preliminary communications in *Chem. Commun.*, **14**, 453 (1966), and *Syn., Int. J. Methods Syn. Org. Chem.*, 38 (1969), and in part in a talk at the International Symposium on the Chemistry of Organic Peroxides in Berlin, DDR, Sept 1967. (c) Part IX: G. Sosnovsky and D. J. Rawlinson, *J. Org. Chem.*, **34**, 3469 (1969). (d) This paper is dedicated to Dr. Eugen Müller, Profesor of chemistry, University of Tübingen, in honor of the occasion of his 65th birthday, June 21, 1970.

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In order to circumvent the purification difficulties encountered in the reactions with **4**, other reducing agents for peroxides were investigated. Although several methods for the reduction of various types of carbon peroxides have been developed,[9] little is known about the reduction of organometallic and organometalloid peroxides.[10] For example, reduction of trimethyl(*t*-butylperoxy)silane[11] and unsymmetrical tin peroxides[12] with sodium sulfite have been reported. Reaction of **2** (R = *i*-Pr) with anhydrous sodium sulfite at 35° for 24 hr does not proceed, and the peroxy phosphate is recovered in high yield. The reaction of **2** (R = *i*-Pr) with sodium bisulfite in refluxing carbon tetrachloride for 2 hr produces **1** (R = *i*-Pr) only in trace amounts. Prolonged reaction times and elevated temperatures effect no improvement in yield. Thus, this reduction method is not applicable to this type of phosphorus peroxide.

The preparation of dialkyl *t*-butylperoxy phosphates (**2**) by the reaction of the corresponding dialkyl phosphorochloridates (**6**) with *t*-butyl hydroperoxide (**7**) in the presence of pyridine has been described.[13]

$$\underset{6}{(RO)_2P(O)Cl} + \underset{7}{Me_3COOH} \xrightarrow{\text{pyridine}} \underset{2}{(RO)_2P(O)OOCMe_3} + Py\cdot HCl$$

R = alkyl, Ph, $PhCH_2$

However, the analogous reaction of dialkyl phosphorochloridites (**8**, R = Me, Et, *i*-Pr) with **7** in the presence of pyridine produces the corresponding dialkyl *t*-butyl phosphate (**1**) and tetraalkyl pyrophosphate (**9**) instead of the trivalent peroxide (**10**).

$$\underset{8}{(RO)_2PCl} + \underset{7}{} \xrightarrow{\text{pyridine}} \underset{1}{(RO)_2P(O)OCMe_3} + \underset{9}{(RO)_2P(O)OP(O)(OR)_2}$$

$$\underset{10}{(RO)_2POOCMe_3}$$

R = Me, Et, *i*-Pr

Similarly, the reaction of diphenylchlorophosphine (**11**) with **7** gives diphenyl *t*-butyl phosphinate (**12**) and diphenylphosphinic acid (**13**).

$$\underset{11}{Ph_2PCl} + 7 \xrightarrow{\text{pyridine}} \underset{12}{Ph_2P(O)OCMe_3} + \underset{13}{Ph_2P(O)OH}$$

Further attempts to prepare peroxide **10** (R = Et) by the reaction of diethyl phosphorochloridite with sodium *t*-butyl peroxide were unsuccessful and produced triethyl phosphate (**14**, R = Et) as the only isolable

$$\underset{8}{(RO)_2PCl} + NaOOCMe_3 \longrightarrow \underset{14}{(RO)_3P(O)}$$

R = Et

product. This result seems to exclude the possibility of formation of **1** *via* the rearrangement of **10** under the present experimental conditions.

On the basis of these results, the following reaction scheme for the formation of **1** is proposed. Reduction of **7** by **8** probably proceeds *via* the intermediate shown[14] to produce dialkyl phosphorochloridate (**6**) and *t*-butyl alcohol. Reaction of **6** with *t*-butyl alcohol in the presence of pyridine produces **1**, whereas the reaction of **6** with *t*-butyl alcohol at room temperature in the absence of pyridine is reported[15] not to proceed.

$$\underset{8}{(RO)_2PCl} + \underset{7}{Me_3COOH} \longrightarrow$$

$$[(RO)_2\overset{+}{P}\!-\!Cl \quad O\text{-----}\bar{O}\cdot CMe_3] \longrightarrow \quad (RO)_2P(O)Cl + Me_3COH$$

$$\underset{6}{}$$

$$6 + Me_3COH \xrightarrow{\text{pyridine}} \underset{1}{(RO)_2P(O)OCMe_3}$$

Simultaneously, **6** reacts with **7** in the presence of pyridine to produce perester **2**. Under the experimental conditions it is not possible to isolate **2**, since we have found[7,16] that **2** undergoes a facile decomposition to give the corresponding dialkyl phosphate **15**, trialkyl phosphate (**14**), and tetraalkyl pyrophosphate (**9**).

$$\underset{2}{(RO)_2P(O)OOCMe_3} \longrightarrow$$

$$\underset{15}{(RO)_2P(O)OH} + \underset{14}{(RO)_3P(O)} + \underset{9}{(RO)_2P(O)OP(O)(OR)_2}$$

Heating of ester **1** (R = *i*-Pr) at 50° and 0.1 mm for 7 hr in the presence of pyridine produced no change in composition. The reaction of **6** (R = Et) with pyridine under anhydrous conditions at room temperature also did not proceed. Thus, it seems that **9**, **14**, and **15** are not derived from ester **1** or peroxide **10**. It appears, therefore, that oxidation of **8** occurs as the first step in its reaction with **7** and that the products are derived from the subsequent reaction of oxidation product **6** with either *t*-butyl alcohol or *t*-butyl hydroperoxide.

On the basis of these results, it is evident that neither the reduction of **2** with triphenylphosphine nor the reaction of **8** with *t*-butyl hydroperoxide is a general method for the preparation of **1**.

The kinetics of the reaction of **6** (R = Ph) with potassium *t*-butoxide have been described; however, no isolation of **1** (R = Ph) has been reported.[17] In

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contrast, the reaction of **6** (R = Me) with sodium *t*-butoxide yields[4a] **1** (R = Me), and the reaction of **6** (R = Et) with a mixture of sodium and boiling *t*-butyl alcohol yields[4b] **1** (R = Et).

Since sodium *t*-butoxide is not a readily available starting material, and reaction of **6** (R = *i*-Pr) with sodium in refluxing *t*-butyl alcohol did not produce the desired product, the reactions of **6** (R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, Ph, $PhCH_2$) with commerically available potassium *t*-butoxide were investigated.

$$\underset{\mathbf{6}}{(RO)_2P(O)Cl} + KOCMe_3 \longrightarrow \underset{\mathbf{1}}{(RO)_2P(O)OCMe_3}$$

R = Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, Ph, $PhCH_2$

The reaction proceeds smoothly in all cases at 10° to produce **1** in good to excellent yield. It has been found, however, that it is necessary to maintain *strictly anhydrous conditions* during the reaction.

Esters **1** (R = Me, Et, *n*-Pr, *i*-Pr) are moderately stable and can be readily distilled under vacuum. However, esters **1** (R = *n*-Bu, *i*-Bu) can be distilled only in small quantities through a short-path distillation head and can be stored for only a few hours at −20°. Esters **1** (R = Ph, $PhCH_2$) are unstable at −20° and cannot be distilled; they have been identified by nmr.

Comparison of the physical constants and spectral characteristics (ir, nmr) of **1** (R = *n*-Bu) with those of the material which we have previously[7] reported to be **1** (R = *n*-Bu) indicates that these materials are not identical. We have now identified this material[7] to be tri-*n*-butyl phosphate **14** (R = *n*-Bu). This result is more compatible with other data of our investigation on the decomposition of dialkyl *t*-butylperoxy phosphates (**2**). The results of that study will be described at a later date.[16]

Experimental Section

Boiling points and melting points are uncorrected. Nmr spectra were obtained on a Varian HA-100 spectrometer on 10% (v/v) samples in carbon tetrachloride using an internal TMS standard. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill., and by Mr. W. Saschek. Molecular weight determinations were performed cryoscopically in benzene.

t-Butyl hydroperoxide (Lucidol Division, Wallace and Tiernan, Inc.) was concentrated by discarding the fraction up to bp 40° (40 mm). Pyridine was distilled under nitrogen and stored over sodium hydroxide. Triethyl phosphate was obtained from Eastman Kodak and was purified by distillation before use. All other materials were best commercial grade used without further purification. The petroleum ether used had bp 20–40°.

Dialkyl phosphorochloridates (**6**) and dialkyl *t*-butylperoxy phosphates (**2**) were prepared by the methods described in an earlier paper.[13b]

Tetraethyl pyrophosphate (**9**, R = Et), bp 104° (0.1 mm), $n^{25}D$ 1.4166, was prepared as described in an earlier paper[7] from diethyl *t*-butylperoxy phosphate (**2**, R = Et).

Anal. Calcd for $C_8H_{20}O_7P_2$: C, 33.00; H, 6.93. Found: C, 32.96; H, 6.84.

Tetraisopropyl pyrophosphate (**9**, R = *i*-Pr), bp 110° (0.1 mm), $n^{25}D$ 1.4163, was prepared as above from diisopropyl *t*-butylperoxy phosphate (**2**, R = *i*-Pr).

Anal. Calcd for $C_{12}H_{28}O_7P_2$: C, 41.67; H, 8.20. Found: C, 41.93; H, 8.37.

Sodium *t*-butyl peroxide was prepared by the method of Bartlett and McBride.[18] Thus, 90 g (1.0 mol) of *t*-butyl hydroperoxide was added at room temperature to a slurry of 24 g (0.5 mol) of sodium hydride (50% dispersion in oil). The mixture was stirred at room temperature for 24 hr and filtered. The precipitate was dried at room temperature (10 mm) for 24 hr.

Anal. Calcd for $C_4H_9O_2Na$: active oxygen, 14.3; equiv wt, 112. Found: active oxygen, 13.9; equiv wt, 108.

Dialkyl Phosphorochloridites. A General Procedure.[19]—To 87 ml (1.0 mol) of phosphorus trichloride in 750 ml of benzene was added at −5 to 0° 80 ml (1.0 mol) of pyridine. The mixture was stirred at 0° for 15 min and then a solution of 160 ml (1.0 mol) of N,N-diethylaniline and 1.0 mol of the required alcohol was added at 0–5°. The mixture was stirred at 0–5° for 15 min and another 1.0 mol of alcohol was added at 0–5°. The mixture was stirred at 10–15° for 1.5 hr and filtered. The filtrate was concentrated [30–40° (30 mm)] and distilled giving dialkyl phosphorochloridite (**8**), Table I.

TABLE I
DIALKYL PHOSPHOROCHLORIDITES (8)

R	Bp, °C (mm)	$n^{25}D$	Yield, %	Lit.[19] bp, °C (mm)
Et	55–57 (25)	1.4365	28	54 (25)
i-Pr	58–60 (12)	1.4260	40	62–64 (12)
n-Pr	69–71 (8)	1.4385	19	80 (17)

Reduction of Dialkyl *t*-Butylperoxy Phosphate. A. Reaction of Dimethyl *t*-Butylperoxy Phosphate (2, R = CH_3) with Triphenylphosphine (4).—To a solution of 26.2 g (0.1 mol) of triphenylphosphine in 200 ml of ether was added at 35° a solution of 19.8 g (0.1 mol) of dimethyl *t*-butylperoxy phosphate in 50 ml of ether. After the addition was complete, the mixture was stirred and refluxed for 2 hr and filtered. The filtrate was concentrated and distilled giving 2 g (11%) of dimethyl *t*-butyl phosphate (1, R = CH_3): bp 53–55° (0.2 mm); $n^{25}D$ 1.4074 [lit.[4a] bp 60° (0.07 mm)]; nmr δ 1.44 [s, 9, $(CH_3)_3CO$], 3.61 [d, J = 11 Hz, $(CH_3O)_2P(O)$].

B. Reaction of Diethyl *t*-Butylperoxy Phosphate (2, R = Et) with Triphenylphosphine (4).—To a refluxing solution of 13.1 g (0.05 mol) of triphenylphosphine in 125 ml of ether was added dropwise over 30 min a solution of 11.3 g (0.05 mol) of diethyl *t*-butylperoxy phosphate in 50 ml of ether. The mixture was refluxed for 3.5 hr after the addition was completed and was treated as above giving 1.45 g (9.1%) of diethyl *t*-butyl phosphate (1, R = Et): bp 48–50° (0.02 mm); $n^{25}D$ 1.4092 [lit.[4b] bp 63–66° (1 mm); $n^{35}D$ 1.4042].

Anal. Calcd for $C_8H_{19}O_4P$: C, 45.71; H, 9.11; mol wt, 210. Found: C, 45.98; H, 9.19; mol wt, 204.

C. Reaction of Diisopropyl *t*-Butylperoxy Phosphate (2, R = *i*-Pr) with Triphenylphosphine (4).—To a solution of 13.1 g (0.05 mol) of triphenylphosphine in 100 ml of ether was added at 25° a solution of 12.7 g (0.05 mol) of diisopropyl *t*-butylperoxy phosphate in 100 ml of ether. After the addition was completed, the mixture was stirred at ambient temperature for 4 hr and was treated as above giving 4.28 g (36%) of diisopropyl *t*-butyl phosphate (1, R = *i*-Pr): bp 53–55° (0.1 mm); $n^{25}D$ 1.4079.

Anal. Calcd for $C_{10}H_{23}O_4P$: C, 50.41; H, 9.73; mol wt, 238. Found: C, 50.23; H, 9.77; mol wt, 225.

D. Reaction of Di-*n*-butyl *t*-Butylperoxy Phosphate (2, R = *n*-Bu) with Triphenylphosphine (4).—To a solution of 2.62 g (0.01 mol) of triphenylphosphine in 100 ml of ether was added at room temperature a solution of 2.82 g (0.01 mol) of di-*n*-butyl *t*-butylperoxy phosphate in 50 ml of absolute ether. After the addition was complete, the mixture was stirred at ambient temperature for 15 hr and was treated as above, giving 2.63 g of an unresolvable mixture of triphenylphosphine oxide (**5**), di-*n*-butyl phosphate (**15**, R = *n*-Bu), and tetra-*n*-butyl pyrophosphate (**9**, R = *n*-Bu), which were identified by tlc on silica gel G.

E. Reaction of Diisopropyl *t*-Butylperoxy Phosphate (2, R = *i*-Pr) with Sodium Bisulfite. 1.—A solution of 12.7 g (0.05 mol) of diisopropyl *t*-butylperoxy phosphate, 50 ml of ether, 10.4 g (0.1 mol) of sodium bisulfite, and 50 ml of water was stirred at 30° for 25 hr. The aqueous layer was separated and extracted with ether (two 50-ml portions). The combined organic solutions were concentrated and distilled giving 8.5 g (67%) of diisopropyl *t*-butylperoxy phosphate [bp 63–66° (0.05 mm); $n^{25}D$ 1.4135] and traces of diisopropyl *t*-butyl phosphate, which was identified by tlc on silica gel G.

2.—A slurry of 10.4 g (0.10 mol) of sodium bisulfite and 12.7 g (0.05 mol) of diisopropyl *t*-butylperoxy phosphate was stirred

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(19) J. Michalski, T. Modro, and A. Zwierzak, *J. Chem. Soc.*, 4904 (1961).

for 168 hr at room temperature and distilled giving 6.2 g (49%) of diisopropyl *t*-butylperoxy phosphate.

3.—A mixture of 10.4 g (0.1 mol) of sodium bisulfite, 25 ml of water, 12.7 g (0.05 mol) of diisopropyl *t*-butylperoxy phosphate, and 50 ml of carbon tetrachloride was refluxed for 2 hr. The aqueous layer was separated and extracted with ether (two 50-ml portions). The combined organic solutions were concentrated and distilled giving 9.7 g (76%) of diisopropyl *t*-butylperoxy phosphate.

F. Reaction of Diisopropyl *t*-Butylperoxy Phosphate (2, R = *i*-Pr) with Sodium Sulfite.—A mixture of 25.2 g (0.2 mol) of sodium sulfite, 12.7 g (0.05 mol) of diisopropyl *t*-butylperoxy phosphate, and 25 ml of ether was refluxed for 24 hr and filtered. The filtrate was concentrated and distilled giving 10 g (79%) of diisopropyl *t*-butylperoxy phosphate.

Reaction of Dimethyl Phosphorochloridite (8, R = Me) with *t*-Butyl Hydroperoxide (7) and Pyridine.—The reaction flask was charged with 12.8 g (0.01 mol) of dimethyl phosphorochloridite and 250 ml of petroleum ether (bp 20–40°) in a nitrogen-filled glove box and was then removed and rapidly fitted with thermometer, dropping funnel, stirrer, and condenser. A slow stream of nitrogen was started and a solution of 9.0 g (0.10 mol) of *t*-butyl hydroperoxide and 7.9 g (0.10 mol) of pyridine was added dropwise at 8–12°. The mixture was warmed to room temperature over 1 hr and filtered. The filtrate was concentrated and fractionated through a 10-cm Vigreux column giving 3.42 g (19%) of dimethyl *t*-butyl phosphate (1, R = CH_3): bp 44–48° (0.1 mm); $n^{25}D$ 1.4075.

Reaction of Diethyl Phosphorochloridite (8, R = Et) with *t*-Butyl Hydroperoxide (7) and Pyridine. 1.—To a solution of 15.6 g (0.10 mol) of diethyl phosphorochloridite and 100 ml of pentane was added under nitrogen at −15° a solution of 10 g (0.11 mol) of *t*-butyl hydroperoxide and 10 ml (0.12 mol) of pyridine. The mixture was stirred at −5 to 5° for 2 hr and then filtered. The filtrate was concentrated and an ethereal solution of the residual oil was washed with 10% (v/v) aqueous sodium bicarbonate, dried (Na_2SO_4), concentrated, and distilled giving 3.5 g (16%) of diethyl *t*-butyl phosphate (1, R = Et): bp 48–51° (0.14 mm); $n^{25}D$ 1.4095.

2.—To a solution of freshly distilled diethyl phosphorochloridite (11.7 g, 0.075 mol) in 100 ml of petroleum ether was added at −20 to −15° a solution of 7.20 g (0.08 mol) of *t*-butyl hydroperoxide in 5.92 g (0.075 mol) of pyridine. The reaction was carried out in a nitrogen filled glove box and a slow stream of dried (H_2SO_4) nitrogen was passed through the reaction vessel during the addition. The mixture was warmed to room temperature over 3 hr and was filtered in the glove box. The filtrate was concentrated and distilled giving 2 g (17%) of tetraethyl pyrophosphate (9, R = Et) [bp 119–121° (0.2 mm); $n^{25}D$ 1.4223] and 7.0 g (44%) diethyl *t*-butyl phosphate (1, R = Et) [bp 53–55° (0.3 mm); $n^{25}D$ 1.4109].

Reaction of Diisopropyl Phosphorochloridite (8, R = *i*-Pr) with *t*-Butyl Hydroperoxide (7) and Pyridine.—To a solution of 18.5 g (0.10 mol) of diisopropyl phosphorochloridite in 100 ml of petroleum ether was added under nitrogen at −15 to −10° a solution of 10 g (0.11 mol) of *t*-butyl hydroperoxide and 10 ml of (0.12 mol) pyridine in 25 ml of petroleum ether. The mixture was stirred for 0.75 hr at 0° and filtered. The filtrate was washed with aqueous sodium bicarbonate (4:1, v/v, 25 ml) and then with 25 ml of water. The organic layer was dried (Na_2SO_4), concentrated, and distilled giving 3.0 g (13%) of diisopropyl *t*-butyl phosphate (1, R = *i*-Pr) [bp 45–46° (0.15 mm), $n^{25}D$ 1.4092] and 2.9 g (17%) of tetraisopropyl pyrophosphate (9, R = *i*-Pr) [bp 114° (0.25 mm), $n^{25}D$ 1.4196].

Reaction of Diethyl Phosphorochloridite (8, R = Et) with Sodium *t*-Butyl Peroxide.—The reaction vessel was charged with 12.3 g (0.11 mol) of sodium *t*-butyl peroxide and 350 ml of petroleum ether in a nitrogen-filled glove box. The flask was fitted rapidly with dropping funnel, stirrer, thermometer, and condenser. A slow stream of nitrogen was maintained in the system during the reaction. Diethyl phosphorochloridite (15.6 g, 0.10 mol) was added over 0.5 hr at 6–10°. The cooling bath was removed and the mixture was stirred for 0.75 hr and then filtered. The filtrate was concentrated (25°) and distilled giving 2.3 g (25%) of triethyl phosphate (14, R = Et): bp 48–51° (0.15 mm); $n^{25}D$ 1.4041; nmr (CCl_4) δ 1.34 (t, 3, J = 6 Hz, CH_3CH_2O), 4.02 (m, 2, CH_3CH_2O); ir 1280 (P=O).

Reaction of Diisopropyl *t*-Butyl Phosphate (1, R = *i*-Pr) with Pyridine.—A solution of 11.9 g (0.05 mol) of diisopropyl *t*-butyl phosphate and 3.95 g (0.05 mol) of pyridine was heated at 50° (0.1 mm) for 7 hr and distilled giving 10.6 g (89%) of diisopropyl *t*-butyl phosphate (1, R = *i*-Pr): bp 54–56° (0.25 mm); $n^{25}D$ 1.4078.

Reaction of Diethyl Phosphorochloridate (6, R = Et) with Pyridine.—A solution of 17.25 g (0.10 mol) of diethyl phosphorochloridate, 8.69 g (0.11 mol) of pyridine, and 50 ml of petroleum ether was stirred under nitrogen at room temperature for 3 hr and distilled yielding 16.5 g (96%) of diethyl phosphorochloridate (6, R = Et), bp 48–50° (0.8 mm) [lit.[13b] bp 42° (0.2 mm)].

Reaction of Diphenylchlorophosphine (11) with *t*-Butyl Hydroperoxide (7) and Pyridine. 1.—To a solution of 22.1 g (0.1 mol) of diphenylchlorophosphine in 100 ml of petroleum ether was added at −15 to −5° a solution of 10 g (0.11 mol) of *t*-butyl hydroperoxide and 10 ml (0.12 mol) of pyridine. The mixture was filtered giving 22 g of a white solid which was washed with water and recrystallized from methanol–benzene giving 12 g (55%) of diphenyl phosphinic acid (13), mp 193.5–194°.

Anal. Calcd for $C_{12}H_{11}O_2P$: C, 66.05; H, 5.08. Found: C, 65.50; H, 5.23.

The filtrate was evaporated to dryness (0.15 mm) leaving 5 g (18%) of diphenyl-*t*-butyl phosphinate (12), mp 111.5–112° (MeOH–H_2O).

Anal. Calcd for $C_{16}H_{19}O_2P$: C, 70.07; H, 6.98; mol wt, 275. Found: C, 70.22; H, 7.07; mol wt, 265.

2.—An analogous reaction of 19 ml (0.1 mol) of diphenylchlorophosphine, 10 g (0.11 mol) of *t*-butyl hydroperoxide and 100 ml of petroleum ether gave 20.5 g (94%) of diphenylphosphinic acid (13).

3.—A similar reaction of 19 ml (0.1 mol) of diphenylchlorophosphine, 10 ml (0.12 mol) of pyridine, and 100 ml of petroleum ether gave 1.2 g of an unidentified polymeric material, 8 g of pyridinium hydrochloride, and 9.4 g (49%) of unchanged diphenyl chlorophosphine (11): bp 108–110° (0.3 mm); $n^{25}D$ 1.5888.

Preparation of Dialkyl *t*-Butyl Phosphates (1) by the Reaction of Dialkyl Phosphorochloridates (6) with Potassium *t*-Butoxide. Dimethyl *t*-Butyl Phosphate (1, R = Me).—The reaction flask was charged with a mixture of 12.1 g (0.11 mol) of potassium *t*-butoxide and 250 ml of petroleum ether in a nitrogen-filled glove box. The flask was removed and rapidly fitted with thermometer, stirrer, condenser, and dropping funnel. A stream of dry nitrogen was maintained during the reaction. Dimethyl phosphorochloridate (14.4 g, 0.10 mol) was added at 5–8°. The mixture was stirred for 15 min and filtered. The filtrate was concentrated and distilled giving 7.9 g (43%) of dimethyl *t*-butyl phosphate (1, R = Me): bp 40–42° (0.15 mm); $n^{25}D$ 1.4073.

Anal. Calcd for $C_6H_{15}O_4P$: C, 39.56; H, 8.30. Found: C, 39.60; H, 8.29.

Diethyl *t*-Butyl Phosphate (1, R = Et).—As above, 17.25 g (0.1 mol) of diethyl phosphorochloridate, 12.32 g (0.11 mol) of potassium *t*-butoxide, and 250 ml of petroleum ether were allowed to react, giving 15 g (71%) of diethyl-*t*-butyl phosphate (1, R = Et): bp 53–55° (0.05 mm); $n^{25}D$ 1.4028; nmr δ 1.32 (t, 6, CH_3CH_2O), 1.44 [s, 9, $(CH_3)_3CO$], 3.98 (m, 4, CH_3CH_2O).

Di-*n*-propyl *t*-Butyl Phosphate (1, R = *n*-Pr).—As above, 20.0 g (0.10 mol) of di-*n*-propyl phosphorochloridate, 12.1 g (0.11 mol) of potassium *t*-butoxide, and 250 ml of petroleum ether were allowed to react, giving 18.8 g (79%) of di-*n*-propyl *t*-butyl phosphate (1, R = *n*-Pr): bp 66–67° (0.1 mm); $n^{25}D$ 1.4156; nmr δ 0.96 [t, 6, J = 8 Hz, $(CH_3CH_2O)_2P(O)$], 1.45 [s, 9, $(CH_3)_3CO$], 1.65 [m, 4, $(CH_3CH_2CH_2O)_2P(O)$], 3.86 [m, 4, J = 8 Hz, $(CH_3CH_2CH_2O)_2P(O)$].

Anal. Calcd for $C_{10}H_{23}O_4P$: C, 50.33; H, 9.73. Found: C, 50.41; H, 9.73.

Diisopropyl *t*-Butyl Phosphate (1, R = *i*-Pr).—As above, 20.05 g (0.1 mol) of diisopropyl phosphorochloridate, 12.32 g (0.11 mol) of potassium *t*-butoxide, and 250 ml of petroleum ether were allowed to react, giving 17.1 g (72%) of diisopropyl *t*-butyl phosphate (1, R = *i*-Pr): bp 51–52° (0.2 mm); $n^{25}D$ 1.4070; nmr δ 1.29 [d, 12, J = 6 Hz, $[(CH_3)_2CHO]_2P(O)$], 1.46 [s, 9, $(CH_3)_3CO$], 4.50 [m, 2, $(>CHO)_2P(O)$].

Di-*n*-butyl *t*-Butyl Phosphate (1, R = *n*-Bu).—As above 22.85 g (0.10 mol) of di-*n*-butyl phosphorochloridate, 12.32 g (0.11 mol) of potassium *t*-butoxide, and 250 ml of petroleum ether were allowed to react, giving after distillation in small batches 22 g (84%) of di-*n*-butyl *t*-butyl phosphate (1, R = *n*-Bu): bp 97–99° (0.2 mm); $n^{25}D$ 1.4212; nmr δ 0.96 [t, 6, $(CH_3CH_2CH_2CH_2O)_2P(O)$], 1.48 [s, 9, $(CH_3)_3CO$], 1.60 [m, 8, $(CH_3CH_2CH_2CH_2O)_2P(O)$], 3.91 [m, 4, $(CH_3CH_2CH_2CH_2O)_2P(O)$].

Anal. Calcd for $C_{12}H_{27}O_4P$: C, 54.12; H, 10.22. Found: C, 53.42; H, 10.16.

Diisobutyl *t*-Butyl Phosphate (1, R = *i*-Bu).—As above, 22.85 g (0.1 mol) of diisobutyl phosphorochloridate, 12.32 g (0.11 mol) of potassium *t*-butoxide, and 250 ml of petroleum ether were allowed to react, giving after distillation in small batches 18.2 g (69%) of diisobutyl *t*-butyl phosphate (1, R = *i*-Bu): bp 87–89° (0.3 mm); $n^{25}D$ 1.4171; nmr δ 0.97 [d, 12, J = 6 Hz, $[(CH_3)_2CHCH_2O]_2P(O)]$], 1.46 [s, 9, $(CH_3)_3CO$], 1.91 [m, 2, $(>CHCH_2O)_2P(O)$], 3.75 [m, 4, $(>CHCH_2O)_2P(O)$].

Anal. Calcd for $C_{12}H_{27}O_4P$: C, 54.12; H, 10.22. Found: C, 53.63; H, 10.09.

Diphenyl *t*-Butyl Phosphate (1, R = Ph).—As above, 21.3 g (0.08 mol) of diphenyl phosphorochloridate,[12b] 9.8 g (0.09 mol) of potassium *t*-butoxide, and 250 ml of petroleum ether were allowed to react. The filtrate was concentrated at −20° (0.1 mm) leaving 23.1 g (95%) of diphenyl *t*-butyl phosphate (1, R = Ph) identified by nmr: nmr δ 1.46 [s, 9, $(CH_3)_3CO$], 6.82 [s, 10, $(C_6H_5O)_2P(O)$].

Dibenzyl *t*-Butyl Phosphate (1, R = PhCH₂).—As above 28.33 g (0.096 mol) of dibenzyl phosphorochloridate,[13b] 12.32 g (0.11 mol) of potassium *t*-butoxide, and 250 ml of petroleum ether were allowed to react. The filtrate was concentrated at −20° (0.1 mm) giving 22 g (68%) of dibenzyl *t*-butyl phosphate (1, R=PhCH₂) identified by nmr: nmr δ 1.47 [s, 9, $(CH_3)_3CO$], 4.71 [d, 4, $(C_6H_5CH_2O)_2P(O)$], 6.87 [s, 10, $(C_6H_5CH_2O)_2P(O)$].

Registry No.—**1** (R = Me), 13232-07-0; **1** (R = Et), 13232-08-1; **1** (R = Pr), 22433-79-0; **1** (R = *i*-Pr), 13232-09-2; **1** (R = Bu), 22433-81-4; **1** (R = *i*-Bu), 22433-82-5; **1** (R = Ph), 22433-83-6; **1** (R = $PhCH_2$), 22433-84-7; **9** (R = Et), 107-49-3; **9** (R = *i*-Pr), 5836-28-2; **12**, 1706-92-9; **13**, 1707-03-5; **14** (R = Et), 78-40-0; diisopropyl *t*-butylperoxy phosphate, 10160-46-0.

Acknowledgment.—We gratefully acknowledge Miss G. Wippich for technical assistance. We thank Carlisle Chemical Works, Inc., Reading, Ohio; M & T Chemicals Inc., Rahway, N. J.; and Stauffer Chemical Co., Dobbs Ferry, N. Y., for supplies of various phosphorus compounds.

Polar Effects on the Formation of Imines from Isobutyraldehyde and Primary Aliphatic Amines[1]

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Received May 21, 1969

The following dimensionless equilibrium constants for the formation of imines and water from isobutyraldehyde and primary amines were determined in aqueous solution at 35°: $MeO(CH_2)_3NH_2$, 3600; $PhCH_2NH_2$, 2500; $MeOCH_2CH_2NH_2$, 2060; $Me_2NCH_2CH_2NH_2$, 1700; $HC{\equiv}CCH_2NH_2$, 1400; $(MeO)_2CHCH_2NH_2$, 1380; $H_2NCH_2CONH_2$, 621; H_2NCH_2CN, 548; $CF_3CH_2NH_2$, 238. The equilibrium constants decrease with increasing electron-withdrawing power of the substituents. A plot of log K *vs.* the pK_a values of the conjugate acids of the amines gives a satisfactory straight line for amines of the type RNH_2 where R contains an sp^3-hybridized β-carbon atom. Deviations from this line in the cases of the imines derived from aminoacetonitrile and propargylamine are attributed to the particular stability of a conformer in which the carbon–nitrogen double bond of the imine is eclipsed by a cyano or ethynyl group. This conclusion is supported by nmr data.

We have previously described methods for determining equilibrium constants for the formation of imines from isobutyraldehyde and primary amines by uv measurements at the aldehyde maximum or at the imine maximum or by measurements of the effect of added aldehyde on the pH of amine buffer solutions.[2] Equilibrium constants were reported for methyl-, ethyl-, isopropyl-, *t*-butyl-, *n*-propyl-, and *n*-butylamine, and the conformational equilibria of the resultant imines were discussed on the basis of their nmr spectra. In these compounds, where polar effects were held relatively constant, differences in ease of formation and in conformational preferences were attributed almost entirely to steric effects. We have now determined the equilibrium constants for the formation of imines from isobutyraldehyde and primary amines of the type RCH_2NH_2, in which steric effects are kept fairly constant and polar effects varied widely.

Results

The equilibrium constant for imine formation is that defined previously[2]

$$K = IW/AB \quad (1)$$

where I, W, B, and A are the equilibrium concentrations of imine, water, amine, and aldehyde (including both free aldehyde and aldehyde hydrate), respectively. For the ultraviolet method of determining K, eq 2 was used when measurements were made at the imine maximum.

$$A_0/[D - A_0\epsilon_A - (B_0 - B')\epsilon_B] = \{1/(\epsilon_I - \epsilon_A - \epsilon_B)\} + \{W/[KB(\epsilon_I - \epsilon_A - \epsilon_B)]\} \quad (2)$$

ϵ_I, ϵ_A, and ϵ_B are the extinction coefficients of the imine, aldehyde, and amine at the wavelength used, A_0 and B_0 are the initial concentrations (before imine formation) of aldehyde and amine, B' is the concentration of amine in the reference cell, and D is the absorbance. In order to calculate the real concentrations of amines present (that is, to correct for the amounts present in the protonated forms), it was necessary to know their ionization constants at the ionic strengths and temperatures used. This knowledge was vital in cases where equilibrium constants were determined by pH measurements. The ion-product constant of water was calculated as described previously.[2] The ionization constants of 2-methoxyethylamine, 3-methoxypropylamine, 2,2-dimethoxyethylamine, 2,2,2-trifluoroethylamine, benzylamine, propargylamine, and 2-dimethylaminoethylamine were determined at 35°. Literature values at 25° were corrected to 35° by the

(1) (a) This investigation was supported in part by Grant DA-ARO-D-31-124-G648 from the U. S. Army Research Office (Durham) and by Public Health Service Grant AM10378 from the National Institute of Arthritis and Metabolic Diseases. (b) Abstracted in part from the Ph.D. thesis of C. Y. Yeh, The Ohio State University, 1968.

(2) J. Hine and C. Y. Yeh, *J. Amer. Chem. Soc.*, **89**, 2669 (1967).

method of Perrin[3] for aminoacetonitrile[4] and glycinamide,[5] whose equilibrium constants were not determined by the pH method and whose basicities were so low that little ionization occurred. The pK_a values for the conjugate acids of the amines studied (including those studied previously for which no pK_a values were given[2]) are listed in Table I.

TABLE I
VALUES OF pK_a FOR PRIMARY AMINES IN WATER AT 35° AND ZERO IONIC STRENGTH[a]

Amine	pK_a
Methylamine	10.31[b]
Ethylamine	10.31[b]
n-Propylamine	10.21[b]
Isopropylamine	10.21[b]
n-Butylamine	10.26[b]
t-Butylamine	9.72[b]
3-Methoxypropylamine	9.83
2-Dimethylaminoethylamine	9.45[c]
2-Methoxyethylamine	9.09
Benzylamine	9.00
2,2-Dimethoxyethylamine	8.35
Propargylamine	7.87
Glycinamide	7.69[d,e]
2,2,2-Trifluoroethylamine	5.52
Aminoacetonitrile	5.16[d,e]

[a] pK_a is the negative logarithm of the acidity constant of the conjugate acid of the amine. [b] Determined as described in ref 2. [c] This refers to the acidity of the monoprotonated form of the diamine, which is a mixture of $Me_2NCH_2CH_2NH_3^+$ and $H_2NCH_2CH_2NHMe_2^+$. [d] Calculated from data at 25°. [e] At ionic strengths around 0.01 *M*.

Equilibrium constants were determined by pH measurements and, in most cases, by measurements at the uv absorption maxima of the imines for all the imines except N-isobutylidene-2-dimethylaminoethylamine and those imines for which *K* is less than 1000. The additional basic functional group in 2-dimethylaminoethylamine made interpretation of the effect of added isobutyraldehyde on the pH of amine buffer solutions excessively complicated. The absorption of 2-dimethylaminoethylamine in the range 2100–2400 Å is so strong as to make equilibrium measurements at the imine maximum relatively unreliable. The addition of isobutyraldehyde to buffers of amines whose equilibrium constants for isobutyraldimine formation were less than about 1000 caused such small changes in the pH that the equilibrium constants could not be determined reliably from them. For these amines the equilibrium constants were determined by measurements at the aldehyde absorption maximum. The values of *K* obtained are listed in Table II.

As pointed out previously,[2] the equilibrium constants determined by the present methods are measures of the extent of formation of carbinolamine (1) plus imine.

$$i\text{-PrCHO} + RNH_2 \rightleftharpoons \underset{1}{i\text{-PrCH(OH)NHR}} \rightleftharpoons i\text{-PrCH=NR} + H_2O$$

Stopped-flow kinetic studies of the reaction of isobutyraldehyde with 2,2,2-trifluoroethylamine in water at 35° have shown that the equilibrium constant for

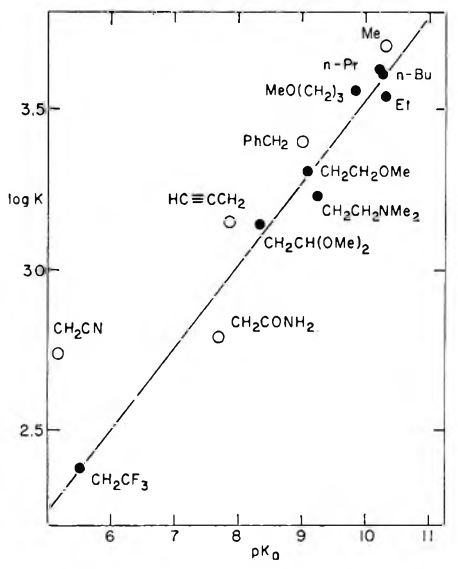

Figure 1.—Plot of log *K* for the formation of *i*-PrCH=NR from *i*-PrCHO and RNH_2 *vs.* pK_a for RNH_3^+. For the solid circles, R contains an sp^3-hybridized β-carbon atom.

TABLE II
EQUILIBRIUM CONSTANTS FOR FORMATION OF IMINES FROM ISOBUTYRALDEHYDE AND PRIMARY AMINES IN WATER AT 35°

		K[a]			
		Uv measurements at absorption maximum		pH measurements	
Primary amine	Registry no.	Imine	Aldehyde		Av
$MeO(CH_2)_3NH_2$	5332-73-0	3570		3620	3600
$C_6H_5CH_2NH_2$	100-46-9			2500	2500
$MeOCH_2CH_2NH_2$	109-85-3	2090		2020	2060
$Me_2NCH_2CH_2NH_2$	108-00-9		1700		1700
$HC{\equiv}CCH_2NH_2$	2450-71-7			1400	1400
$(MeO)_2CHCH_2NH_2$	22483-09-6	1200		1570	1380
$H_2NCOCH_2NH_2$	598-41-4	606[b]	636		621
$NCCH_2NH_2$	540-61-4		548		548
$CF_3CH_2NH_2$	753-90-2		238		238

[a] The dimensionless equilibrium constant defined by eq 1. [b] The experimental method used is of diminished reliability for *K* values this small.

carbinolamine formation is no more than one-tenth as large as that for imine formation.[6] Equilibrium constants for the formation of carbinolamines have been found to be decreased only slightly by electron-withdrawing substituents.[7,8] It therefore seems fairly well assured that the equilibrium constants we have measured are very largely for imine formation. Kinetic studies have also shown that equilibrium in reactions of the type studied is reached in a minute or less.[6] This adds to the evidence that equilibrium had been reached in our measurements, which were made a number of minutes after mixing and in which no drift was noted.

All of the isobutyraldimines except the one derived from glycinamide were isolated and characterized by their ir, nmr, and in most cases uv spectra. All the compounds showed a strong absorption maximum at 1672 ± 5 cm^{-1}, which we attribute to the C=N stretching vibration. The uv and nmr spectral data are summarized in Tables III and IV.

(3) D. D. Perrin, *Aust. J. Chem.*, **17**, 484 (1964).
(4) G. W. Stevenson and D. Williamson, *J. Amer. Chem. Soc.*, **80**, 5943 (1958).
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(6) F. A. Via, The Ohio State University, personal communication, 1968.
(7) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, **241**, 5864 (1966).
(8) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968).

TABLE III
ULTRAVIOLET DATA ON ISOBUTYRALDIMINES

Imine	Registry No.	$Me_3CCH_2CHMe_2$ λ_{max}, Å	$Me_3CCH_2CHMe_2$ ϵ, M^{-1} cm^{-1}	MeCN λ_{max}, Å	MeCN ϵ, M^{-1} cm^{-1}	Water λ_{max}, Å	Water ϵ, M^{-1} cm^{-1}
i-PrCH=N$(CH_2)_3$OMe	22483-13-2	2450	90			2300	138
i-PrCH=NCH_2CH_2OMe	22483-14-3	2360	169	2360	195	2200	118
i-PrCH=N$CH_2CH_2NMe_2$	22483-15-4	2075[a]	2980[a]	2175[a]	1560[a]		
i-PrCH=N$CH_2CH(OMe)_2$	22483-16-5	2425	95	2300	199	2275	193
i-PrCH=NCH_2CF_3	22483-17-6	2400	87	2300	130	2300	126
i-PrCH=NCH_2CONH_2	22483-18-7					2350	157
i-PrCH=NCH_2CN	22483-19-8	2310	159	2300	177	2250	111
i-PrCH=N$CH_2C{\equiv}CH$	22483-20-1	2370	119	2300	181		

[a] These results are not very reliable, but they do illustrate the shift in λ_{max} and increase in ϵ that we have attributed to the tertiary amino group in the molecule.

TABLE IV
NMR SPECTRA OF N-ISOBUTYLIDENEALKYLAMINES[a]

Chemical shifts, τ, and types of protons							Coupling constants, cps					
A	B[b]	C	D	E	F	G	J_{AB}	J_{BC}	J_{CD}	J_{DE}	J_{EF}	J_{BD}
$(CH_3)_2CH$—	CH=	N—	CH_2—	CH_2—	CH_2—	O—CH_3	6.9	4.0	1.3	6.8	6.3	
8.99	2.49		6.7	8.27	6.7	6.79						
$(CH_3)_2CH$—	CH=	N—	CH_2—	C_6H_5[c]			7.0	4.2	1.4			
8.99	2.34		5.45	2.70								
$(CH_3)_2CH$—	CH=	N—	CH_2—	CH_2—	O—	CH_3	7.0	4.3				
8.96	2.52		6.55	6.55		6.75						
$(CH_3)_2CH$—	CH=	N—	CH_2—	CH_2—	N$(CH_3)_2$		6.7	4.0	1.3	6.8		1.0
8.98	2.56		6.62	7.63	7.84							
$(CH_3)_2CH$—	CH=	N—	$CH_2C{\equiv}CH$				7.2	4.3	1.8	2.5		1.3
8.95	1.95		5.70	7.45								
$(CH_3)_2CH$—	CH=	N—	CH_2—	$CH(OCH_3)_2$			6.8	4.1	1.3	5.3		
8.99	2.54		6.57	5.54	6.75							
$(CH_3)_2CH$—	CH=	N—	CH_2—	CF_3[d]			7.0	4.3	1.3	9.4		1.0
8.93	2.34		6.17									
$(CH_3)_2CH$—	CH=	N—	CH_2—	CN[e]			6.8	4.3	1.8			1.3
9.01	2.23		5.71									

[a] Run neat, using internal tetramethylsilane unless otherwise indicated. [b] Absorption by type B protons was too broad and weak to permit a reliable determination of the chemical shift, but this shift corresponded to a τ of about 7.7 ppm in all cases except those of N-isobutylidene-2,2,2-trifluoroethylamine, N-isobutylidenebenzylamine, N-isobutylidenepropargylamine, and N-isobutylideneaminoacetonitrile, where it was about 7.6 ppm. [c] Registry no.: 22483-21-2. [d] The hydrogen–fluorine coupling constant J_{CE} was 1.2 cps. [e] Using external tetramethylsilane as reference.

Discussion

From the results shown in Table II it may be seen that electron-withdrawing substituents tend to decrease the equilibrium constants for the formation of isobutyraldimines from primary amines. One might examine this tendency quantitatively by making a Taft equation plot, but most of the required σ^* values do not appear to be directly available. We have therefore plotted log K *vs.* the pK_a values of the conjugate acids of the amines studied. To the extent to which the amine basicities follow the Taft equation[9] this procedure constitutes a test of the applicability of the Taft equation to our equilibrium constants. In the plot (Figure 1) all of the equilibrium constants determined in the present investigation were used; in addition, data on all the amines of the type RNH_2, where R is primary, that were previously studied[2] are included. (The equilibrium constants for isopropylamine and *t*-butylamine are relatively small because of greater steric hindrance.) The appropriate K_a value that should be used for the case of 2-dimethylaminoethylamine is

$$K_a = [H^+][Me_2NCH_2CH_2NH_2]/[Me_2NCH_2CH_2NH_3^+]$$

That is, the denominator should contain the concentration of only that monoprotonated species that is protonated at the primary amino group. This species has been found to comprise 62% of the total monoprotonated form of 2-dimethylaminoethylamine.[6] Therefore the K_a value given in Table I was divided by 0.62 and the resultant pK_a value (9.24) used in plotting Figure 1. The slope of the line shown in the figure was calculated by the method of least squares, using all of the solid circles, which refer to amines of the type RNH_2 where R contains an sp^3-hybridized β-carbon atom. This value, 0.256, may be multiplied by the ρ^* value for the acidity of primary ammonium ions (−3.14)[9] to give −0.80 as an estimate of ρ^* for the formation of isobutyraldimines from primary amines. The ρ^* value has the expected algebraic sign. Electron-withdrawing substituents would be expected to discourage the transformation of the amino group, in which the nitrogen is probably approximately sp^3 hybridized, to an imino group, in which the nitrogen is sp^2 hybridized and hence more electron withdrawing. The situation is somewhat similar to that found in the case of olefins, aldehydes, and ketones, whose enthalpies and free energies of hydrogenation are made more negative by electron-withdrawing substituents.[10]

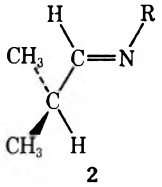
The fact that the equilibrium constant for formation of the N-methylimine is somewhat larger than those for the ethyl-, propyl-, and butylimines has already been

(9) *Cf.* H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5441 (1957).

(10) R. W. Taft, Jr., and M. M. Kreevoy, *ibid.*, **79**, 4011 (1957).

explained in terms of the three stable conformations with respect to rotation around the carbon–nitrogen single bond that exist for this imine compared with only two for the other imines.[2] If the equilibrium constant for the methyl compound were only two-thirds as large as it is, the point for methyl in Figure 1 would lie slightly below the line. The deviations of the other open circles from the line are also best discussed in terms of conformational equilibria.

All of the values of J_{BC} fall in the range 4.1 ± 0.2 cps previously observed.[2] We had estimated that this indicates that 32 ± 3% of these imines exist in conformation **2**, with the two hydrogens *trans* to each



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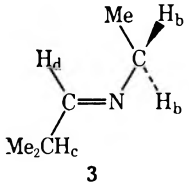
other. A more reliable estimate is now available from the work of Karabatsos and Lande, who made measurements at several temperatures using imines derived from a number of aldehydes.[11] From their values of J_{trans} and J_{gauche} and their alkyl correction factor, a coupling constant of 4.1 ± 0.2 cps may be calculated to correspond to 35 ± 3% conformation **2**.

In our previous analysis of conformational isomerization due to rotation around the carbon–nitrogen single bond,[2] we described evidence that conformation **3**, in which the carbon–nitrogen double bond is eclipsed by a carbon–methyl bond, is about 2.0 kcal/mol less stable than **4**, in which the carbon–nitrogen double bond is



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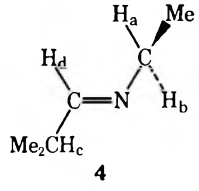

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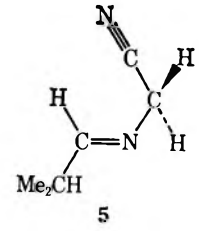
eclipsed by a carbon–hydrogen bond. Inasmuch as the previously undetectable J_{CD} for N-isobutylideneisopropylamine has subsequently been found to be 0.7 cps, our previous estimates of the H_a–H_d and H_b–H_d (see **3** and **4**) coupling constants have been revised to 0.5 and 2.1 cps, respectively. From the values of J_{CD} in Table IV it follows that the 3-methoxypropyl-, 2-dimethylaminoethyl-, 2,2-dimethoxyethyl-, and 2,2,2-trifluoroethylimines, like the ethyl-, propyl-, and butylimines studied previously, all exist almost entirely in conformations analogous to **4**, in which the carbon–nitrogen double bond is not eclipsed by a carbon–carbon bond in the amine part of the molecule. From the considerably larger coupling constant found for the imines derived from propargylamine and aminoacetonitrile, it may be calculated that these imines exist to an extent of about 63% in conformations like **5**. This conclusion is supported qualitatively by the facts that J_{BD} is larger for these imines than for any others and that the hydrogen atom attached to sp^2 carbon, which, in a conformation like **5**, would lie in a deshielding region



5

with respect to the triple bond, absorbs at lower field in the cases of these two imines than in any others. If it were not possible for these two imines to exist in the particularly stable conformers like **5**, the equilibrium constants for their formation would be only about 37% as large as they are. If the equilibrium constants were only 37% as large, the agreement with the straight line in Figure 1 would be better.

The tendency of the cyano group to eclipse the carbon–nitrogen double bond is analogous to (but stronger than) its tendency to eclipse a carbon–carbon double bond. Allyl cyanide exists to the extent of about 44% in the conformation analogous to **5** and only about 28% in each of the other two conformations.[12] It seems possible that the particular stability of conformations like **5** for the imines derived from propargylamine and aminoacetonitrile should be attributed to stabilizing van der Waals interactions; the cyano and ethynyl groups are smaller (in the relevant direction) than alkyl groups. If this explanation is correct, then it would seem possible that stabilizing van der Waals interactions would also be found in N-isobutylidenebenzylamine and N-isobutylideneglycinamide if they existed in conformations analogous to **5** with the phenyl or carbamido group oriented in a plane perpendicular to the plane of the aldimino group. However, it is known that the phenyl group in allylbenzene has a smaller tendency to eclipse the carbon–carbon double bond than does the cyano group in allyl cyanide.[12] To freeze a phenyl or a carbamido group perpendicular to the plane of the aldimino group would result in unfavorable entropy effects that have no analogs in the cases of the cyano and ethynyl compounds. Furthermore, in such an orientation the carbon–oxygen double bond of the carbamido group would not be eclipsed by any of the bonds of the adjacent carbon atom, as would be required for maximum stability. Finally, there is, of course, no reason to believe that the van der Waals forces due to the π electrons would be the same for the phenyl, carbamido, ethynyl, and cyano groups. Therefore, it is not surprising that the N-isobutylideneglycinamide compound shows no tendency to exist in a conformation like **5**, and the tendency of N-isobutylidenebenzylamine to exist in such a conformation is small at best (J_{CD} = 1.4 cps).

The preceding interpretation of part of our results in terms of conformational stabilities may be complicated by the fact that most of our information concerning conformational stabilities comes from nmr measurements on neat imines rather than on imines in aqueous solution where the equilibrium constants for imine formation were determined.

(11) G. J. Karabatsos and S. S. Lande, *Tetrahedron*, **24**, 3907 (1968).

(12) A. A. Bothner-By and H. Günther, *Discussions Faraday Soc.*, **34**, 127 (1962).

TABLE V
PROPERTIES OF ISOBUTYRALDIMINES

Imine	Bp, °C	$d^{t_1}_4$	t_1, °C	$n^{t_2}_D$	t_2, °C	Cald, % C	Cald, % H	Cald, % N	Found, % C	Found, % H	Found, % N
i-PrCH=N(CH$_2$)$_3$OMe	160	0.820	35	1.4245	25	67.09	11.82	9.93	67.07	11.97	9.79
i-PrCH=NCH$_2$CH$_2$OMe	142	0.839	35	1.4139	25	65.07	11.70	10.84	64.93	11.80	10.67
i-PrCH=NCH$_2$CH$_2$NMe$_2$	110[a]	0.796	25	1.4283	27	67.54	12.76	19.70	67.67	12.88	19.48
i-PrCH=NCH$_2$CH(OMe)$_2$	127[b]	0.899	25	1.4237	27	60.34	10.76	8.80	60.52	10.93	8.64
i-PrCH=NCH$_2$CF$_3$[c]	102	1.036	26	1.3632	27.5	47.07	6.58	9.14	47.28	6.67	9.17
i-PrCH=NCH$_2$CN	35[d]			1.4326	28	65.43	9.15	25.42	65.34	9.42	25.40
i-PrCH=NCH$_2$C≡CH	132	0.841	26	1.4443	26	77.01	10.16	12.83	76.92	10.23	12.97
i-PrCH=NCH$_2$C$_6$H$_5$	66[e]	0.856	26	1.5079	26	81.94	9.38	8.69	81.84	9.32	8.74

[a] At 138 mm. [b] At 143 mm. [c] Calcd: F, 37.23. Found: F, 37.12. [d] At 2.5 mm. [e] At 0.26 mm.

It may be that some of the deviations from linearity in the plot in Figure 1 arise from complications that affect only the pK_a values.

Experimental Section

Unless otherwise stated, the experimental methods were the same as those used previously.[2]

Aminoacetonitrile bisulfate and glycinamide hydrochloride were recrystallized from 95% ethanol and dried in a desiccator. All the other amines used were tested by gas–liquid partition chromatography and found to contain less than 0.5% impurity, except for 2,2,2-trifluoroethylamine, which contained about 1.5% impurity.

Imines.—The various imines were prepared from isobutyraldehyde and the appropriate primary amine by methods like that described previously,[2] except in the cases of the 2,2-dimethoxyethyl and the 2,2,2-trifluoroethyl compounds, where magnesium sulfate was used as the drying agent instead of potassium hydroxide, and the case of N-isobutylideneaminoacetonitrile, which was prepared as follows. A mixture of 15.4 g (0.1 mol) of aminoacetonitrile bisulfate and 18 g (0.18 mol) of triethylamine was stirred at 0° while 7.2 g (0.1 mol) of isobutyraldehyde was added. After 2 hr the reaction mixture was dried over molecular sieves, Type 5A, and distilled under vacuum. Data on the imines prepared are listed in Table V. Attempts to isolate N-isobutylideneglycinamide were unsuccessful.

Registry No.—Isobutyraldehyde, 78-84-2.

Acknowledgment.—We acknowledge our indebtedness to Dr. J. Christopher Philips for the ultraviolet spectra and analytical samples of N-isobutylidenepropargylamine.

A New Addition Reaction of Chloromethyl Methyl Sulfide to Olefins in Sulfuric Acid. A New Synthesis of 3-(Methylthio)propionaldehyde

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Received June 4, 1968

Chloromethyl methyl sulfide (**10**) has been found to add to vinyl chloride in sulfuric acid to give 3-(methylthio)-propionaldehyde. The addition reaction of **10** with other olefins was investigated, but similar reactions did not occur in the case of cyclohexene, acrylonitrile, or 1-chlorocyclohexene.

Presently, *dl*-methionine, an essential amino acid, is produced from acrolein and methanethiol.[1] The present study has been undertaken to find a new synthetic route from dimethyl sulfide and vinyl chloride (**11**). The chlorination of dimethyl sulfide is known to give chloromethyl methyl sulfide (**10**)[2] in good yields. The electrophilic addition of α-chloro ethers to olefins has been widely investigated[3] but the analogous reaction of α-chloro sulfides seems not to have been, presumably because of the weak reactivities of the sulfides compared with the ethers.[4] The Markovnikov addition of **10** to **11** would give rise to 1,1-dichloro-3-(methylthio)propane (**1**), which might in turn be converted into *dl*-methionine.

On exploring this possibility, it has been found that **10** adds to **11** in the presence of aluminum chloride yielding **1** in low yield. This result has led to the investigation of other Lewis acids as catalysts for this reaction, and to success with sulfuric acid.

Reaction of Chloromethyl Methyl Sulfide with Vinyl Chloride in Sulfuric Acid.—When the sulfide **10** was treated with sulfuric acid, it gradually dissolved with the evolution of hydrogen chloride to give a clear solution. The solution was allowed to react with **11** in a pressure vessel, and 3-(methylthio)propionaldehyde (**4**) was found in the ether extract of the hydrolysate of the reaction mixture and was isolated as its 2,4-dinitrophenylhydrazone (**13a**). A part of unreacted **10** was recovered as the methylthiomethyl derivatives of the hydrazine (**15a**), one of which was isolated and identified as 1-(2,4-dinitrophenyl)-1,2-bis(methylthiomethyl)hydrazine (**15b**). There were also found some by-products, among which formaldehyde and acetaldehyde were isolated as **13b** and **13c**, respectively. From the ether extract of the original hydrolysate, bis(methylthio)methane (**5**),[5] *cis*- and *trans*-1,3-bis(methylthio)propene (**6a** and **b**), and 3-(methylthio)-propionaldehyde dimethyl mercaptal (**9**) were separated

(1) J. R. Catch, A. H. Cook, A. R. Graham, and I. Heilbron, *J. Chem. Soc.*, 1609 (1947); E. Pierson, M. Giella, and M. Tishler, *J. Amer. Chem. Soc.*, **70**, 1450 (1948).

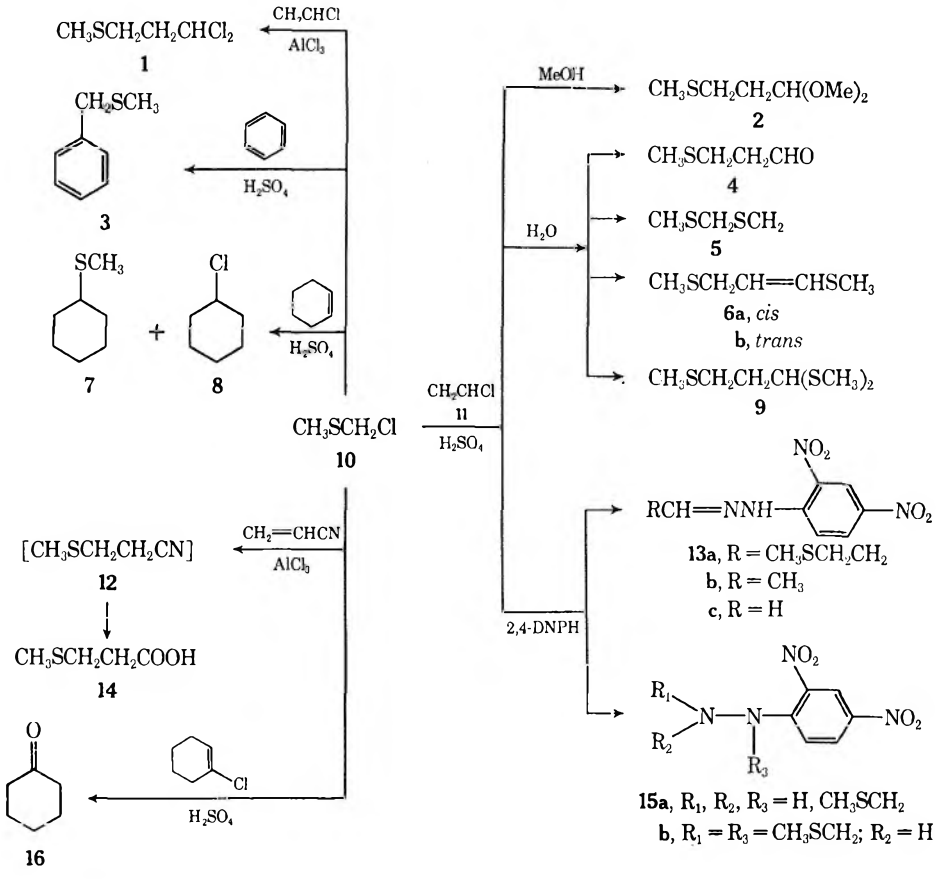
(2) F. Boberg, G. Winter, and J. Moos, *Ann. Chem.*, **616**, 1 (1958); W. E. Truce, G. H. Birum, and E. T. McBee, *J. Amer. Chem. Soc.*, **74**, 3594 (1952).

(3) S. A. Vartanyan and A. O. Tosunyan, *Russ. Chem. Rev.*, **34**, 267 (1965).

(4) H. Böhme, *Chem. Ber.*, **74**, 248 (1941).

(5) L. Horner and P. Kaiser, *Ann. Chem.*, **626**, 19 (1959).

SCHEME I



by vpc and identified by nmr. The methanolysis of the initial reaction mixture gave 3-(methylthio)propionaldehyde dimethyl acetal (**2**). Good yields were obtained when amounts greater than 4 mol of sulfuric acid of above 95% concentration to 1 mol of **10** were used and the reaction was carried out at around 0°. Among other catalysts, chlorosulfonic acid has been found to be effective, but the yields were generally inferior to those obtained using sulfuric acid.

Reaction with Other Olefins.—When treated with **10** in sulfuric acid, benzene gave benzyl methyl sulfide (**3**), suggesting electrophilic attack of the methylthiomethyl cation. A similar result has been reported for the reaction of **10** with *o*-nitrophenol in the presence of aluminum chloride,[6] but the reaction of **10** in sulfuric acid with vinyl acetate, vinyl ethyl ether, or styrene gave only the polymerization product. Cyclohexene yielded cyclohexyl methyl sulfide (**7**) and chlorocyclohexane (**8**) as the result of the addition of methanethiol and hydrogen chloride originated from **10**.[7] The reaction of 1-chlorocyclohexene gave only cyclohexanone (**16**) as the hydrolyzed product. Acrylonitrile gave 3-(methylthio)propionitrile (**12**), the identity of which was confirmed by converting the product into 3-(methylthio)propionic acid (**14**). These results seem to suggest that the olefin would have to be intact in the reaction medium to be attacked by the methylthiomethyl cation.

Experimental Section

All melting points are uncorrected. The nmr spectra were measured with a Varian A-60 spectrometer. Chemical shifts were determined using the δ convention relative to tetramethylsilane (TMS) as internal standard. Ultraviolet absorption spectra were taken with a Hitachi Type EPS-2U automatic recording spectrophotometer, and infrared absorption spectra were measured with Jasco Model IR-S spectrophotometer. Analyses by vpc were carried out using a Shimazu GC-2B apparatus with a 4 mm × 3 m, 10% Carbowax 20M on 40–60 mesh Chromosorb W column. The concentration of sulfuric acid or oleum was determined by melting point.[8]

3-Methylthio-1,1-dichloropropane (**1**).—To powdered aluminum chloride (12 g, 0.09 mol) in 40 ml of methylene chloride was added with stirring 7.7 g (0.08 mol) of **10** at 10°. The mixture was stirred for 20 min at 10° and transferred to a pressure vessel; **11** (5.6 g, 0.09 mol) was added. The mixture was kept for 2 days at room temperature with occasional shaking, then poured into 100 ml of 3 *N* hydrochloric acid, and extracted with ether which was washed with water, dried over calcium chloride, and evaporated. Distillation of the residue gave 0.45 g, bp 40–42° (1 mm), of **1**. The identity of the product was confirmed by nmr, compared with that of authentic **1** prepared from **4** by the method of Hill and Tyson.[9]

3-(Methylthio)propionaldehyde 2,4-Dinitrophenylhydrazone (**13a**).—To 98% sulfuric acid (19.6 g, 0.2 mol) was added **10** (3.8 g, 0.04 mol) at 0–2°, dropwise and with stirring. After 5 min at 0°, the mixture was transferred to a cooled pressure vessel and **11** (3.7 g, 0.06 mol) was added. The mixture was kept for 4 hr at 0° with occasional shaking and then poured into a solution of 2,4-dinitrophenylhydrazine (16 g, 0.08 mol) in 800 ml of 6 *N* sulfuric acid to give crude hydrazone (11.4 g). A mixture of accurately weighed samples of *t*-butyl alcohol and the hydrazone was analyzed by nmr in pyridine. From the peak ratios of the methyl signals of **13a** (δ 2.07, s, CH_3S), **13b** (δ 1.95 and 1.85, d, J = 6 Hz, CH_3CH), and **15a** (δ 2.2–2.4, m, CH_3S) to that of *t*-butyl alcohol, it was found that the hydrazone contained 7.9 g of **13a** (70% from **10**), 1.7 g of **13b** (13% from **11**), and **15a**, the methylthio groups of which corresponded to 8 mol % of the amount of **10** employed. Recrystallization from methanol gave

(6) S. W. Long and R. D. Moss, U. S. Patent 2,976,325 (1961); *Chem. Abstr.*, **55**, 16484*h* (1961).

(7) H. Böhme, H. Fischer, and R. Frank, *Ann. Chem.*, **563**, 54 (1949).

(8) C. M. Gable, H. F. Betz, and S. H. Maron, *J. Amer. Chem. Soc.*, **72**, 1445 (1950).

(9) A. J. Hill and F. Tyson, *ibid.*, **50**, 172 (1928).

13a (mp 120.5°), the ir and nmr of which were identical with those of the hydrazone prepared from authentic **4**.

3-(Methylthio)propionaldehyde Dimethyl Acetal (2).—The reaction mixture, worked up as in the previous experiment from **10** (7.6 g, 0.08 mol), in oleum (31.2 g, SO_3 6.8%) with **11** (7.4 g, 0.12 mol), was poured into 200 ml of anhydrous methanol and boiled under reflux for 2 hr. The solution was poured into sodium bicarbonate solution and extracted with ether. The extract was washed with water, dried over magnesium sulfate, filtered, and evaporated. Distillation of the residue gave 3.0 g (25%), bp 72–78° (15 mm), of **2**. The identity was confirmed by nmr, compared with that of authentic **2** prepared from **4** and methanol by the conventional method.

Identification of Side Products.—A reaction mixture, worked up as in the previous experiment from **10** (7.6 g, 0.08 mole), in 100% sulfuric acid (63 g, 0.64 mol) and **11** (7.4 g, 0.12 mol), was poured into 400 ml of water–ice slurry and extracted with chloroform which was washed with sodium bicarbonate solution and water, dried over magnesium sulfate, and filtered. The vpc of the extract at 122° with helium gas flow rate of 73 ml/min exhibited the peaks of **4** [retention time (t_r) 7.0 min] and **5** (t_r 3.8 min) along with two peaks at t_r of 14.3 (A) and 17.5 min (B). Vpc also showed the peak of **9** (t_r 21.4 min) at 150° with helium gas flow rate of 60 ml/min. The identity was confirmed by comparison with the t_r of authentic compounds. The compounds A and B were separated by vpc. Elemental analysis showed that both compounds have a composition close to $C_6H_{10}S_2$. The nmr spectrum of A (CCl_4) exhibited 3 H singlets at δ 2.02 (CH_3SCH_2) and 2.26 ($CH_3SCH{=}C$), a 2 H doublet at 3.12 (J = 8 Hz $SCH_2CH{=}C$), a 1 H multiplet at 5.2–5.8 (CH_2-$CH{=}CHS$), and a 1 H doublet at 6.12 ($CH_A{=}CH_BS$, J_{AB} = 9 Hz) along with small peaks of impurities at 1.9–2.5. Compound B exhibited a very similar nmr spectrum at δ 1.98 (s, 3), 2.25 (s, 3), 3.12 (d, 2, J = 8 Hz), 4.9–5.7 (m, 1), and 6.05 (d, 1, $CH_A{=}CH_BS$, J_{AB} = 15 Hz), along with small peaks of impurities at 1.9–2.5. These results and the fact that J_{AB} of B is larger than that of A indicate that A and B are **6a** and **6b**, respectively.

Sulfuric acid (100%, 2.5 g, 0.025 mol) followed by **10** (3.8 g, 0.04 mol) was added dropwise to trimethyl phosphate (10 ml) at 0–4°. After 5 min, the solution was allowed to react with **11** (3.7 g, 0.06 mol) in a pressure vessel at 0° for 3 hr. The mixture was poured into a solution of 2,4-dinitrophenylhydrazine (16 g, 0.08 mol) in 6 *N* sulfuric acid (800 ml). The orange-red precipitate was filtered, washed with water, and dried. Recrystallization from benzene gave yellow needles of **13c**, the identity of which was confirmed by infrared spectrum. The mother liquor was evaporated and the residue was chromatographed over alumina. From the petroleum ether–benzene (4:1) eluate, a yellow prism of **15b**, mp 97–98° (recrystallized from petroleum ether–benzene), was obtained: λ_{max}^{EtOH} 342 mμ (ε 17,200);[10] nmr (C_6D_6) δ 1.85 (s, 6, SCH_2), 3.70 (broad s, 2, NCH_2S), 3.71 (broad s, 2, NCH_2S), 6.9–8.7 (m, 3, ArH), and 9.26 (broad s, 1, NH). The nmr spectrum (pyridine) indicated that it corresponds to one of the peaks of the side product **15a** (δ 2.2–2.4).

(10) The hydrazone **13a** had the uv absorption maximum (EtOH) of 360 mμ (ε 31,900).

Anal. Calcd for $C_{10}H_{14}N_4O_4S_2$: C, 37.72; H, 4.43; N, 17.60, S, 20.14. Found: C, 38.09; H, 4.62; N, 17.69; S, 20.10.

Reactions of 10 in Sulfuric Acid. A. With Benzene.—To oleum (SO_3 5.7%, 68 g) was added **10** (16 g, 0.17 mol), dropwise and with stirring at 0–2°, followed by 13 g of benzene (0.17 mol). After being kept for 2 hr at 0–2° and overnight at room temperature, the mixture was poured into 150 ml of water–ice slurry and extracted with ether which was dried over magnesium sulfate and evaporated. Distillation of the residue gave 6.7 g (29%), bp 94–96° (18 mm), of **3**: nmr (CCl_4) δ 1.86 (s, 3, SCH_3), 3.53 (s, 2, CH_2S), and 7.20 (s, 5, ArH).

Anal. Calcd for $C_8H_{10}S$: C, 69.51; H, 7.29; S, 23.20. Found: C, 69.36; H, 7.53; S, 23.40.

B. With Cyclohexene.—Sulfide **10** (16 g, 0.17 mol) was added dropwise with stirring to oleum (SO_3 5.7%, 68 g) followed by cyclohexene (13.7 g, 0.17 mol) at 0–2°. After 3 hr at 0°, the mixture was poured into 200 ml of water–ice slurry and extracted with ether; the extract was dried over sodium sulfate and evaporated. Distillation gave an oil (5.4 g), bp 131–132.5°, which was identified as **8** containing about 10% **5** by nmr and vpc, compared with those of authentic samples.

The mother liquor of the ether extract was boiled under reflux for 2 hr, neutralized with sodium hydroxide solution, and extracted with ether; the extract was dried over sodium sulfate and evaporated. Distillation of the residue gave 2.0 g (9%), bp 59–62° (11.5 mm), of an oil, rectification of which gave **7**: bp 59.5–60.5° (13 mm); nmr (CCl_4) δ 2.00 (s, 3, SCH_3), 1.0–2.2 (broad hump 10, CH_2), and 2.2–2.7 (broad hump, 1, CHS).

Anal. Calcd for $C_7H_{14}S$: C, 64.55; H, 10.83; S, 24.62. Found: C, 64.39; H, 10.86; S, 25.16.

C. With Acrylonitrile.—Sulfide **10** (16 g, 0.17 mol) was added with stirring to oleum (SO_3 5.7%, 68 g) followed by acrylonitrile (8.9, 0.18 mol) at 0–2°. After 4 hr at 0°, the mixture was poured into 200 ml of water–ice slurry and extracted with ether. The aqueous layer was made slightly alkaline with sodium hydroxide solution, the deposited sodium sulfate removed by decantation, and the solution boiled under reflux for 4 hr. It was then acidified with sulfuric acid and extracted with ether; the extract was dried over sodium sulfate and evaporated. Distillation of the residual oil gave 7.1 g (35%), bp 135–135.5° (19 mm), of **14**: ir 1710 cm^{-1} (C=O); nmr (CCl_4) δ 2.12 (s, 3, SCH_3), 2.68 (m, 4, CH_2CH_2S), and 11.32 (s, 1, COOH).

Anal. Calcd for $C_4H_8O_2S$: C, 39.98; H, 6.71; S, 26.68. Found: C, 39.97; H, 6.78; S, 26.47.

Registry No.—Sulfuric acid, 7664-93-9; **1**, 22433-40-5; **2**, 13214-29-4; **3**, 766-92-7; **6a**, 22433-04-1; **6b**, 22433-05-2; **7**, 7133-37-1; **10**, 2373-51-5; **13a**, 7372-49-8; **14**, 646-01-5; **15a**, 22433-47-2; **15b**, 22433-48-3.

Acknowledgment.—The authors wish to express their thanks to Dr. Tadio Takenishi of Ajinomoto Co., Inc., for his encouragement, and also to Mr. Tomiyasu Ito and Hideomi Saito for their help throughout this work.

Stereochemical Study of Sodium–Ammonia Reduction of Acyclic Allenes

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Received April 15, 1969

The sodium–ammonia reduction of alkyl-substituted allenes (1,2-octadiene, 1,2-nonadiene, 2,3-nonadiene, 4,5-nonadiene, 3-ethyl-1,2-pentadiene, and 2,4-dimethyl-2,3-pentadiene) and aryl-substituted allenes (phenylpropadiene and 3-phenyl-1,2-butadiene) has been described. Alkyl-substituted allenes were reduced smoothly to give good yields of olefins, while aryl-substituted allenes provided principally alkylbenzenes. Potential routes for the formation of these products have been investigated. Evidence has been obtained for the isomerization of allenes to internal alkynes, wherever possible, before reduction. The allenes, which are not capable of isomerization to internal alkynes, seem to undergo reduction directly.

It has been shown earlier that the blue solution formed by dissolving sodium in liquid ammonia is an excellent reagent for reducing allenes to olefins.[1] This particular method of reduction, in combination with an elegant two-step synthesis of allenes,[2,3] has proved to be advantageous for synthesizing a higher homolog of an olefin in good yield.

Medium-sized cyclic allenes are found to yield *cis* olefins[1,4] on reduction with sodium–ammonia. This reaction has been used recently in the synthesis of *cis,cis*-1,5-cyclononadiene[1,5] and *cis,cis*-1,6-cyclodecadiene[6] because of the advantage offered in selectivity of reduction. Allenes have been proposed as intermediates in the metal–ammonia reduction of certain medium-sized cyclic acetylenes which also form *cis* olefins.[7–9] Since some confusion exists as to the nature of the products in the reduction of acyclic allenes,[1,10] we undertook a study of the reduction of representative acyclic allenes with sodium–liquid ammonia, with the intention of examining the stereospecificity of the reduction and of establishing, if possible, the potential path through which the olefins arise.

Results and Discussion

For the present investigation, we have made use of the following acyclic allenes—mono-, di-, and tetraalkyl allenes (1,2-octadiene, 1,2-nonadiene, 2,3-nonadiene, 4,5-nonadiene, 3-ethyl-1,2-pentadiene, and 2,4-dimethyl-2,3-pentadiene), and aryl allenes (phenylpropadiene and 3-phenyl-1,2-butadiene). All of the allenes except 2,4-dimethyl-2,3-pentadiene were prepared according to the general two-step method for synthesizing allenes.[2,3] They showed properties which were identical with the reported values.[10–13]

The reductions were conducted using commercial ammonia and pieces of freshly cut sodium. The required amount of allene in dry ether was added and worked up after the requisite time.

All the allenes underwent reduction smoothly giving good yields of the products. Yields and product composition are reported in Table I. The products were separated, wherever necessary, by preparative gas chromatography, and subjected to infrared and nuclear magnetic resonance spectral analysis.

TABLE I
REDUCTION OF ACYCLIC ALLENES BY SODIUM IN LIQUID AMMONIA

Allene	Total yield, %	Product (composition, %)
1,2-Octadiene[a]	77	*trans*-2-Octene (96.8) *cis*-2-Octene (2.5) 1-Octene (0.7)
1,2-Nonadiene[a]	80	*trans*-2-Nonene (92.8) *cis*-2-Nonene (7.2)
2,3-Nonadiene[a]	85	*trans*-2-Nonene (49.2) *cis*-2-Nonene (1.5) *trans*-3-Nonene (47.9) *cis*-3-Nonene (1.4)
4,5-Nonadiene[a]	82	*trans*-4-Nonene (96.6) *cis*-4-Nonene (3.4)
3-Ethyl-1,2-pentadiene[a]	81	3-Ethyl-2-pentene (100)
2,4-Dimethyl-2,3-pentadiene[a]	76	2,4-Dimethyl-2-pentene (100)
Phenylpropadiene[b]	72	*n*-Propylbenzene (82.0) Allylbenzene (18.0)
3-Phenyl-1,2-butadiene[b]	42[c]	*sec*-Butylbenzene (100)

[a] Products were analyzed on a 15-ft propylene glycol–$AgNO_3$ column. [b] Products were analyzed on a 10-ft 20% Carbowax column. [c] A large portion of allene was found to undergo polymerization, hence the low yield.

Alkyl-Substituted Allenes.—1,2-Octadiene and 1,2-nonadiene, on reduction, gave good yields of *trans*-2 olefin as the major product instead of *cis*-2 olefin as reported earlier.[1] 4,5-Nonadiene provided *trans*-4-nonene as the major product. The reduction of 2,3-nonadiene gave mainly *trans*-2- and *trans*-3-nonene in almost equal amounts. 3-Ethyl-1,2-pentadiene gave only 3-ethyl-2-pentene. 2,4-Dimethyl-2,3-pentadiene underwent reduction smoothly to yield 2,4-dimethyl-2-pentene.

Scheme I shows the possible routes (A and B) for the reduction of allenes to *trans* olefins. According to route A the *trans* olefin arises by isomerization of allene to acetylene followed by *trans* addition of electrons to form the dianion (I) which then undergoes protonation to give the *trans* olefin. This route is similar to the one

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(2) W. von E. Doering and A. K. Hoffmann, *ibid.*, **76**, 6162 (1954).
(3) W. R. Moore and H. R. Ward, *J. Org. Chem.*, **25**, 2073 (1960).
(4) P. D. Gardner and M. Narayana, *ibid.*, **26**, 3518 (1961).
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(11) W. R. Moore and H. R. Ward, *J. Org. Chem.*, **27**, 4179 (1962).
(12) L. Skattebol, *Tetrahedron Lett.*, 167 (1961).
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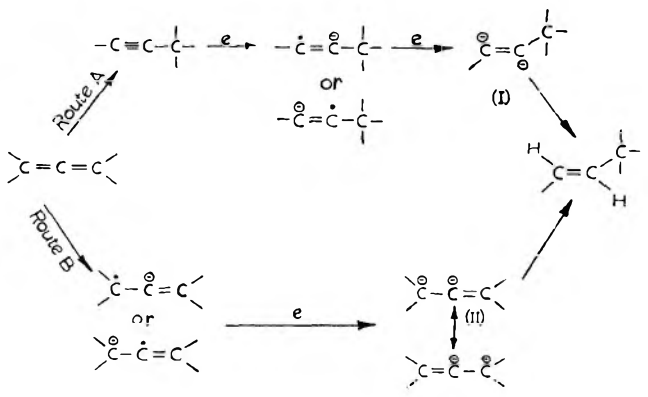
SCHEME I



proposed by earlier workers[14] for the reduction of acetylenes in the absence of an external proton donor. Alternatively, the allene can undergo direct reduction through route B. The reaction presumably proceeds by addition of one electron to give radical anions. Subsequent addition of one more electron followed by rotation of charged carbon atoms gives an allylic dianion (II) which can exist in resonance forms. The intermediate allylic anions can have both *cis* and *trans* configurations. Further, the least substituted end of the molecule probably carries the greater amount of charge, since the electron pair could occupy an orbital containing more s character when concentrated there. If this is so, one expects preferential protonation at the least substituted carbon to yield the thermodynamically more stable olefin (or higher degree of substitution).[15]

The predominance of the *trans*-2 olefin as reduction product made us to suspect that it might be arising from the reduction of a possible 2-alkyne intermediate, in view of the fact that terminal allenes are known to undergo isomerization to 2-alkynes by bases.[16] Also, Moore and Ward[17] have shown by calculations based on heats of formation and hydrogenation that 2-alkynes are thermodynamically more stable than terminal allenes. The most likely reagent in our experiments causing the isomerization seems to be sodium amide, whose concentration increases as reduction proceeds. In support of our proposal, we have observed 36% 2-nonyne along with 18% *trans*-2-nonene and 46% unreacted allene, when 1,2-nonadiene was subjected to partial reduction (using about half the theoretical amount of sodium required to reduce only one double bond). This confirms that some or all of the *trans*-2-nonene is arising *via* a 2-nonyne intermediate. However, the result does not exclude the possibility of the direct reduction of the allene to olefin, since it can be argued that the formation of 2-nonyne could be independent of the reduction of the allene, but the high concentration of 2-nonyne in comparison with that of *trans*-2-nonene could be best explained by 1,2-nonadiene undergoing isomerization faster than the direct reduction. Similar extremely fast isomerization of 1,2-hexadiene to 2-hexyne has been noted by Wotiz and coworkers.[18] The same argument holds for 2,3-nonadiene and 4,5-nonadiene. In the case of the former both 2- and 3-nonyne can be intermediates and the latter can undergo reduction through 4-nonyne. Our results with 1,2-nonadiene and 2,3-nonadiene are completely consistent with the observation of Benkeser and Tincher,[19] who have obtained principally *trans*-2-octene from 1,2-octadiene, and *trans*-2- and *trans*-3-octene in almost equal amounts from 2,3-octadiene in electrolytic reduction. Similar overall results have been obtained by Brown[10] and also Gardner and de Montellano[20] in the reduction of 2,3-nonadiene by alkali metal in ammonia.

The result with 3-ethyl-1,2-pentadiene reveals that the least substituted double bond of the allene is reduced specifically to yield the highly substituted olefin. Since this allene cannot isomerize to the corresponding 2-alkyne, and because of the conspicuous absence of conjugated dienes in the partial reduction product of 1,2-nonadiene, we propose, in this case, that the reduction follows only route B of Scheme I to give the resonance stabilized allylic dicarbanion followed by preferential protonation at the least substituted carbon atom, for reasons already discussed. The result with 2,4-dimethyl-2,3-pentadiene demonstrates that a simple tetrasubstituted allene offers no hindrance to sodium–ammonia reduction.

Aryl-Substituted Allenes.—In this series the allenes used for the present investigation were phenylpropadiene and 3-phenyl-1,2-butadiene, both of which have the allenic double bond in conjugation with the phenyl ring. The former gave *n*-propylbenzene with some amount of allylbenzene, and the latter gave only *sec*-butylbenzene. These results, wherein the alkyl benzenes are formed, are very similar to those observed by Wooster and Ryan,[21] who obtained 1,1,3,3-tetraphenylpropane by sodium–ammonia reduction of tetraphenylpropadiene. It can also be pointed out here that the complete reduction of unsaturated bonds in conjugation with phenyl ring can be a general phenomenon, which has been noticed by Benkeser and coworker,[19] who have shown the formation of alkylbenzenes by electrolytic reduction of 1-arylacetylenes.

The observed facts can be rationalized as follows. In the case of phenylpropadiene it can be presumed that both allene and its isomerized product, 1-phenylpropyne, are undergoing reduction. The former gives rise to the intermediates allylbenzene and propenylbenzene, and the latter gives rise to propenylbenzene which, we think, undergoes further reduction to *n*-propylbenzene, while allylbenzene undergoes isomerization to propenylbenzene before reduction. This assumption of isomerization of allylbenzene to propenylbenzene is not unreasonable since such isomerization under the influence of various bases has been well established by many workers.[22] It is interesting to note at this point that we have found in a separate experiment that even allylbenzene, on reduction with excess sodium under similar conditions, gives rise to *n*-propylbenzene.

(14) K. W. Greenlee and W. C. Fernelius, *J. Amer. Chem. Soc.*, **64**, 2505 (1942).
(15) E. J. Lampher, *ibid.*, **79**, 5578 (1957).
(16) T. L. Jacobs, R. Akawie, and R. G. Cooper, *ibid.*, **73**, 1273 (1951).
(17) W. R. Moore and H. R. Ward, *ibid.*, **85**, 86 (1963).
(18) J. H. Wotiz, W. E. Billups, and D. T. Christian, *J. Org. Chem.*, **31**, 2069 (1966).
(19) R. A. Benkeser and C. A. Tincher, *ibid.*, **33**, 2727 (1968).
(20) P. D. Gardner and B. R. O. de Montellano, *Dissertation Abstr.*, **26**, 2482 (1965).
(21) C. B. Wooster and J. F. Ryan, *J. Amer. Chem. Soc.*, **56**, 1133 (1934).
(22) (a) A. Schriesheim, C. A. Rowe, Jr., and L. Noslund, *ibid.*, **85**, 2111 (1963); (b) D. J. Cram and R. T. Uyeda, *ibid.*, **86**, 5466 (1964).

To check the possibility of the aforesaid intermediates, partial reduction (with about half the amount of sodium required to reduce only one double bond) of phenylpropadiene was carried out. When the reaction was arrested after about 15 min, the gas chromatographic analysis of the product after usual work-up showed the presence of *n*-propylbenzene, allylbenzene, and 1-phenylpropyne. No other product including the starting allene itself was observed. In another experiment, when the partial reduction was allowed to proceed for about 3 hr, the product analysis showed *n*-propylbenzene, propenylbenzene, and 1-phenylpropyne only. This clearly indicates that the reduction proceeds, at least partly, through a 1-phenylpropyne intermediate, and that allylbenzene, which is observed in the short-period experiment, isomerizes to the propenylbenzene observed in the long-period experiment. Formation of allylbenzene in the absence of formation of 3-phenylpropyne in the partial reduction of phenylpropadiene, indicates that the former arises out of direct reduction of the allene.

The reduction of 3-phenyl-1,2-butadiene to *sec*-butylbenzene can be explained as arising from direct reduction of allene through the possible 2-phenyl-2-butene and 3-phenyl-1-butene intermediates. Among these two intermediates one cannot be favored over the other, but it can be recalled, however, that 3-ethyl-1,2-pentadiene gives exclusively 3-ethyl-2-pentene, which suggests the likelihood of formation of 2-phenyl-2-butene in preference to the other isomer which, of course, can go over to the former reasonably fast.

Experimental Section

All boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 521 spectrophotometer using cesium bromide plates for liquid film spectra and sodium chloride cells for solution spectra. The nmr spectra were recorded on a Varian Associates A-60 spectrometer, in carbon tetrachloride with tetramethylsilane as the internal standard. The peaks are reported in δ (ppm). Gas chromatographic analysis of the reduction products of the alkyl-substituted allenes was carried out on a 0.25 in $\times$ 15 ft column packed with 20% propylene glycol–silver nitrate (F & M Scientific Corp., Avondale, Pa.) on 60–80 mesh Chromosorb P. The efficiency of the column was checked with authentic samples of *cis*- and *trans*-nonenes and was found to be quite satisfactory for our present investigation. The glpc analysis of the reduction products of phenyl substituted allenes was carried out using a 1/4 in. $\times$ 10 ft 20% Carbowax column. 2,4-Dimethyl-2,3-pentadiene was obtained from Aldrich Chemical Co. and showed no detectable impurities by glpc and nmr. All of the other allenes were prepared by known procedures reported in the literature,[2,3] and their properties corresponded well with those reported.[10–13] The elemental analyses were carried out by A. H. Siddiqui, microanalyst of this department.

General Procedure for Sodium–Ammonia Reduction.—Commercial ammonia was directly condensed without purification into the reaction flask fitted with a dropping funnel, a stirrer, and a Dry Ice condenser. A calculated quantity of dried sodium (freshly cut with a clean stainless steel knife) was dissolved in liquid ammonia. To the blue solution, the allene in dry ether was added dropwise. After complete addition of the allene, the stirring was continued for *ca.* 1 hr to ensure completion of the reaction, even though the reaction was found to be instantaneous. The excess sodium was then destroyed by adding ammonium chloride in small amounts. The excess ammonia was allowed to evaporate. The product was isolated by adding water to the residue and extraction of the product with ether. The combined extracts were washed twice with water and dried over anhydrous magnesium sulfate. The product was distilled after removal of the solvent through an efficient column.

Reduction of 1,2-Octadiene.—1,2-Octadiene (3.30 g, 0.03 mol) was reduced with 2.76 g (0.12 g-atom) of sodium in *ca.* 100 ml of liquid ammonia to give 2.57 g (77%) of octene mixture, bp 121–122° (754 mm). Analysis by glpc showed that the product consisted of 1-octene (0.7%), *cis*-2-octene (2.5%), and *trans*-2-octene (96.8%). The infrared spectrum (liquid film) showed a strong band at 963 cm^{-1} (*trans* out-of-plane hydrogen bending). All three components were identified by comparing the glpc retention times with those of authentic samples. Only *trans*-2-octene was separated by glpc, and it was identified by comparison of the infrared and nmr spectra with those of an authentic sample.

Reduction of 1,2-Nonadiene.—1,2-Nonadiene (2.48 g, 0.02 mol) was reduced with 2.06 g (0.09 g-atom) of sodium in *ca.* 80 ml of liquid ammonia. The usual work-up gave 2.0 g (80%) of nonenes, bp 69–70° (45 mm). The glpc analysis showed that the product consisted of *cis*-2-nonene (7.2%) and *trans*-2-nonene (92.8%). The identity of each of these isomers was established by comparison of glpc retention times with those of authentic samples. The major component was isolated by glpc, and its identity was established by comparison of the infrared and nmr spectra with those of an authentic sample.

Reduction of 2,3-Nonadiene.—A 2.48-g (0.02 mol) sample of 2,3-nonadiene was reduced by 2.08 g (0.09 g-atom) of sodium in *ca.* 80 ml of liquid ammonia. The usual work-up and distillation yielded 2.16 g (85%) of product, bp 68–69° (49 mm). Careful analysis by glpc indicated that the product consisted of *cis*-2-nonene (1.5%), *trans*-2-nonene (49.2%), *cis*-3-nonene (1.4%), and *trans*-3-nonene (47.9%). The minor components were identified by glpc analysis, while the major components were separated by glpc and identified by comparison of the infrared and nmr spectra with those of authentic samples.

Reduction of 4,5-Nonadiene.—4,5-Nonadiene (2.48 g, 0.02 mol) was reduced with 2.06 g (0.09 g-atom) of sodium in *ca.* 80 ml of liquid ammonia to obtain 1.98 g (79%) of 4-nonene isomers, bp 58–59° (49 mm). Analysis by glpc indicated 3.4% *cis*-4-nonene and 96.6% *trans*-4-nonene. *trans*-4-Nonene was separated and identified by infrared and nmr. The infrared spectrum had a strong band at 966 cm^{-1} (lit.[23] 969 cm^{-1}). The nmr spectrum showed a triplet at δ 0.9 (6 H), multiplets at 1.22 (6 H) and 1.95 (4 H), and a septet at 5.38 (2 H).

Reduction of 2,4-Dimethyl-2,3-pentadiene.—2,4-Dimethyl-2,3-pentadiene (2.88 g, 0.03 mol) was reduced with 2.76 g (0.12 g-atom) of sodium in 100 ml of liquid ammonia to give 1.23 g (76%) of 2,4-dimethyl-2-pentene, bp 78–79° (754 mm), $n^{28}D$ 1.4005 (lit.[24] bp 83–84°, $n^{20}D$ 1.4016). The product was found to be pure by glpc. The infrared spectrum showed a band at 1670 cm^{-1} (C=C). The nmr spectrum had a doublet at δ 0.87 (6 H), multiplets at 1.56 (6 H), 2.42 (1 H), and 4.88 (1 H).

Reduction of 3-Ethyl-1,2-pentadiene.—3-Ethyl-1,2-pentadiene (1.92 g, 0.02 mol), on reduction with 2.06 g (0.09 g-atom) of sodium in *ca.* 80 ml of liquid ammonia, gave 1.57 g (81%) of 3-ethyl-2-pentene, bp 91–92° (754 mm), $n^{28}D$ 1.4135 (lit.[25] bp 94–95°, $n^{20}D$ 1.4148). The glpc analysis showed the sample to be pure. The infrared spectrum exhibited a band at 1673 cm^{-1} (C=C). The nmr spectrum had a triplet (with further fine splitting) at δ 0.98 (6 H), a doublet at 1.59 (3 H), mainly a quartet with fine structure at 2.05 (4 H), and a quartet at 4.19 (1 H).

Reduction of Phenylpropadiene.—Phenylpropadiene (2.90 g, 0.025 mol) was reduced with 2.30 g (0.10 g-atom) of sodium in *ca.* 100 ml of liquid ammonia to obtain 2.15 g (72%) of the product, bp 52–55° (16 mm). The glpc analysis showed the presence of *n*-propylbenzene (82%) and allylbenzene (18%). They were separated by glpc and identified by comparison of the infrared and nmr spectra with those of authentic samples.

Reduction of 3-Phenyl-1,2-butadiene.—3-Phenyl-1,2-butadiene (2.60 g, 0.02 mol) was reduced with 0.06 g (0.09 g-atom) of sodium in *ca.* 80 ml of liquid ammonia to yield 1.62 g (42%) of product, bp 60–62° (12 mm). The undistilled polymeric residue accounted for *ca.* 40% of the product. The glpc analysis of the product indicated it to be pure. The product was identified as *sec*-butylbenzene by comparison of the infrared and nmr spectra with those of an authentic sample.

Partial Reduction of 1,2-Nonadiene.—Partial reduction of 1,2-nonadiene (1.24 g, 0.01 mol) using 0.23 g (0.01 g-atom) of sodium in 50 ml of liquid ammonia gave a product mixture (1.01 g) which was found to contain *trans*-2-nonene (18%), 1,2-nonadiene

(23) K. D. Berlin and B. S. Rathore, *Tetrahedron Lett.*, 2547 (1964).
(24) W. J. Hickinbottom, D. Peters, and D. G. M. Wood, *J. Chem. Soc.*, 1360 (1955).
(25) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **88**, 1433 (1966).

(46%), and 2-nonyne (36%) by glpc analysis. These were separated by glpc and identified by infrared and nmr.

Partial Reduction of Phenylpropadiene.—Phenylpropadiene (1.16 g, 0.01 mol) was reduced with 0.23 g (0.01 g-atom) of sodium in 50 ml of liquid ammonia. The reaction product was stirred for 3 hr and worked up in the usual manner. The glpc analysis of the product (0.95 g) showed the presence of *n*-propylbenzene (17.2%), propenylbenzene (22.5%), 1-phenylpropyne (56.8%), and an unidentified product (3.5%). The first three components were separated by glpc and identified by nmr.

When the reaction in another lot was arrested and worked up after just 15 min, the product analysis showed 15.7% *n*-propylbenzene, 19.5% allylbenzene, and 64.8% 1-phenylpropyne.

Reduction of Phenylpropadiene with Equivalent Quantity of Sodium.—Phenylpropadiene (1.16 g, 0.01 mol) in dry ether was added into a solution of 0.46 g (0.02 g-atom) of sodium in 50 ml of liquid ammonia. The reaction mixture was stirred only for 15 min and worked up in the usual way. The product (0.92 g) analysis by glpc showed the presence of *n*-propylbenzene (21.9%), allylbenzene (15.3%), and 1-phenylpropyne (62.8%). These were separated and identified by nmr.

Registry No.—1,2-Octadiene, 1072-19-1; 1,2-nonadiene, 22433-33-6; 2,3-nonadiene, 22433-34-7; 4,5-nonadiene, 821-74-9; 3-ethyl-1,2-pentadiene, 2384-96-5; 2,4-dimethyl-2,3-pentadiene, 1000-87-9; phenylpropadiene, 2327-99-3; 3-phenyl-1,2-butadiene, 22433-39-2.

Acknowledgment.—The authors are indebted to Dr. Nityanand, Assistant Director, Central Drug Research Institute, Lucknow, India, for the nmr spectra.

Syntheses of All of the Racemic Diastereoisomers of Phytosphingosine

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Received June 19, 1969

Ethyl 2-acetamido-3-octadecynoate (**8**), derived from the 2,4-dinitrophenylhydrazone (**4**) of ethyl 2-oxo-3-octadecynoate (**1**) by reductive acetylation, was converted into *trans*- and *cis*-2-acetamido-1-acetoxy-3-octadecenes (**13** and **16**). Dihydroxylation in *trans* fashion of the *trans* compound **13** with performic acid followed by saponification afforded racemic N-acetyl phytosphingosine, the DL-*ribo* isomer **14**, together with the DL-*arabino* isomer **15**. From the *cis* compound **16** there was obtained in the same way the DL-*lyxo* isomer **17**, but the DL-*xylo* compound **18** was not obtained. *cis* dihydroxylation of **13** by silver iodoacetate furnished the DL-*xylo* isomer **18**.

In the previous paper,[1] a synthesis of racemic phytosphingosine and the *lyxo* isomer was described. The procedure was based on the stereospecific reaction of *trans*-glycidic acid with benzylamine to give 2,3-*erythro*-2-benzylamino-3-hydroxy acid.[2] The present paper deals with syntheses of all of the racemic diastereoisomers of phytosphingosine by stereospecific dihydroxylations[3] of 3-octadecene derivatives.

The stereochemical assignments of the products as compared with the natural and the diastereomeric compounds described in the previous paper[1] confirmed that all of the reactions proceeded with known stereochemistry.

The reaction of *n*-hexadecynylmagnesium bromide with diethyl oxalate[4] gave ethyl 2-oxo-3-octadecynoate (**1**) (identified by the semicarbazone **1′**) accompanied by a small amount of tetrakis(1-hexadecynyl)ethylene glycol (**2**), whose constitution was confirmed by oxidation with lead tetraacetate to afford bis(1-hexadecynyl) ketone (**3**) (identified by the 2,4-dinitrophenylhydrazone **3′**). On heating an alcoholic solution of the 2,4-dinitrophenylhydrazone (**4**) of the acetylenic keto ester **1** cyclization into the pyrazole derivative (**5**)[5] was observed. When **1** was treated with hydroxylamine hydrochloride, similar cyclization reaction occurred and the isoxazole derivative (**6**)[6] was formed. On the other hand, the treatment of **1** with hydroxylamine hydrochloride in the presence of sodium acetate furnished an addition–cyclization product (**7**).[7]

Reductive acetylation of the 2,4-dinitrophenylhydrazone **4** to the acetylenic amido ester **8** was carried out with zinc dust.[8] The ester group of **8** was selectively reduced with lithium aluminum hydride to give acetylenic amido alcohol **9**, which was partially hydrogenated to 2-acetamido-1-hydroxy-*trans*-3-octadecene (**10**) with sodium in liquid ammonia,[9] or to the *cis* isomer **12** with Lindlar's catalyst.[10] Alternatively, the same *cis* compound **12** was obtained from **8** by catalytic hydrogenation followed by reduction with lithium aluminum hydride or lithium borohydride.[11]

The *trans*-amido alcohol **10** was transformed into the O-acetate **13** and dihydroxylated in *trans* fashion with performic acid[12] followed by saponification to furnish racemic N-acetyl phytosphingosine (**14**) and the DL-*arabino* isomer **15**. The separation was carried out by fractional recrystallization. Excellent crystallizability of the DL-*arabino* compound **15** aided the isolation of both isomers. The compound **14** was identical

(1) K. Sisido, N. Hirowatari, and T. Isida, *J. Org. Chem.*, **34**, 3539 (1969).

(2) (a) Y. Liwschitz, Y. Rabinsohn, and D. Perera, *J. Chem. Soc.*, 1116 (1962); (b) K. Sisido, N. Hirowatari, and T. Isida, *J. Org. Chem.*, **29**, 2783 (1964).

(3) (a) D. Swern, G. N. Billen, T. W. Findley, and J. T. Scanlan, *J. Amer. Chem. Soc.*, **67**, 1786 (1945); (b) R. B. Woodward and F. V. Brutcher, Jr., *ibid.*, **80**, 209 (1958).

(4) I. I. Lapkin and Yu. S. Andreichikov, *Zh. Org. Knim.*, **1**, 480 (1965); *Chem. Abstr.*, **63**, 1692*h* (1965).

(5) (a) K. Bowden and E. R. H. Jones, *J. Chem. Soc.*, 953 (1946); (b) A. Vaitiekunas, R. E. Miller, and F. F. Nord, *J. Org. Chem.*, **16**, 1603 (1951); (c) K. Sisido, K. Hukuoka, M. Tuda, and H. Nozaki, *ibid.*, **27**, 2663 (1962).

(6) (a) L. Claisen, *Ber.*, **44**, 1161 (1911); (b) A. Quilico, G. Gaudiano, and L. Merlini, *Tetrahedron*, **2**, 359 (1958).

(7) H. Reimlinger and J. J. M. Vandewalle, *Ann. Chem.*, **720**, 117 (1968).

(8) D. Shapiro, H. Segal, and H. M. Flowers, *J. Amer. Chem. Soc.* **80**, 1194 (1958).

(9) (a) F. Sondheimer, *J. Chem. Soc.*, 877 (1950); (b) F. Asinger, B. Fell, and G. Steffan, *Chem. Ber.*, **97**, 1555 (1964).

(10) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

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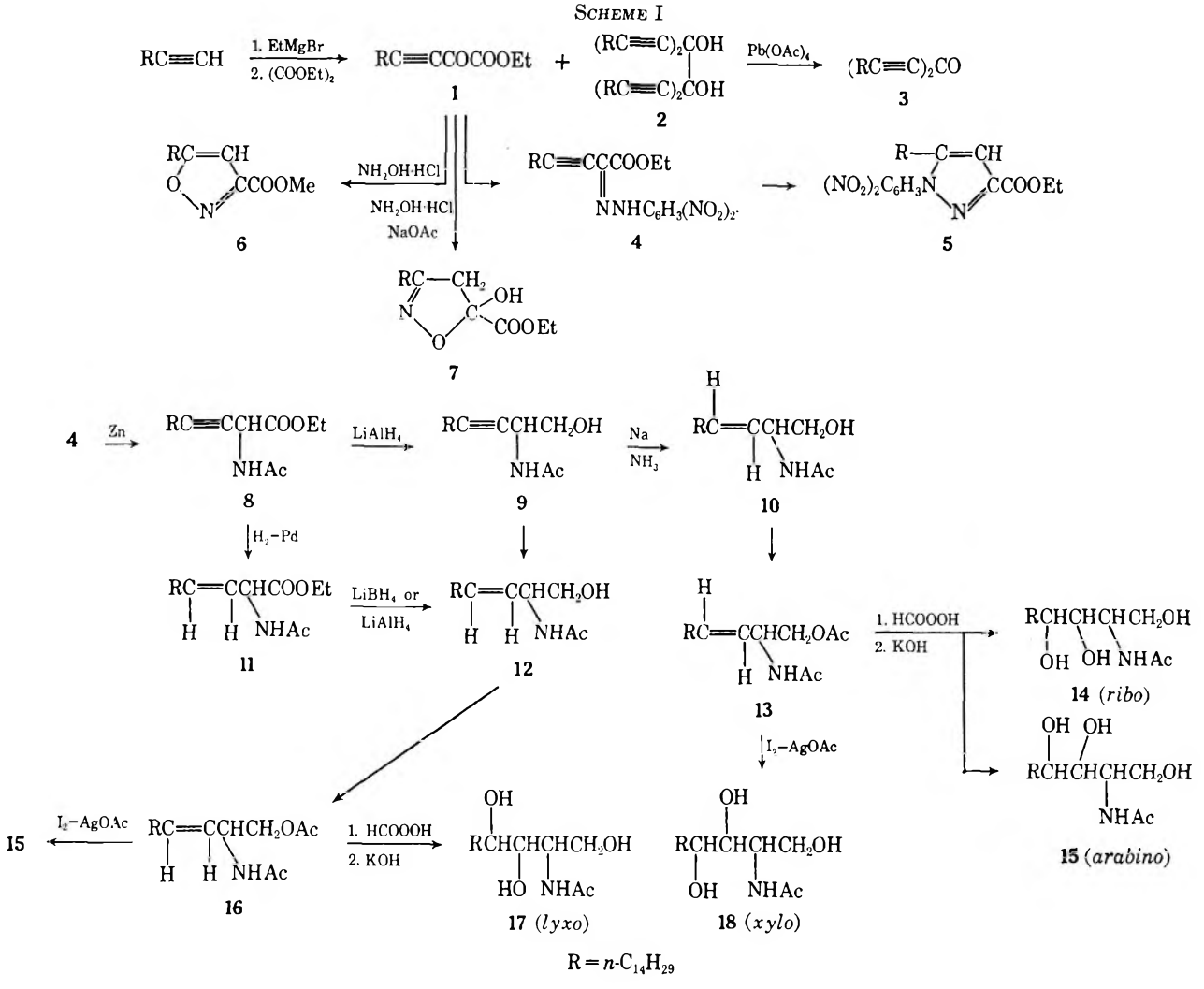
(12) (a) See ref 3a; (b) J. D. Roberts and C. W. Sauer, *J. Amer. Chem. Soc.*, **71**, 3925 (1949); (c) L. F. Fieser and S. Rajagopalan, *ibid.*, **71**, 3938 (1949); (d) J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 3634 (1950); (e) O. Mancera, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **16**, 192 (1951); (f) W. J. Gensler and H. N. Schlein, *J. Amer. Chem. Soc.*, **77**, 4846 (1955).

SCHEME I



in all respects with racemic *ribo*-2-acetamido-1,3,4-trihydroxyoctadecane reported previously[1] and may readily be converted into racemic phytosphingosine.[13]

By similar *trans* dihydroxylation of 2-acetamido-1-acetoxy-*cis*-3-octadecene (**16**) with performic acid, there was obtained the DL-*lyxo* compound **17**; however, the DL-*xylo* isomer **18** was not obtained. By comparison of the spectroscopic data it was proved that the compound **17** was identical with racemic *lyxo*-2-acetamido-1,3,4-trihydroxyoctadecane reported previously.[1]

The failure of the isolation of the DL-*xylo* compound **18** might be accounted for by the preferential formation of the DL-*lyxo* isomer **17** due to the intramolecular asymmetric induction of the groups at the β carbon to the epoxidation point. The opening of the epoxide ring would occur at the δ-carbon position (not at the γ-carbon position) with Walden inversion,[14] owing to the steric effect of the groups at the β carbon. It is presumed that performic acid associates with the acetoxy group (the acetamido group is too short for further reaction), probably by hydrogen bonding with the carbonyl oxygen; as evidenced by the Dreiding model, the attack on the double bond would take place from the side opposite to the acetamido group in the conformation, which avoids the steric interaction between the tetradecyl group and the substituent at the β carbon, thus producing the DL-*lyxo* isomer **17**.

On the other hand, since in the *trans* compound **13** the steric interaction by the tetradecyl group would disappear, the epoxidation could occur irrespective of the conformation, so that there were obtained both DL-*ribo* **14** and DL-*arabino* **15** isomers. The detailed analyses of the products by gas chromatography as well as by thin layer chromatography failed, owing to low separability.

By *cis* dihydroxylation of **13** with silver iodoacetate according to Woodward's procedure[3b,15] there was isolated the DL-*xylo* compound **18**. The corresponding DL-*lyxo* isomer **17**, however, could not be obtained, presumably because of low separability. The infrared spectrum of the mother liquor concentrate showed that this consisted of the mixture. The infrared spectrum of **18** differed distinctly from those of the other three isomers. By the same procedure the DL-*arabino* compound **15** was obtained from **16**, but the DL-*ribo* isomer **14** was not isolated. This result would be consistent with the above reasoning.

Use of the free hydroxyl compounds **10** and **12** instead of **13** and **16** did not give satisfactory results.

(13) D. Shapiro, H. Segal, and H. M. Flowers, *J. Amer. Chem. Soc.*, **80**, 2170 (1958).

(14) D. Swern, *Org. Reactions*, **7**, 378 (1953).

(15) (a) D. Ginsburg, *J. Amer. Chem. Soc.*, **75**, 5746 (1953); (b) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson, and Q. E. Thompson, *ibid.*, **76**, 5014 (1954); (c) P. R. Jefferies and B. Milligan, *J. Chem. Soc.*, 2363 (1956); (d) F. D. Gunstone and L. J. Morris, *ibid.*, 487 (1957); (e) Md. E. Ali and L. N. Owen, *ibid.*, 1066 (1958).

TABLE I
LIST OF NEW COMPOUNDS

Compound	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1′	85–87	$C_{21}H_{37}N_3O_3$	66.45	9.83	11.07	66.19	9.88	11.15
2	62–63.5	$C_{66}H_{118}O_2$	84.00	12.60		83.92	12.78	
3′	59.5–60.5	$C_{39}H_{62}N_4O_4$	71.71	9.79		71.96	9.60	
4	87–90	$C_{26}H_{38}N_4O_6$	62.13	7.62	11.15	62.01	7.71	11.14
5	154–155	$C_{26}H_{38}N_4O_6$	62.13	7.62	11.15	62.38	7.81	10.91
6	72–73	$C_{19}H_{33}NO_3$	70.55	10.28	4.33	70.45	10.44	4.48
7	91.5–92.5	$C_{20}H_{37}NO_4$	67.57	10.49	3.94	67.68	10.65	4.14
8	81–82	$C_{22}H_{39}NO_3$	72.28	10.75	3.83	72.23	10.68	3.73
9	94–95	$C_{20}H_{37}NO_2$	74.25	11.53	4.33	73.98	11.36	4.22
10	81.5–82.5	$C_{20}H_{39}NO_2$	73.79	12.08	4.30	73.59	12.16	4.38
11	70–71	$C_{22}H_{41}NO_3$	71.88	11.24	3.81	71.66	11.12	3.81
12	69.5–70.5	$C_{20}H_{39}NO_2$	73.79	12.08	4.30	73.62	12.33	4.26
13	87.5–89	$C_{22}H_{41}NO_3$	71.88	11.24	3.81	72.00	11.31	3.98
15	138–139.5	$C_{20}H_{41}NO_4$	66.81	11.49	3.90	66.55	11.69	4.14
16	60–61.5	$C_{22}H_{41}NO_3$	71.88	11.24	3.81	71.64	11.36	3.71
18	107.5–109	$C_{20}H_{41}NO_4$	66.81	11.49	3.90	66.52	11.69	3.88
19	133	$C_{18}H_{39}NO_3$	68.09	12.38	4.41	67.86	12.65	4.39
20	101–103	$C_{18}H_{39}NO_3$	68.09	12.38	4.41	68.29	12.67	4.41

Attempted *cis* dihydroxylation with potassium permanganate[16] to yield 3,4-*erythro* compounds did not give the desired acetamidotriols.

Experimental Section[17]

Ethyl 2-Oxo-3-octadecynoate (1) and Tetrakis(1-hexadecynyl)-ethylene Glycol (2).—Using an inverse addition technique, *n*-hexadecynylmagnesium bromide, prepared from 11.1 g (0.05 mol) of 1-hexadecyne[18] and 0.055 mol of ethylmagnesium bromide in 200 ml of anhydrous ether, was added dropwise at −30° to a solution of 7.3 g (0.05 mol) of diethyl oxalate in 50 ml of dry ether. After stirring for 15 min at −30°, the reaction mixture was decomposed with a saturated ammonium chloride solution. After evaporation of the ether, the crystalline glycol **2** separated and was recrystallized from hexane in 6% yield: ir (Nujol) 3490 (OH), 2260 cm^{-1} (C≡C).

The mother liquor of **2** was concentrated and distilled under reduced pressure to give 6.6 g (41%) of **1**: bp 184–186° (2 mm); ir (neat) 2220 (C≡C), 1750 (ester C=O), 1690 cm^{-1} (C=O). Because of the lability of the compound **1** to heat, the elemental analyses did not give correct values for $C_{20}H_{34}O_3$.

Semicarbazone 1′ was recrystallized from hexane: ir (Nujol) 3425, 3340, 3240 and 1690 (=NNHCONH$_2$), 2220 (C≡C), 1740 (ester C=O), 1595 cm^{-1} (C=N).

The 2,4-dinitrophenylhydrazone[19] **(4) of 1**, was recrystallized from benzene–ethanol: ir (Nujol) 3270 and 3140 (NH), 2230 (C≡C), 1745 (ester C=O), 1620 and 1595 cm^{-1} (C=N).

When the Grignard reaction was carried out by a normal addition procedure, **1** and **2** were produced in 7.1 and 39% yields, respectively.

Bis(1-*n*-hexadecynyl) Ketone (3).—A mixture of 3.8 g (0.0022 mol) of **2**, 0.62 g of potassium carbonate, and 1.3 g (0.0022 mol) of lead tetraacetate in 50 ml of dry benzene was stirred for 3 hr at room temperature. The filtrate was concentrated and distilled under reduced pressure to furnish 1.3 g (62%) of **3**: bp 175–180° (1 mm); ir (neat) 2220 (C≡C), 1625 cm^{-1} (C=O).

The 2,4-dinitrophenylhydrazone (3′) was recrystallized from ethanol: ir (Nujol) 3280 and 3090 (NH), 2220 (C≡C), 1620, 1595 cm^{-1} (C=N).

1-(2,4-Dinitrophenyl)-3-ethoxycarbonyl-5-(1-tetradecyl)pyrazole (5).—When the 2,4-dinitrophenylhydrazone **4** was heated in boiling ethanol, the pyrazole derivative **5** was formed and was recrystallized from ethanol: ir (Nujol) 3080 (CH), 1735 (ester C=O), 1610 cm^{-1} (C=N).

3-Methoxycarbonyl-5-(1-tetradecyl)isoxazole (6) and 5-Ethoxycarbonyl-5-hydroxy-3-(1-tetradecyl)isoxazoline (7).—A mixture of 3.17 g (0.00984 mol) of **1** and 0.84 g (0.012 mol) of hydroxylamine hydrochloride in 100 ml of methanol was allowed to stand for 3 days at room temperature. Addition of water afforded precipitates, from which 1.8 g (57%) of the isoxazole derivative[20] **6** was obtained and was recrystallized from hexane: ir (Nujol) 3180 (CH), 1740 (ester C=O), 1605 cm^{-1} (C=N); nmr ($CDCl_3$), δ 2.78 (t, 2, J = 7 Hz), 3.96 (s, 3), 6.42 (s, 1).

When the same reaction was carried out in the presence of anhydrous sodium acetate, the addition product **7** was obtained in 40% yield and recrystallized from hexane: ir (Nujol) 3400 (OH), 1735 (ester C=O), 1625 cm^{-1} (C=N); nmr ($CDCl_3$), δ 1.35 (t, 3, J = 7 Hz), 2.35 (m, 2), 3.00 (d, 1, J = 18 Hz), 3.57 (d, 1, J = 18 Hz), 3.88 (s, 1), 4.32 (q, 2, J = 7 Hz).

Ethyl DL-2-Acetamido-3-octadecynoate (8).—To a suspension of 25 g (0.383 g-atom) of zinc powder in 60 ml of glacial acetic acid and 25 ml of acetic anhydride was added dropwise a solution of 4.00 g (0.00795 mol) of the hydrazone **4** in 100 ml of glacial acetic acid, with vigorous stirring. Filtration of the reaction mixture into ice-water yielded precipitates, from which 2.85 g (98%) of the acetylenic amido ester **8** was obtained and recrystallized from hexane: ir (Nujol) 3300, 1650, and 1535 (amide), 2250 (C≡C), 1760 cm^{-1} (ester C=O).

DL-2-Acetamido-1-hydroxy-3-octadecyne (9).—To a suspension of 0.32 g (0.0084 mol) of lithium aluminum hydride in 50 ml of dry ether was added dropwise[21] a solution of 2.2 g (0.006 mol) of **8** in 100 ml of dry ether at −15°, and the mixture was stirred for 5 hr. The reaction mixture was worked up in the usual way to give 1.5 g (78%) of the product **9**, which was recrystallized from ethyl acetate: ir (Nujol) 3290, 1630 and 1575 (amide), 3160, 3080, 1080, and 1055 cm^{-1} (hydroxy).

DL-2-Acetamido-1-hydroxy-*trans*-3-octadecene (10).—A solution of 2.1 g (0.0065 mol) of **9** in 30 ml of anhydrous tetrahydrofuran was added dropwise to a stirred solution of 3 g (0.13 g-atom) of sodium in 150 ml of liquid ammonia. The mixture was stirred for 3 hr and worked up in the usual way to furnish 1.6 g (76%) of **10**, recrystallized from hexane–ethyl acetate: ir (Nujol) 3270, 1635 and 1585 (amide), 3200, 3120, and 1075 (hydroxy), 965 cm^{-1} (*trans* CH=CH).

Ethyl DL-2-Acetamido-*cis*-3-octadecenoate (11).—A mixture of 2.0 g (0.00548 mol) of **8** and 0.25 g of Lindlar's catalyst in 100

(16) (a) R. P. Linstead, L. N. Owen, and R. F. Webb, *J. Chem. Soc.*, 1225 (1953); (b) P. D. Bartlett and A. Bavley, *J. Amer. Chem. Soc.*, **60**, 2416 (1938).

(17) Ir spectra were measured on Shimazu IR-27B spectrophotometer. Nmr spectra were determined as solutions in $CDCl_3$ with TMS as an internal standard on Japan Electron Optics Laboratory JEOL C-60-H apparatus. The purity of the compounds was established by thin layer chromatography using "Kieselgel G nach Stahl." Microelemental analyses were performed by Mrs. K. Huzimoto of this laboratory on a Yanagimoto Autoanalyzer CHN Corder MT-1. In Table I are listed the new compounds prepared in this experiment. All melting points were corrected.

(18) E. F. Jenny and J. Druey, *Helv. Chim. Acta*, **42**, 401 (1959).

(19) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 219.

(20) Under the acidic conditions, transesterification occurred.

(21) When the addition was carried out as fast as possible at −50°, a large amount of unidentifiable oily materials were formed. The yield depended on the rate of addition and the reaction temperature.

ml of ethyl acetate was hydrogenated at room temperature under hydrogen at atmospheric pressure until the calculated amount of hydrogen (135 ml) was absorbed. In a usual treatment 1.9 g (94%) of **11** was obtained, and recrystallized from hexane: ir (Nujol) 3300, 1650 and 1555 (amide), 3060 and 810 (*cis* CH=CH), 1755 cm^{-1} (ester C=O).

DL-**2-Acetamido-1-hydroxy-*cis*-3-octadecene (12). A. By Reduction of 11 with Lithium Aluminum Hydride.**—To a suspension of 0.273 g (0.007 mol) of lithium aluminum hydride in 20 ml of dry ether was added dropwise a solution of 1.84 g (0.005 mol) of **11** in 100 ml of dry ether at −10° and the mixture was stirred for 5 hr. Upon working up in the usual way there was obtained 1.37 g (84%) of **12**, recrystallized from hexane: ir (Nujol) 3300, 1640 and 1585 (amide), 3240, 3120, 1080, and 1045 cm^{-1} (hydroxy).

B. By Reduction of 11 with Lithium Borohydride.—Selective reduction of **11** to **12** was carried out according to the procedure used by Sallay and coworkers[11] and the product **12** was obtained in 68% yield.

C. By Partial Hydrogenation of 9.—The *cis*-amido alcohol **12** was also prepared in 74% yield by partial hydrogenation of **9** using Lindlar's catalyst.

DL-**2-Acetamido-1-acetoxy-*trans*-3-octadecene (13).**—To a solution of 6.2 g (0.019 mol) of **10** in 100 ml of pyridine was added 30 ml (0.294 mol) of acetic anhydride and the mixture was allowed to stand for 24 hr. There was obtained 4.8 g (69%) of the acetoxy compound **13**, recrystallized from ethyl acetate: ir (Nujol) 3300, 1645, and 1570 (amide), 3090, 1675, and 980 (*trans* CH=CH), 1725 cm^{-1} (ester C=O); R_f 0.40 in chloroform–ethyl acetate–methanol (5:3:1).

DL-**2-Acetamido-1-acetoxy-*cis*-3-octadecene (16).**—In a way similar to that described above the *cis* isomer **16** was prepared in 85% yield and recrystallized from methanol: ir (Nujol) 3320, 1660, 1650, and 1550 (amide), 3120 (*cis* CH=CH), 1740 cm^{-1} (ester C=C); R_f 0.87 in chloroform–ethyl acetate–methanol (5:3:1).

DL-*ribo*-**2-Acetamido-1,3,4-trihydroxyoctadecane (14) and the** DL-*arabino* **Isomer 15.**—A mixture of 3.043 g (0.00828 mol) of **13** and 2 ml of 30% hydrogen peroxide in 50 ml of formic acid was stirred for 24 hr at 40°, during which time, at 7-hr intervals, two 2-ml portions of 30% hydrogen peroxide were added. The reaction mixture was poured into ice–water and the resulting dihydroxylated products were extracted with ether. The combined ether extracts were washed successively with sodium bisulfite, sodium bicarbonate, and water. After drying over sodium sulfate the solvent was removed, and the residue was dissolved in 150 ml of methanol and treated with a saturated aqueous potassium hydroxide solution for 24 hr at room temperature. After removal of the solvent *in vacuo* water was added and the precipitates formed were extracted with ether–chloroform. From this solution there was obtained 2.644 g (88.9%) of a mixture of diastereoisomers, which were recrystallized from ethanol–ethyl acetate–hexane to give 0.563 g (18.9%) of the *arabino* isomer **15**: ir (Nujol) 3440, 1605 and 1585 (amide), 3330, 3240, 3100, and 1060 cm^{-1} (hydroxy); R_f 0.48 in chloroform–methanol–2.8% ammonium hydroxide (50:10:1).

The residue obtained from the mother liquor was recrystallized from acetone to furnish 0.441 g (14.9%) of the *ribo* isomer **14**, identical in all respects with racemic N-acetyl phytosphingosine reported previously.[1]

DL-*lyxo*-**2-Acetamido-1,3,4-trihydroxyoctadecane (17).**—By similar *trans* dihydroxylation of **16** with performic acid followed by saponification as described above, there was isolated in 63% yield the racemic N-acetylaminotriol **17**, identical in all respects with the racemic *lyxo* compound reported previously.[1]

From the mother liquor the DL-*xylo* isomer **18** could not be isolated.

DL-*xylo*-**2-Acetamido-1,3,4-trihydroxyoctadecane (18) and the** DL-*arabino* **Isomer 15.**—To a vigorously stirred mixture of 3.68 g (0.01 mol) of **13** and 3.7 g (0.022 mol) of silver acetate in 65 ml of glacial acetic acid was added at room temperature 2.6 g (0.0102 mol) of finely powdered iodine, in small portions. After stirring for 30 min, 10 ml of aqueous acetic acid (containing 0.20 g of water) was added and the reaction mixture was heated at 90–95° for 6 hr with vigorous stirring. After the usual work-up,[3b] there was obtained 0.54 g (15%) of the racemic *xylo* compound **18**, recrystallized from acetone: ir (Nujol) 3300, 1635, and 1540 (amide), 3200 and 1065 cm^{-1} (hydroxy); R_f 0.40 in chloroform–methanol–2.8% ammonium hydroxide (50:10:1).

The DL-*lyxo* compound **17** could not be isolated.

When **16** was treated similarly, the *arabino* isomer **15** was obtained in 29% yield. The *ribo* compound **14** was not obtained.

DL-*arabino*-**2-Amino-1,3,4-trihydroxyoctadecane (19) and the** DL-*xylo* **Isomer 20.**—A solution of 0.32 g of **15** and 1.5 g of potassium hydroxide in 100 ml of 90% methanol was heated under reflux for 6 hr.[13] After removal of the solvent *in vacuo*, water was added, and the precipitate formed was recrystallized from acetonitrile–ethanol to give 0.22 g (78%) of **19**: ir (Nujol) 3370, 1595, and 1575 (amino), 3350–2770 and 1040 cm^{-1} (hydroxy); R_f 0.42 in chloroform–methanol–2.8% ammonium hydroxide (35:10:1).

Similarly, the *xylo* compound **20** was obtained from **18** in 73% yield and was recrystallized from hexane–ethanol: ir (Nujol) 3330 and 1600 (amino), 3300–2740 and 1100–970 cm^{-1} (hydroxy); R_f 0.51 in chloroform–methanol–2.8% ammonium hydroxide (35:10:1).

Registry No.—**1**, 22566-56-9; **1′**, 22577-01-1; **2**, 22566-57-0; **3**, 22566-58-1; **3′**, 22566-59-2; **4**, 22566-60-5; **5**, 22594-00-9; **6**, 22566-24-1; **7**, 22566-25-2; **8**, 22565-70-4; **9**, 22565-71-5; **10**, 22565-72-6; **11**, 22577-02-2; **12**, 22565-73-7; **13**, 22565-76-0; **15**, 22565-77-1; **16**, 22565-78-2; **18**, 22565-79-3; **19**, 22565-80-6; **20**, 22565-81-7.

The Addition of Bromotrichloromethane to α,β-Unsaturated Ketones. A Nuclear Magnetic Resonance Study of the Addition Products

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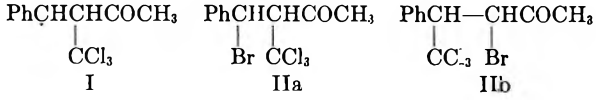
Received June 24, 1969

The free-radical addition of bromotrichloromethane to benzylideneacetone and benzylideneacetophenone yielded mainly $PhCHBrCH(CCl_3)CCCH_3$ and $PhCHBrCH(CCl_3)COPh$, respectively. The structures of the adducts have been assigned unambiguously through nmr study involving solvent effects on acyclic ketones and comparison of data of several related compounds of known structures.

The free-radical addition of bromotrichloromethane to unsymmetrical olefins RCH=CHR′ has been studied,[1,2] and the mode of addition in each case afforded an intramolecular comparison of the stabilizing influences of the substituents R and R′ on the free alkyl radicals. The scale of relative stabilizing effects[1] was found to be Ph > CN ≈ CO > CO_2Et ≈ CO_2H > Me. Considering the stabilizing effects of the phenyl and ketonic groups, the addition of bromotrichloromethane to benzylideneacetone would be expected to lead to the intermediate radical I and hence the product IIa.



I IIa IIb

Although this reaction was reported, attempts to degrade the adducts to known products were not successful.[1] Further, it was also recorded[3] that in the addition of thiyl radicals (R·) to α,β-unsaturated ketones, including benzylideneacetone, the radical (R·) adds at the carbon β to the carbonyl. In view of the difference in the orientation of free-radical addition, we thought that it would be important to determine the structure of the adduct II.

Nmr study of several acyclic ketones indicates that protons α to the carbonyl group are subject to benzene-induced solvent shifts, as in the case of alicyclic ketones,[4] and thus can be distinguished from other protons. Therefore the nmr signals can be accurately assigned to the protons in II. By comparing the chemical-shift data of several related compounds of known structures, it is possible to determine unambiguously the positions of the Br and CCl_3 groups. This study was extended to the reaction of bromotrichloromethane and benzylideneacetophenone. The adduct III is expected to have the structure IIIa. Detailed discussion of the nmr study is given below.

IIIa IIIb

The nmr signals of protons α to the carbonyl group in alicyclic compounds are known to shift upfield in benzene solution relative to deuteriochloroform solution.[4] The nmr spectra of several acyclic ketones have been obtained in both benzene and deuteriochloroform solutions. The chemical-shift data are tabulated below.

TABLE I
NMR CHEMICAL-SHIFT DATA FOR ACYCLIC KETONES[a]

Compd	Formula	Protons	$\tau_{C_6H_6}$	τ_{CDCl_3}	$\Delta = \tau_{C_6H_6} - \tau_{CDCl_3}$
IV	$CH_{3a}COCH_{3a}$	a	8.44	7.85	0.59
V	$CH_{3a}COCH_b(CH_{3c})_2$	a	8.32	7.87	0.45
		b	7.90	7.43	0.47
		c	9.16	8.90	0.26
VI	$CH_{3a}COCH_{2b}CH_{3c}$	a	8.42	7.86	0.56
		b	8.18	7.54	0.64
		c	9.17	8.95	0.22
VII	$PhCOCH_{2b}CH_{3c}$	b	7.54	7.03	0.51
		c	8.95	8.78	0.17
VIII	$(CH_{3c}CH_{2b})_2CO$	b	8.11	7.57	0.54
		c	9.10	8.94	0.16
IX	$PhCH_cCH_bCOCH_{3a}$ (Br, Br)	a	8.05	7.54	0.51
		b	5.38	5.07	0.31
		c	4.73	4.69	0.04

[a] Values are in parts per million. All determinations were carried out in dilute solutions (<2%).

Table I shows that, for compounds IV–VIII, methyl protons α to the carbonyl group shift upfield by 0.45–0.59 ppm in benzene solution relative to deuteriochloroform solution; methylene or methine protons α to the carbonyl also shift upfield by about the same amount. Methyl protons β to the carbonyl group are also observed to shift upfield in these compounds, but by lesser amounts. These results are used to assign the pair of AB doublets due to protons b and c in the nmr spectrum of compound IX.

These chemical-shift data observed for acyclic ketones in benzene and chloroform solutions are consistent with similar data observed for alicyclic ketones, such as keto steroids.[4] Certainly, it is the same solute–solvent interaction that gives rise to this benzene-induced upfield shift in these ketones. An explanation in terms of a collision complex between the ketone compound and the benzene molecule has been offered by Bhacca and Williams.[4]

The upfield shift of protons α to the carbonyl group may be used to help in elucidating the correct structures of the reaction products II and III described above. The nmr spectra of these compounds have been determined in both benzene and deuteriochloroform solutions at *ca.* 0.25 *M* or less.

The nmr spectrum of II consists of a pair of AB doublets and a methyl peak, plus the phenyl-proton peaks, with parameters shown in Table II. As the methyl peak and the higher field doublet (τ 5.78)

(1) R. L. Huang, *J. Chem. Soc.*, 1342 (1957).
(2) J. I. G. Cadogan, E. G. Duell and P. W. Inward, *ibid.*, 4164 (1962).
(3) F. W. Stacey and J. F. Harris, Jr., *Org. Reactions*, **13**, 150 (1963).
(4) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 7.

shift upfield in benzene solution, this higher field doublet may be assigned to the proton α to the carbonyl group.

TABLE II
NMR DATA FOR COMPOUND II

AB doublets, τ, ppm		J, Hz	Methyl, τ, ppm	Solvent
4.52	5.52	10.3	7.37	$CDCl_3$
4.55	5.78	10.0	7.75	C_6H_6
0.03	0.26		0.38	$\Delta = \tau_{C_6H_6} - \tau_{CDCl_3}$

The nmr spectrum of III consists of a pair of AB doublets for the aliphatic protons, plus the phenyl-proton peaks, with parameters shown in Table III. In this case the relative shifts in the two solvents are too small to be significant. In view of the large groups near the aliphatic protons, the lack of any significant relative shift in the two solvents can be explained in terms of steric factors preventing any substantial interaction between the molecule and the solvent molecules.

TABLE III
NMR DATA FOR COMPOUND III

AB doublets, τ, ppm		J, Hz	Solvent
4.26	4.54	10.2	$CDCl_3$
4.19	4.57	10.2	C_6H_6

The benzene-induced solvent shifts found for the benzylidene–acetone product assign chemical shifts to the protons α and β to the carbonyl group, respectively. Reference compounds may be used to establish the chemical shifts of protons adjacent to bromine and trichloromethyl groups and thus to locate these groups relative to the carbonyl group. To this end the nmr spectra of the following compounds have been obtained, with the chemical-shift data in deuteriochloroform solution indicated below the respective protons.

$PhCHBrCH_2Br$	$PhCHBrCH_2CCl_3$
X	XI
4.91 6.01	4.60 6.25
$PhCHBrCHBrPh$	$PhCHBrCHCCl_3Ph$
XII	XIII
4.55	4.13 5.70

Comparison of the τ values in compounds X and XI shows that the protons in the fragment CH_2Br have a lower τ value than those in the fragment CH_2CCl_3. This may indicate that Br as a substituent in a molecule confers a lower τ value on protons attached to the same carbon atom than does the substituent CCl_3, other conditions being the same. This point, together with the chemical-shift datum of the aliphatic protons of compound XII, may be used to assign the nmr spectrum of the aliphatic protons of compound XIII.

Compound IX–XIII show that the proton in the fragment PhCHBr in various molecular environments has a τ value less than 5. In compound IX, if the Br on the carbon adjacent to the carbonyl group is replaced by a trichloromethyl group, CCl_3, to give $PhCHBrCHCCl_3COCH_3$ (IIa), it is expected that the proton in the PhCHBr fragment has a τ value less than 5 and that of the proton in the fragment $CHCCl_3CO$ has a τ value higher than 5. If compound II is assigned the structure as shown, the observed τ values of the aliphatic protons, which are 4.52 and 5.52 ppm in deuteriochloroform solution, would be consistent with this structure.

If compound II is assigned the alternative structure $PhCHCCl_3CHBrCOCH_3$ (IIb), the proton in the fragment $PhCHCCl_3$ should be assigned the higher τ value, 5.52, on the basis of the data for compound XIII. However, it has been shown above that the benzene-induced solvent shift involves the proton associated with this τ value, and the resonance signal of the proton in this fragment, $PhCHCCl_3$, is not expected to involve this shift in this structure. Hence this structure is ruled out.

The τ values 4.26 and 4.54 for III indicate that the fragment $PhCHCCl_3$ is not present. This is obvious from examination of the data for compound XIII, in which the proton in the fragment $PhCHCCl_3$ has a τ value of 5.70. This rules out structure IIIb for the adduct. Further, by analogy with the reaction of benzylideneacetone, it may be deduced that the adduct has structure IIIa.

Experimental Section

The nmr measurements were made with a Hitachi Perkin-Elmer R-20A high-resolution nmr spectrometer. Proton chemical shifts are reported in parts per million with respect to tetramethylsilane (TMS) as internal standard and frequently checked with the cyclohexane signal at 1.42 ppm from TMS. Thus the chemical-shift data are accurate to within ±0.02 ppm.

Acetone, methyl isopropyl ketone, methyl ethyl ketone, diethyl ketone, and propiophenone were of reagent grade and distilled twice before use. Benzylideneacetone dibromide, mp 123.5–124.5° (lit.[5] mp 124–126°), styrene dibromide, mp 74–75° (lit.[6] mp 74–74.5°), and stilbene dibromide, mp 236–238° (lit.[6] mp 237°), were prepared from benzylideneacetone, styrene, and stilbene, respectively, by the addition of bromine in carbon tetrachloride. 1-Bromo-2-trichloromethylethylbenzene,[7] mp 51–52°, 1-bromo-2-trichloromethylhydrostilbene,[2] mp 112–113°, and 4-bromo-4-phenyl-3-trichloromethylbutan-2-one,[1] mp 98–99°, were prepared according to the methods reported in the literature.

The addition of bromotrichloromethane (80 g, 400 mmol) to benzylideneacetophenone (14.3 g, 69 mmol) catalyzed by benzoyl peroxide (4.0 g, 17 mmol) was carried out under the same conditions as in the preparation of 4-bromo-4-phenyl-3-trichloromethylbutan-2-one.[1] The crude adduct, yield 13 g (46%), mp 118–133°, was recrystallized from methanol to give 2-bromo-2-phenyl-1-trichloromethylethyl phenyl ketone, mp 140.4–141°.

Anal. Calcd for $C_{16}H_{12}OBrCl_3$: C, 47.3; H, 2.9. Found: C, 47.4; H, 3.2.

Registry No.—Bromotrichloromethane, 75-62-7; IIa, 22431-13-6; IIIa, 22431-14-7; IV, 67-64-1; V, 563-80-4; VI, 78-93-3; VII, 93-55-0; VIII, 96-22-0; IX, 6310-44-7.

Acknowledgment.—One of us (S. N.) wishes to acknowledge a Visiting Lectureship in the Department of Chemistry, University of Hong Kong, 1969, during which period the nmr work reported here was carried out, as well as a travel grant from the Lee Foundation, Kula Lumpur.

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Acid-Catalyzed Isomerizations of β,γ-Unsaturated Ketones[1]

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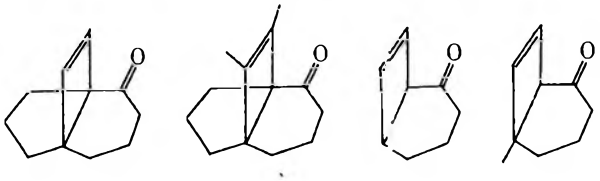
Received April 10, 1969

The tricyclo[4.3.2.0^{1,6}]undec-10-en-2-ones (**1** and **2**) undergo acid-catalyzed isomerization to the tricyclo-[3.3.3.0^{1,6}]undec-3-en-2-ones (**5** and **8**), respectively. On the other hand, the more reactive bicyclo[4.2.0]oct-7-en-2-ones (**3** and **4**) isomerize to bicyclo[3.2.1]oct-6-en-8-ones (**13** and **21**), respectively, rather than to bicyclo-[3.3.0]oct-3-en-2-ones. The isomerizations of the bicyclic ketones occur under conditions considerably milder than those required for rearrangement of the tricyclic ketones. Possible mechanisms for these isomerizations are offered.

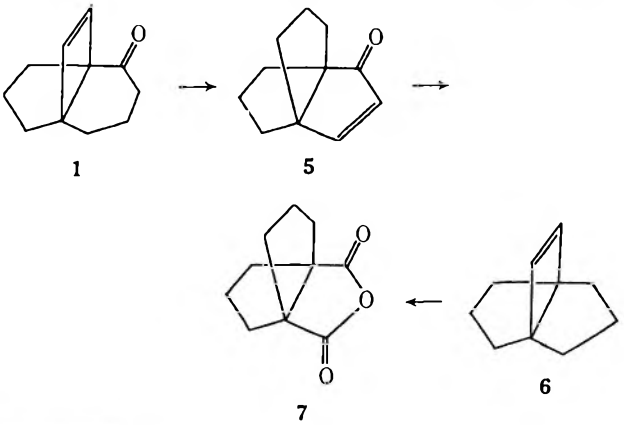
As part of a general study of the effects of acids on polycyclic β,γ-unsaturated ketones,[3,4] we have examined the acid-catalyzed rearrangements of the ketones **1**, **2**, **3**, and **4**. We report our findings here.



1 **2** **3** **4**

The synthesis of **1** involved photocycloaddition of 1,2-dichloroethylene to bicyclo[4.3.0]non-1(6)-en-2-one followed by dehalogenation with sodium in liquid ammonia. When care was taken to ensure the anhydrous nature of the ammonia, we found no further reduction of **1** to the corresponding alcohol. Ketone **2** was obtained from photocycloaddition of 2-butyne to the previously mentioned bicyclononenone. Ketones **3** and **4** were obtained by hydrolysis of the corresponding ketals[5,6] in 5% sulfuric acid.

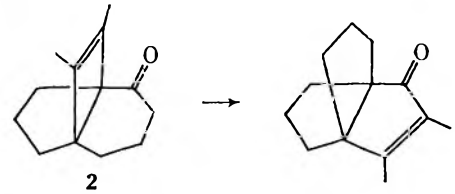
When ketone **1** was treated with *p*-toluenesulfonic acid in boiling benzene, a new α,β-unsaturated ketone [λ_{max}^{EtOH} 228 nm (ε 7200), $\bar{\nu}_{max}^{CCl_4}$ 1710 cm^{-1}, and δ 5.91 and 7.33 ppm (doublets, J_{AX} = 6 Hz)] was obtained in 68% yield, uncontaminated with other species of similar volatility. The rearranged ketone is assigned structure **5** on the basis of the above spectra and its oxidation to



1 **5** **7** **6**

anhydride **7** which has also been obtained from olefin **6**.[7]

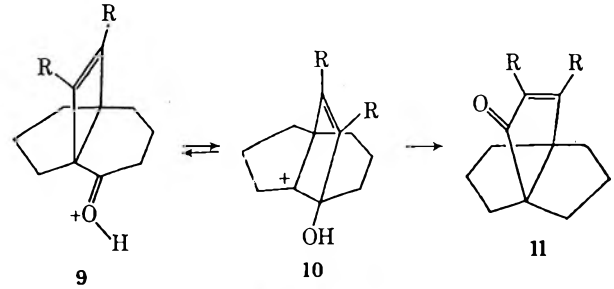
Similar treatment of **2** led to the formation of an isomeric, conjugated ketone in 85% yield, having the spectral properties expected for **8**, the structure assigned to this new ketone. The latter change, **2** → **8**, is exactly analogous with the previously mentioned **1** → **5** change.



2 **8**

We suggest that the two isomerizations discussed above occur as is outlined in Scheme I. Net migration of the etheno bridge from C-1 to C-2 in the protonated ketone **9**, a process in which considerable strain relief is realized, leads to **10**, a substituted 8-bicyclo[3.2.1]-octenyl cation which is presumably well stabilized.[8] A Wagner–Meerwein shift leads to the observed products **11** (**11a** ≡ **5**, **11b** ≡ **8**).

SCHEME I



9 **10** **11**

a, R = H
b, R = CH_3

Attempts to purify ketone **3** by gas chromatography under conditions which **1** and **2** survived without any rearrangement or decomposition were unsuccessful in that the collected material exhibited spectra and tlc data indicative of the presence of two compounds; however, pure **3** (tlc, nmr) could be obtained after ketal hydrolysis by distillation. Injection of pure **3** into the gas chromatograph led to the formation of a second compound, whereupon we suspected that an acid-catalyzed rearrangement had occurred on the column.

(1) We thank the National Science Foundation for their generous support of this research.

(2) National Science Foundation Trainee, 1966–1969.

(3) For a preliminary account of this work, see F. L. Cargill and J. W. Crawford, *Tetrahedron Lett.*, 169 (1967).

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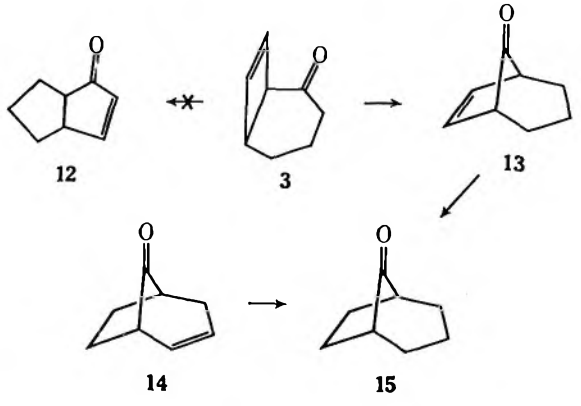
(8) G. W. Klumpp, G. Ellen, and F. Bickelhaupt, *Rec. Trav. Chim. Pays-Bas*, **88**, 474 (1969).

Several attempts to carry out the presumed rearrangement with various acids in solution led only to rapid decomposition of **3**; no volatile material was detected.[9] However, when **3** was passed in a stream of helium through a column of acid-washed alumina maintained at 200°, a new crystalline ketone was obtained in 28% yield. No starting material was recovered, indicating that considerable decomposition of either **3** or the new product had occurred.

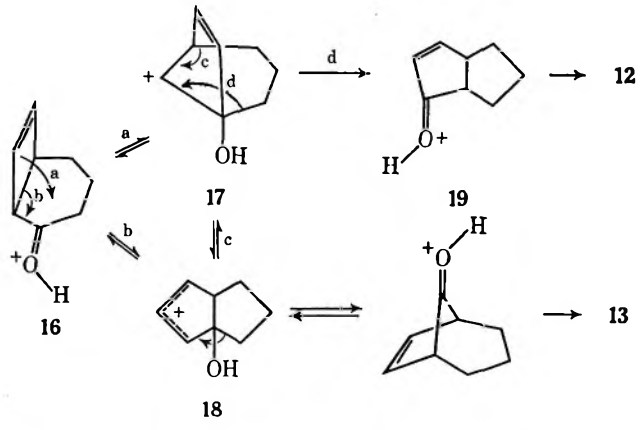
Based on the analogy of the rearrangements discussed above in terms of Scheme I, we felt that **3** should undergo isomerization to **12**; however, comparison of the spectral data for the new ketone [λ_{max}^{EtOH} 272 nm (ϵ 13) and $\nu_{max}^{CCl_4}$ 1750, 1720, 1660, and 1620 cm^{-1}] with those of **12**[10,11] [λ_{max}^{EtOH} 224 nm (ϵ 11,600) and 319 (39) and $\nu_{max}^{CCl_4}$ 1705 and 1590 cm^{-1}] clearly showed our reasoning to be in error. That the product of this rearrangement is **13** became evident from its hydrogenation to the known ketone **15**[12,13] coupled with its nonidentity with the known enone **14** (see Scheme II).

SCHEME II

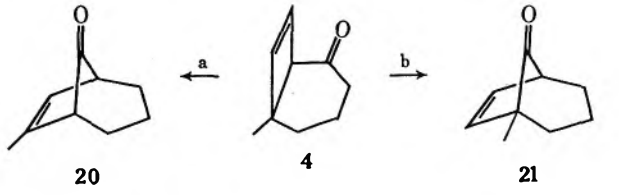


The intermediacy of ion **18** is almost certainly required for the conversion of **3** into **13**. Two paths from **3** to **18** are evident (Scheme III). One, path a, is similar to the changes outlined earlier in Scheme I: migration of the etheno bridge to yield **17** followed by an alkyl shift *via* path c leads to **18**. The second, path b, only requires a shift of the C-1–C-6 bond in **16** from C-1 to C-2, giving **18** directly.[14] The absence of **12** in the product would be very difficult to rationalize if path a were the preferred one, since **17** would be expected to rearrange to the more stable ion **19** (*via* path d) in the manner already outlined in the isomerizations of **1** and **2**.

SCHEME III

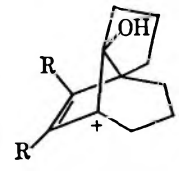


The question of which of the two proposed paths is in fact the favored one is easily resolved by a simple labeling experiment. Thus, rearrangement *via* path a leads to conversion of C-6 of **3** into a trigonal C-6 in **13**, whereas isomerization *via* path b allows the bridgehead C-6 of **3** to remain at a bridgehead in **13**. Rearrangement of ketone **4** may yield either **20** or **21** *via* path a or b, respectively.



Ketone **4** was found to undergo isomerization when warmed in benzene containing *p*-toluenesulfonic acid to yield a single product. That the new isomer is **21** follows from the nmr spectrum, which shows the presence of two vinyl hydrogens and a methyl on quaternary carbon, as well as other spectroscopic data (see Experimental Section). Path a is therefore eliminated and the correctness of path b is corroborated, if not established.

The absence of **12** in the rearrangement product from **3** is now readily explained: the required intermediate, **17**, is bypassed in favor of direct isomerization of **16** to **18**, thus providing no path from **3** to **12**. In the tricyclic systems, **1** and **2**, isomerization *via* path b leads to ion **22**, a relatively poor bridgehead carbonium ion and one whose only available path of deactivation, if formed in the absence of nucleophiles, is reversion to starting material. The next higher energy path is, therefore, followed.



22

In summary, we have described acid-catalyzed isomerizations which lead in two cases to the [3.3.3]-propellane system[15,16] and in a second pair of cases to the previously unknown bicyclo[3.2.1]oct-6-en-8-ones.

(9) Similar attempts to observe the acid-catalyzed isomerization of quadricyclanone to bicyclo[3.2.0]hepta-3,6-dien-2-one in solution were unsuccessful: P. R. Story and S. R. Farenholtz, *J. Amer. Chem. Soc.*, **87**, 1623 (1965). We thank Professor Story for informing us of these nonresults.

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(13) C. S. Foote and R. B. Woodward, *Tetrahedron*, **20**, 687 (1964).

(14) Although path b is inoperative in the related bicyclo[3.2.0]heptenyl systems, it is evidently the favored path in the less rigid bicyclo[4.2.0]-octyl and -octenyl systems. See G. Büchi and E. M. Burgess, *J. Amer. Chem. Soc.*, **82**, 4333 (1960); S. C. Lewis and G. H. Whitham, *J. Chem. Soc., C*, 274 (1967); R. L. Cargill, D. M. Pond, and S. O. LeGrand, *J. Org. Chem.*, **35**, 359 (1970); A. C. Cope, R. W. Gleason, S. Moon, and C. H. Park, *ibid.*, **32**, 942 (1967); and S. P. Pappas, B. C. Pappas, and N. A. Portnoy, *ibid.*, **34**, 520 (1969).

(15) D. Ginsburg, *Accounts Chem. Res.*, **2**, 120 (1969).

(16) H. W. Thompson, *J. Org. Chem.*, **32**, 1222 (1967).

The synthetic utility of these rearrangements is obvious, and in subsequent publications we shall discuss other examples of the usefulness of these transformations as well as the chemistry of the isomerization products.

Experimental Section[17]

Tricyclo[4.3.2.0^{1,6}]undec-10-en-2-one (1).—A solution of 2.60 g (0.0191 mol) of bicyclo[4.3.0]non-1(6)-en-2-one[18] and 3 ml of a mixture of *cis*- and *trans*-1,2-dichloroethylenes in 80 ml of pentane was irradiated (Corex) for 30 min. Progress of the reaction was measured by glpc (3% DEGS, 8 ft × 0.125 in., 120°, 12 ml/min He). Removal of the solvent and excess dichloroethylene by distillation left a brown oil, which was dissolved in 100 ml of dry ether and introduced into a 3-l. flask containing 2 l. of freshly distilled, anhydrous ammonia. Small pieces of sodium metal were added until the solution remained dark blue. After the blue solution had stirred for an additional 10 min, ammonium chloride was added to destroy excess sodium and the ammonia was allowed to evaporate. Water was added to the residue and the resulting solution was extracted with three 100-ml portions of ether. The ethereal extract was dried (Na_2SO_4), concentrated, and distilled, giving 2.38 g (77.0%) of **1**: bp 71–73° (0.25 Torr); uv max (95% C_2H_5OH) 296 nm (ϵ 85); ir (CCl_4) 3120, 3030 (HC=CH), and 1700 cm^{-1} (C=O); nmr (CCl_4) δ 5.97 (q, 2, J_{AB} = 2.8 Hz, Δ_{AB} = 10.5 Hz) and 1.75 ppm (m, 12).

The 2,4-dinitrophenylhydrazone was recrystallized from methanol–water, mp 123.0–123.5°.

Anal. Calcd for $C_{17}H_{18}N_4O_4$ (mol wt 342.35): C, 59.64; H, 5.30; N, 16.37. Found: C, 59.61; H, 5.40; N, 16.28.

10,11-Dimethyltricyclo[4.3.2.0^{1,6}]undec-10-en-2-one (2).—A solution of 2.40 g (0.0176 mol) of bicyclo[4.3.0]non-1(6)-en-2-one and 4 ml of 2-butyne in 80 ml of pentane was irradiated (Corex) for 30 min. The progress of the reaction was measured by glpc (3% DEGS, 8 ft × 0.125 in., 120°, 12 ml/min He). Removal of the pentane and excess 2-butyne left a residue from which 2.23 g (66.5%) of **2** was distilled: bp 114–116° (7 Torr); uv max (95% C_2H_5OH) 296 nm (ϵ 168); ir (CCl_4) 1695 (C=O) and 1410 cm^{-1} ($COCH_2$); nmr (CCl_4) δ 1.45 ppm (m).

An analytical sample was further purified by preparative glpc (20% DEGS, 10 ft × 0.25 in., 160°, 120 ml/min He) and subsequent distillation.

Anal. Calcd for $C_{13}H_{18}O$ (mol wt 190.27): C, 82.06; H, 9.54. Found: C, 81.88; H, 9.67.

The *p*-toluenesulfonylhydrazone was recrystallized from methanol–water, mp 136.0–136.5°.

Anal. Calcd for $C_{20}H_{26}N_2O_2S$: (mol wt 347.50): C, 67.02; H, 7.31; N, 7.82. Found: C, 67.17; H, 7.25; N, 7.89.

Bicyclo[4.2.0]oct-7-en-2-one (3).—A solution of 5.95 g (0.0359 mol) of bicyclo[4.2.0]oct-7-en-2-one ethylene ketal[5,6] in 200 ml of ether was stirred at 25° with 30 ml of 5% sulfuric acid for 15 hr. The aqueous phase was extracted with 100 ml of ether and the ethereal solutions were combined, washed with aqueous sodium bicarbonate and water, dried ($MgSO_4$), concentrated, and distilled, giving 3.34 g (76.3%) of **3**: bp 78–80° (20 Torr); ir (neat) 3105, 3040 (HC=CH), 1700 (C=O), and 780 and 700 cm^{-1} (*cis* HC=CH); nmr (CCl_4) δ 6.0 (q, 2, J_{AB} = 5.0 Hz, Δ_{AB} = 20.0 Hz, vinyl), 3.30 (m, 2, bridgehead), and 1.90 ppm (m, 6, methylene).

The *p*-toluenesulfonylhydrazone was recrystallized from methanol–water, mp 146–147°.

Anal. Calcd for $C_{15}H_{18}N_2O_2S$ (mol wt 290.31): C, 62.05; H, 6.25; N, 9.65. Found: C, 62.02; H, 6.08; N, 9.80.

Tricyclo[3.3.3.0^{1,5}]undec-3-en-2-one (5).—A solution of 1.92 g (0.0118 mol) of **1** and 0.8 g of *p*-toluenesulfonic acid monohydrate in 50 ml of benzene was refluxed for 10 min. The cooled reaction mixture was washed with 20% sodium bicarbonate, concentrated, and distilled, giving 1.32 g (68.7%) of **5**: bp 95° (bath) (0.25 Torr); uv max (95% C_2H_5OH) 228 nm (ϵ 7200) and 314 (73); ir (CCl_4) 1710 (C=O) and 1595 cm^{-1} (C=C); nmr (CCl_4) δ 7.33 (d, 1, J_{AX} = 6.0 Hz), 5.91 (d, 1, J_{AX} = 6.0 Hz, O=CCH=CH), and 1.3–2.1 ppm (m, 12, methylene).

An analytical sample was further purified by preparative glpc (20% DEGS, 10 ft × 0.25 in., 180°, 50 ml/min He) and subsequent distillation.

Anal. Calcd for $C_{11}H_{14}O$ (mol wt 162.22): C, 81.44; H, 8.70. Found: C, 81.37; H, 8.65.

3,4-Dimethyltricyclo[3.3.3.0^{1,5}]undec-3-en-2-one (8).—A solution of 0.92 g (0.0048 mol) of **2** and 50 mg of *p*-toluenesulfonic acid monohydrate in 50 ml of benzene was refluxed for 72 hr. The cooled reaction mixture was washed with 5% sodium bicarbonate, concentrated, and distilled, giving 0.78 g (85%) of **8**: bp 125° (bath) (0.55 Torr); uv max (95% C_2H_5OH) 248 nm (ϵ 10,380) and 314 (83); ir (CCl_4) 1700 (C=O) and 1645 cm^{-1} (C=C); nmr δ 1.91 (m) and 1.50 ppm (m).

An analytical sample was further purified by preparative glpc (20% DEGS, 10 ft × 0.25 in., 160°, 120 ml/min He) and subsequent distillation.

Anal. Calcd for $C_{13}H_{18}O$ (mol wt 190.27): C, 82.06; H, 9.54. Found: C, 81.81; H, 9.41.

Bicyclo[3.2.1.]oct-6-en-8-one (13).—A total of 0.573 g (0.00421 mol) of **3** was injected in 50-μl portions into a stream of helium flowing at 4 ml/min over a column (1 × 15 cm) of acid-washed alumina (Merck), which was maintained at 200° by means of a heating tape. The eluate was trapped in an air-cooled U tube and amounted to 0.147 g (28.8%) of **13**: mp 110.5–111°; uv max (95% C_2H_5OH) 272 nm (ϵ 13); ir (CCl_4) 3050 (=CH), 1750, 1720 (C=O), 1650, 1620 (C=C), and 750 and 720 cm^{-1} (HC=CH); nmr (CCl_4) δ 6.12 (t, 2, J = 2 Hz, vinyl), 2.61 (m, 2, bridgehead), and 1.68 ppm (m, 6, methylene).

The 2,4-dinitrophenylhydrazone was recrystallized from methanol–water, mp 158–159°. The 2,4-dinitrophenylhydrazone of bicyclo[3.2.1]oct-2-en-8-one had a melting point of 176.4–177.2°.[13]

Anal. Calcd for $C_{14}H_{14}N_4O_4$ (mol wt 302.28): C, 55.62; H, 4.67; N, 18.54. Found: C, 55.81; H, 4.82; N, 18.70.

Bicyclo[3.2.1]octan-8-one (15).—A solution of 0.298 g (0.00244 mol) of **13** in 50 ml of methanol was hydrogenated over 50 mg of palladium (5% on charcoal) at 1-atm pressure. The catalyst was removed and the filtrate was combined with 75 ml of water and extracted with three 50-ml portions of pentane. The pentane extracts were combined, dried ($MgSO_4$), and concentrated, and the residue was purified by glpc (20% DEGS, 10 ft × 0.25 in., 170°, 50 ml/min He), giving 0.113 g (38.1%) of **15**, mp 140–141° (lit.[13] mp 140–141°).

The 2,4-dinitrophenylhydrazone was recrystallized from methanol–water, mp 174–175° (lit.[13] mp 175.4–176.2°).

***cis*-Bicyclo[3.3.0]octan-1,5-dicarboxylic Acid Anhydride (7).—A. From Tricyclo[3.3.2.0^{1,6}]dec-9-ene (6).**—A solution of 33 mg (0.20 mmol) of ruthenium tetroxide in 20 ml of carbon tetrachloride, generated by the method of Mercer and Meyer,[19] was combined with a solution of 427 mg (3.19 mmol) of **6** in 50 ml of carbon tetrachloride. After ruthenium dioxide began to precipitate a solution of g of sodium *m*-periodate in 50 ml of water was added and the resulting two-phase mixture was stirred at 25° for 12 hr. The organic phase was separated, stirred with 3 ml of isopropyl alcohol for 20 min, filtered to remove ruthenium dioxide, dried ($MgSO_4$), and concentrated to yield 300 mg of a yellow oil. The oil was treated with ethereal diazomethane and the resulting mixture of anhydride **7** and the corresponding diester was separated by preparative glpc (20% DEGS, 10 ft × 0.25 in., 180°, 300 ml/min He). The collected diester, 30 mg, had ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 3.57 (s, 6, CO_2CH_3) and 1.80 ppm (br m, 12). The collected anhydride **7** amounted to 183 mg (31.9%), mp 111–112°. An analytical sample of **7** was obtained by sublimation at 80°: mp 112–113°; ir (CCl_4) 1840 and 1783 cm^{-1}; nmr (CCl_4) δ 1.90 ppm (br m). Continuous extraction of the acidified aqueous phase (see above) for 48 hr gave an additional 353 mg (61.5%) of **7**.

Anal. Calcd for $C_{11}H_{12}O_3$ (mol wt 180.20): C, 66.65; H, 6.71. Found: C, 66.62; H, 6.78.

B. From Tricyclo[3.3.3.0^{1,5}]undec-3-en-2-one (5).—A solution containing *ca.* 5 mg of potassium permanganate and 1.0 g of sodium *m*-periodate in 20 ml of water was stirred along with

(17) All boiling points and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach über Engelskirken, Germany, or by Gailbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined in carbon tetrachloride unless otherwise stated, using a Perkin-Elmer Model 337 or 257 grating spectrophotometer. All nmr spectra were determined in carbon tetrachloride containing tetramethylsilane as an internal standard using a Varian A-60 nmr spectrometer. Analytical gas–liquid partition chromatograms were determined using a Varian Aerograph Model 1200 chromatograph and preparative glpc separations were conducted using a Varian Aerograph 90-P-3 chromatograph. Irradiations were carried out using a Hanovia high-pressure mercury arc (450 W), internal probe, type L, and the filter specified.

(18) R. K. Hill and R. T. Conley, *J. Amer. Chem. Soc.* **82**, 645 (1960).

(19) E. E. Mercer and S. M. Meyer, personal communication.

57 mg (0.35 mmol) of **5** at 25°. After 12 hr the mixture was acidified with 5% sulfuric acid and extracted with three 20-ml portions of carbon tetrachloride. The organic extract was dried ($MgSO_4$) and concentrated, and the residue was sublimed to give 20 mg (32%) of **7**, mp 112–113°. The two samples of **7** were shown to be identical by comparison of ir and nmr spectra as well as by the mixture melting point, 112–113°.

6-Methylbicyclo[4.2.0]oct-7-en-2-one (4).—A solution of 10.25 g (0.0925 mol) of 3-methylcyclohex-2-enone (Aldrich Chemical Co.) and 30 ml of a mixture of *cis*- and *trans*-dichloroethylenes in 1 l. of pentane was irradiated (Corex) for 5 hr. Progress of the reaction was measured by glpc (3% Carbowax 20 M, 8 ft × 0.125 in., 130°, 12 ml/min He). Removal of the solvent and excess dichloroethylene by distillation left a brown oil which was dissolved in 500 ml of benzene. This solution, together with 20 ml of ethylene glycol and a crystal of *p*-toluenesulfonic acid, was refluxed with the separation of water. After 10 hr, 100 ml of 10% sodium bicarbonate was added to the cooled reaction mixture. The organic layer was separated, extracted with water, and concentrated, and the residue was dissolved in 300 ml of anhydrous ether. The ethereal solution was then introduced into a 3-l. flask containing 2 l. of freshly distilled anhydrous ammonia. Small pieces of sodium metal were added until the solution remained dark blue. After the blue solution had stirred for an additional 2 hr, ammonium chloride was added to destroy excess sodium and the ammonia was allowed to evaporate. Water was added to the residue and the resulting solution was extracted with three 300-ml portions of ether. The ethereal extract was dried ($MgSO_4$), concentrated, and distilled to give 13.65 g (82.1%) of 6-methylbicyclo[4.2.0]oct-7-en-2-one ethylene ketal, bp 60–65° (4.0 Torr). A 13.65-g portion of the above ketal was dissolved in 200 ml of ether and stirred at room temperature along with 50 ml of 5% aqueous sulfuric acid. After 12 hr, the ethereal phase was separated, extracted with dilute sodium bicarbonate solution, dried ($MgSO_4$), concentrated, and distilled to give 8.53 g (82.6%) of **4**: bp 70–74° (5.0 Torr); ir (CCl_4) 3120, 3030 (HC=CH), and 1700 cm^{-1} (C=O); nmr (CCl_4) δ 6.00 (q, 2, J_{AB} = 4.0 Hz, Δ_{AB} = 8.0 Hz), 2.85 (s, 1), 2.4–1.5 (m, 6), and 1.30 ppm (m, 3).

The 2,4-dinitrophenylhydrazone was recrystallized from methanol–water, mp 124–125°.

Anal. Calcd for $C_{15}H_{16}N_4O_4$ (mol wt 316.30): C, 56.96; H, 5.10; N, 17.71. Found: C, 56.89; H, 4.97; N, 17.60.

1-Methylbicyclo[3.2.1]oct-6-en-8-one (21).—A solution of 1.50 g (0.0111 mol) of **4** and 50 mg of *p*-toluenesulfonic acid in 200 ml of benzene was refluxed for 5 min. The cooled reaction mixture was washed with 5% sodium bicarbonate solution, concentrated, and distilled to give 0.0472 g (3.14%): bp 90° (bath) (0.005 Torr); ir (CCl_4) 3050 (HC=CH), 1760, 1700 (C=O), and 1650 cm^{-1} (C=C); nmr (CCl_4) δ 5.95 (t, 2, J = 3.0 Hz), 2.68 (m, 1), 2.0–1.4 (m, 6), and 1.00 ppm (s, 3). The low yield of isolated **21** reflects the fact that this substance is very labile and it undergoes resinification upon distillation. No products other than **21** could be detected in the crude reaction mixture.

The 2,4-dinitrophenylhydrazone was recrystallized from methanol–water, mp 154–155°.

Anal. Calcd for $C_{15}H_{16}N_4O_4$ (mol wt 316.30): C, 56.96; H, 5.10; N, 17.71. Found: C, 57.17; H, 5.00; 6, 17.89.

Registry No.—**1**, 22241-68-5; 2,4-dinitrophenylhydrazone of **1**, 22241-69-6; **2**, 22241-70-9; *p*-toluenesulfonylhydrazone of **2**, 22241-71-0; **3**, 21604-44-4; *p*-toluenesulfonylhydrazone of **3**, 22297-90-1; **4**, 22241-72-1; 2,4-dinitrophenylhydrazone of **4**, 22297-91-2; **5**, 15674-27-8; **7**, 22241-74-3; **8**, 22241-75-4; **13**, 22241-76-5; 2,4-dinitrophenylhydrazone of **13**, 22241-77-6; **21**, 22241-78-7; 2,4-dinitrophenylhydrazone of **21**, 22241-79-8.

Acknowledgment.—It is a pleasure to thank Professor James L. Marshall, North Texas State University, for his helpful suggestions.

Rearrangement–Addition Reactions of β,γ-Unsaturated Ketones in Aqueous Acid[1]

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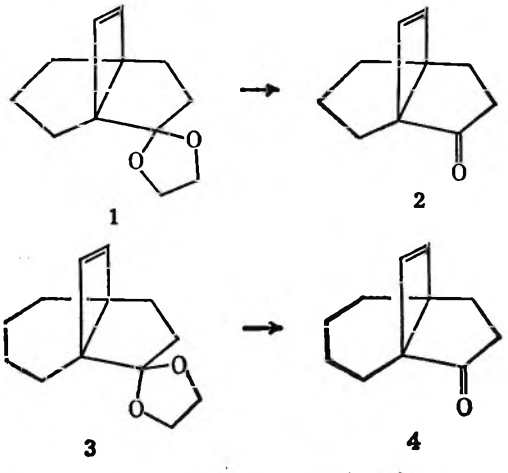
Received July 1, 1969

The rearrangement–addition reactions of a series of bicyclo[3.2.0]hept-6-en-2-ones are described. Thus 6,7-dimethyl- and 1,7-dimethylbicyclo[3.2.0]hept-6-en-2-one (**5** and **8**) yield *endo*-3-hydroxy-1-methyl-*anti*-7-methylbicyclo[2.2.1]heptan-2-one (**6**) and *endo*-3-hydroxy-1,3-dimethylbicyclo[2.2.1]heptan-2-one (**9**), respectively. However, bicyclo[2.2.1]hept-6-en-2-one (**19**) yields *anti*-7-chloro-1-hydroxybicyclo[2.2.1]hept-2-ene (**20**). These rearrangement–additions are rationalized in terms of Scheme I. Ketone **20** yields **19** when treated with potassium *t*-butoxide.

In this paper we report some novel rearrangement–addition reactions of certain β,γ-unsaturated ketones in aqueous acid. As will be seen, these rearrangement–additions proceed cleanly to provide high yields of otherwise difficultly available products, thereby providing a new and useful synthetic method.

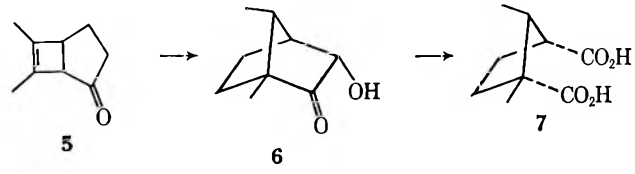
The synthesis of the tricyclic β,γ-unsaturated ketone **2**, in which the final step is removal of the ketal function of **1** in aqueous acid, has been described.[2] Hydrolysis of the ketal **3** under identical conditions, 6 *M* aqueous hydrochloric acid–ether, provided not the desired ketone **4**, but a crystalline tertiary alcohol. The latter was presumed to arise from initially formed **4** by a subsequent rearrangement. We have, therefore, examined the action of 6 *M* hydrochloric acid on a series of β,γ-unsaturated ketones, and the results of this investigation are reported here.



(1) We thank the National Science Foundation for generous support of this work.

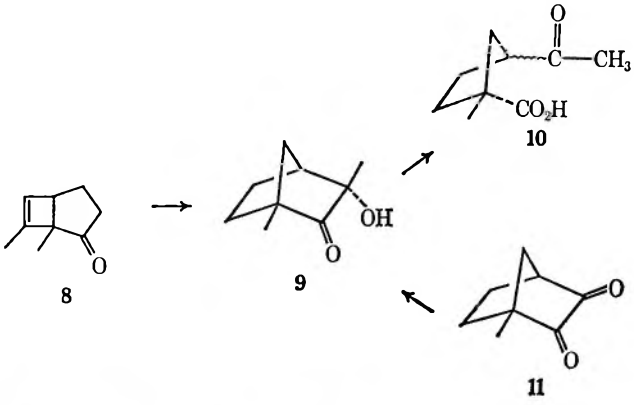
(2) (a) R. L. Cargill, J. R. Damewood, and M. M. Cooper, *J. Amer. Chem. Soc.*, **88**, 1330 (1966); (b) R. L. Cargill, *et al.*, in preparation; (c) see also H. O. House and T. H. Cronin, *J. Org. Chem.*, **30**, 1061 (1965).

The reaction of ketone **5**[3] in 6 *M* hydrochloric[4a] acid yielded a single liquid hydroxy ketone. The new material ($C_9H_{14}O_2$) exhibits spectral characteristics[4b] typical of a cyclopentanone, a secondary alcohol, one methyl on quarternary carbon, and one methyl on tertiary carbon. The new hydroxy ketone was shown to be **6** by oxidation with potassium permanganate to santenic acid (**7**).[5] Coupling of the carbinol proton with the adjacent bridgehead hydrogen (J = 4.5 Hz) shows the hydroxyl to be *endo*.[6,7]



5 6 7

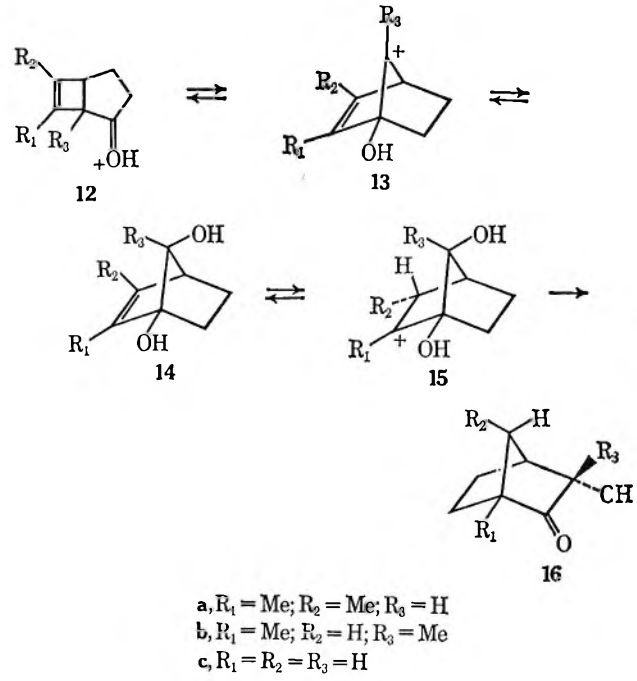
Similar treatment of **8** provided a single crystalline hydroxy ketone **9**, the structure of which was established as follows. The spectral data[4b] clearly show the presence of a tertiary alcohol and two methyls on completely substituted carbons. Oxidation with aqueous potassium permanganate gave an epimeric mixture of the keto acids **10**. Reaction of the diketone **11** with methylmagnesium iodide yields **9** as the major product. The formation of both epimers of a keto acid demonstrates that the hydroxyl is attached at C-3 and not at C-2 in **9**, and the formation of **9** from **11** indicates that the hydroxyl group is again *endo*.



8 9 10 11

The conversions, **5** → **6** and **8** → **9**, are rationalized in terms of Scheme I. Net migration of the etheno bridge in the protonated ketone **12** leads to ion **13**, which is a 7-norbornenyl cation and is presumably well stabilized.[8] Rapid hydration of ion **13** (from the *anti* side) is followed by slow protonation of the olefinic bond of **14** from the *exo* side and a Wagner–Meerwein shift to produce the observed hydroxy ketones **16** (**16a** ≡ **6**, **16b** ≡ **9**). This sequence accounts for the gross

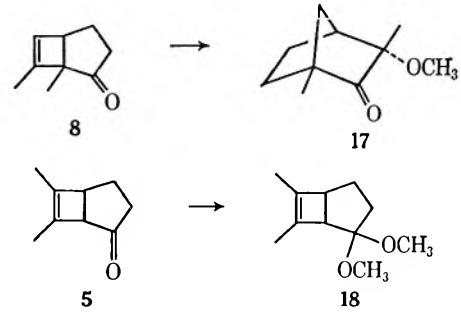
SCHEME I



a, R_1 = Me; R_2 = Me; R_3 = H
b, R_1 = Me; R_2 = H; R_3 = Me
c, R_1 = R_2 = R_3 = H

structure of the observed ketones and also for the observed stereospecificity of the reactions.

In an effort to demonstrate the role of solvent in the rearrangement–hydration reaction, a mixture of **5** and **8** was stirred in 6 *M* methanolic hydrochloric acid. Two new products, a methoxy ketone **17** and a ketal **18**, the structures of which were assigned on the basis of spectral data,[4b] were obtained. The formation of **17** from **8** is in agreement with the suggested mechanism depicted in Scheme I; the formation of **18** merely indicates that ketalization of **5** is fast and that the ketal occupies a relatively deep energy minimum.



8 17 5 18

It is of interest to note that rearrangement–addition of ketones **5** and **8** is faster than is equilibration of the two; however, when **5** and **8** are heated separately in benzene containing *p*-toluenesulfonic acid, the same equilibrium mixture containing 95% **5** and 5% **8** was obtained.[9,10]

(3) (a) P. E. Eaton, *Tetrahedron Lett.*, 4395 (1964); (b) R. Criegee and H. Furrer, *Chem. Ber.*, **97**, 2949 (1964).

(4) (a) All acid-catalyzed reactions described in this paper were carried out in a two phase, ether–aqueous hydrochloric acid system; see Experimental Section for details. (b) See Experimental Section for spectral data.

(5) We are grateful to Professor S. Beckmann for authentic sample of santenic acid (**7**): S. Beckmann and R. Schafer, *Justus Liebigs Ann. Chem.*, **585**, 154 (1954).

(6) By way of comparison, *endo*-2-hydroxy-3,3-dimethylbicyclo[2.2.1]-heptane exhibits a doublet at 3.53 ppm (J = 4.5 Hz) for the carbinol hydrogen.

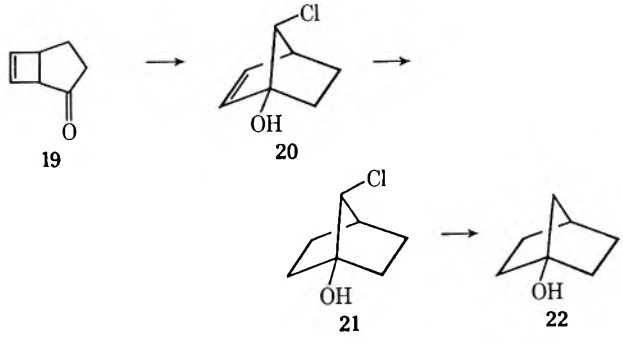
(7) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(8) See P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, Inc., New York, N. Y., 1965, for leading references.

(9) G. Büchi and E. M. Burgess, *J. Amer. Chem. Soc.*, **82**, 4333 (1960).

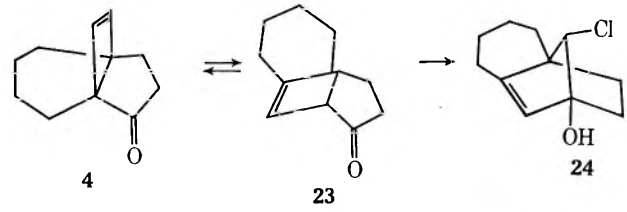
(10) For other examples of acid-catalyzed isomerizations and additions to β,γ-unsaturated ketones, see (a) R. Caple, H. W. Tan, and F. M. Hsu, *J. Org. Chem.*, **33**, 1542 (1968); (b) W. F. Erman, *J. Amer. Chem. Soc.*, **89**, 3828 (1967); (c) W. F. Erman, *ibid.*, **91**, 799 (1969); (d) J. J. Beereboom, *J. Org. Chem.*, **30**, 4230 (1965); *J. Amer. Chem. Soc.*, **85**, 3525 (1963); (e) R. B. Bates, M. J. Onore, S. K. Paknikar, C. Steelink, and E. P. Blanchard, *Chem. Commun.*, 1037, (1967); (f) R. L. Cargill and J. W. Crawford, *Tetrahedron Lett.*, 169 (1967); (g) R. L. Cargill, M. E. Beckham, A. E. Siebert, and J. Dorn, *J. Org. Chem.*, **30**, 3647 (1965); (h) R. L. Cargill, M. E. Beckham, and J. R. Damewood, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, No. P179.

When ketone **19** was stirred in a mixture of ether and 6 *M* hydrochloric acid, it was very slowly converted into a new unsaturated chloro alcohol, **20**. The presence of a single chlorine atom was established from elemental analysis and by mass spectrometry. The two vinyl protons give a three-line multiplet centered at 6.08 ppm,[11] and the C-7 proton gives a broadened singlet[12] at 3.54 ppm. That the alcohol is tertiary was established by determination of the nmr spectrum in dimethyl sulfoxide, whereupon the hydroxyl proton signal appears as a sharp singlet (5.68 ppm). Catalytic hydrogenation of **20** gave the saturated **21**, which upon dechlorination (sodium–liquid ammonia) gave the known alcohol **22**.[13] The stereochemistry of the chlorine is inferred from the solvolytic half-life of **20**, 180 min in 50% aqueous ethanol (55.53°), which is only a factor of 60 greater than that of *anti*-7-chloronorbornene.[14]

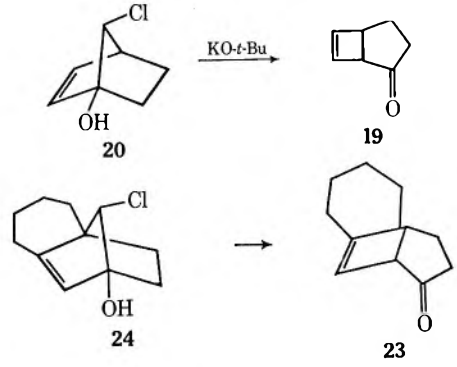


That ketone **19** yields the chloro alcohol **20** rather than the expected hydroxy ketone may be explained in terms of Scheme I as follows. Conversion of **19** (**12c**) into the diol **14c** is rapid and reversible *via* ion **13c**. Protonation of the disubstituted double bond in **14c** is very slow compared with that in **14a**, or **b**, which gives in each case tertiary carbonium ion **15a**, or **b**. The slow rate of protonation of **14c** allows ion **13c** to be captured by chloride ion. The resulting **20** is effectively inert under the reaction conditions.

We now return to the experiment which led us into the present study. Removal of the ketal function from **3** with 6 *M* hydrochloric acid gave in low yield a crystalline tertiary alcohol. Subsequent experiments showed, however, that hydrolysis of **3** with 3 *M* hydrochloric acid provides **4** in good yield. When **4** was subjected to the rearrangement–hydration conditions described above, a new crystalline chloro alcohol was obtained. The new chloro alcohol is assigned structure **24** on the basis of spectral data,[4b] which show the presence of a single vinyl hydrogen, a secondary chlorine, and a tertiary alcohol. The stereochemistry of the chlorine follows from the solvolytic half-life of 2.38 min (50% aqueous ethanol, 55.53°) which is only slightly different from that of *anti*-7-chloronorbornene under similar conditions.[14] Furthermore, ketone **23**, which may be obtained from **4** by photoisomerization,[15] also yields **24** when subjected to the rearrangement–addition conditions.[16]



In addition to the synthetically useful rearrangement–additions described above, we have found that the chloro alcohols **20** and **24** undergo base-induced rearrangement–elimination to provide in each case the ketonic precursor, **19** or **23**, respectively, in high yield. The use of this transformation allows the synthesis, for example, of **23** in a pure state. Irradiation of **4** leads to a photostationary mixture of **4** and **23** (30:70).[15]



Experimental Section[17]

Acid-Catalyzed Interconversion of 6,7-Dimethylbicyclo[3.2.0]-hept-6-en-2-one (5) and 1,7-Dimethylbicyclo[3.2.0]hept-6-en-2-one (8). A.—A rapidly stirred solution containing 0.091 g (0.00067 mol) of **5** and 0.010 g of *p*-toluenesulfonic acid in 5 ml of dry benzene was refluxed for 10 hr. Gas–liquid partition chromatography (3% DEGS, 8 ft × 0.125 in., 100°, 25 ml/min He) indicated that the reaction mixture consisted of 95% **5** and 5% **8**. Continued refluxing led to decomposition of the ketones.

B.—A solution containing 0.078 g (0.00057 mol) of **8** and 0.009 g of *p*-toluenesulfonic acid in 5 ml of dry benzene was refluxed for 10 hr. Analysis by glpc indicated that the reaction mixture consisted of 5% **8** and 95% **5**.

Acid-Catalyzed Rearrangement of 1,7-Dimethylbicyclo[3.2.0]-hept-6-en-2-one (8) in Hydrochloric Acid.—A solution containing 0.060 g (0.00044 mol) of **8** in 10 ml of ether was stirred at room temperature with 3 ml of 6 *N* hydrochloric acid for 10 hr. The reaction mixture was poured into 10 ml of water and extracted with ether. The extracts were combined, dried ($MgSO_4$), and concentrated to dryness by distillation (steam bath), giving 0.066

(11) The nmr spectrum of 1-hydroxybicyclo[2.2.1]hept-2-ene exhibits a similar multiplet at 5.87 ppm.

(12) Failure to detect resolvable coupling in a similar case has been reported by S. Ho, T. Omoto, Y. Fujise, and K. Sakan, *Chem. Commun.*, 782 (1968).

(13) C. J. Norton, Ph.D. Thesis, Harvard University, Cambridge, Mass., 1955.

(14) W. G. Woods, R. A. Carboni, and J. D. Roberts, *J. Amer. Chem. Soc.*, **78**, 5653 (1956).

(15) D. M. Pond, Ph.D. Thesis, University of South Carolina, Columbia, S. C., 1968. A manuscript describing the photochemistry of a series of bicyclic and tricyclic β,γ-unsaturated ketones, including **4** and **23**, is in preparation. The characterization of **23** will be described there.

(16) The interconversion of **4** and **23** in the aqueous acid system used here and the absence of such interconversion in the case of **5** and **8**, merely indicates that the activation free energy for the **4** → **23** change is lower than that of the rearrangement–addition, whereas $\Delta G^{\ddagger}$ for **5** → **8** is greater than that for rearrangement–addition.

(17) All boiling points and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach über Engleskirken, Germany, or by Gailbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined in carbon tetrachloride unless otherwise stated, using a Perkin-Elmer Model 337 or 257 grating spectrophotometer. All nmr spectra were determined in carbon tetrachloride containing 5% tetramethylsilane as an internal standard using a Varian A-60 nmr spectrometer. Analytical gas–liquid partition chromatograms were determined using a Varian Aerograph Model 1200 chromatograph and preparative glpc separations were conducted using a Varian Aerograph 90-P-3 chromatograph.

g of *endo*-3-hydroxy-1,3-dimethylbicyclo[2.2.1]heptan-2-one (**9**) as a solid residue. Preparative glpc (20% SE-52, 10 ft × 0.25 in., 150°, 100 ml/min He) gave a pure sample of **9**: mp 85–86°; ir (CCl_4) 3570, 3460 (OH), 1745 (C=O), and 1156 cm^{-1} (CO); nmr (CCl_4) δ 3.22 (s, 1, COH), 1.20 (s, 3, $COHCH_3$), 1.12 (s, 3, CCH_3), and 1.44–2.32 ppm (m, 7); nmr (DMSO)[18] 5.23 ppm (s, 1 COH); mass spectrum[19] (70 eV) *m/e* (rel intensity) 154 (1), 126 (17), 111 (4), 95 (1), 94 (2), 71 (100), 70 (1), and 57 (3).

Anal. Calcd for $C_9H_{14}O_2$ (mol wt 154.21): C, 70.10; H, 9.15. Found: C, 70.22; H, 9.10.

Acid-Catalyzed Rearrangement of 6,7-Dimethylbicyclo[3.2.0]-hept-6-en-2-one (5) in Hydrochloric Acid.—A solution of 0.511 g (0.00375 mol) of **5** in 15 ml of ether was stirred at room temperature with 10 ml of 6 *N* hydrochloric acid for 48 hr. The reaction mixture was poured into 100 ml of water and extracted with ether. The ether extracts were combined, washed with 5% sodium bicarbonate and water, dried ($MgSO_4$), and concentrated by distillation to give 0.521 g of a brown oil. Preparative glpc (20% SE-52, 10 ft × 0.25 in., 150°, 100 ml/min He) gave a pure sample of *endo*-3-hydroxy-1-methyl-*anti*-7-methylbicyclo[2.2.1]-heptan-2-one (**6**): ir (CCl_4) 3560, 3440 (OH), 1750 (C=O), and 1080 cm^{-1} (CO); nmr (CCl_4) δ 4.20 (br s, 1, CHOH), 3.86 (d, 1, J = 4.5 Hz, CHOH), 1.02 (s, 3, CCH_3), 0.97 (d, 3, J = 5.0 Hz, $CHCH_3$), and 1.30–2.50 ppm (m, 6); nmr (DMSO) δ 5.53 ppm (d, 1, J = 5.0 Hz, CHOH); mass spectrum (70 eV) *m/e* (rel intensity) 154 (39), 126 (21), 111 (21), 95 (47), 71 (57), 70 (100), and 57 (67).

Anal. Calcd for $C_9H_{14}O_2$ (mol wt 154.21): C, 70.10; H, 9.15. Found: C, 70.13; H, 9.11.

Acid-Catalyzed Rearrangement of 6,7-Dimethylbicyclo[3.2.0]-hept-6-en-2-one (5) and 1,7-Dimethylbicyclo[3.2.0]hept-6-en-2-one (8) in Hydrochloric Acid.—A solution containing 1.877 g (0.01378 mol) of a mixture of **5** and **8** (ratio 2:1) in 100 ml of ether was stirred at room temperature with 60 ml of 6 *N* hydrochloric acid for 40 hr. The reaction mixture was poured into 200 ml of water and extracted with ether. The extracts were combined, washed with 5% sodium bicarbonate and water, dried (Na_2SO_4), concentrated, and distilled to give 1.649 g (77.60%) of a mixture consisting of *ca.* 65% *endo*-3-hydroxy-1-methyl-*anti*-7-methylbicyclo[2.2.1]heptan-2-one (**6**) and *ca.* 35% *endo*-3-hydroxy-1,3-dimethylbicyclo[2.2.1]heptan-2-one (**9**), bp 65–70° (0.30 Torr). Pure samples of **6** and **9** were obtained by preparative glpc (20% SE-52, 10 ft × 0.25 in., 155°, 100 ml/min He).

1-Methylbicyclo[2.2.1]heptane-2,3-dione (11).—To a solution containing 2.51 g (0.0179 mol) of 1-methylbicyclo[2.2.1]heptan-2-one[20] in 20 ml of *o*-xylene was added at once 2.25 g (0.0203 mol) of selenium dioxide[21] and the resulting solution was refluxed for 17 hr. The reaction mixture was filtered and concentrated by distillation (steam bath) at reduced pressure (*ca.* 22 Torr) to give a dark yellow oil. Trituration with cold hexane gave a bright yellow oil which amounted to 0.916 g (33.2%). Preparative glpc (20% SE-30, 8 ft × 0.125 in., 130°, 120 ml/min He) and subsequent sublimation (bath temperature 54–55°) at reduced pressure (0.1 Torr) gave a pure sample of 1-methylbicyclo[2.2.1]-heptane-2,3-dione (**11**): mp 46.0–47.5°; uv max (95% C_2H_5OH) 266 nm (ϵ 80.7) and 312 (34.6); ir (CCl_4) 1770 and 1745 cm^{-1} (C=O); nmr (CCl_4) δ 2.88 (d, 1, J = 3.5 Hz, C-4 bridgehead proton), 1.27 (s, 3, CCH_3), and 1.78 ppm (m, 6).

Anal. Calcd for $C_8H_{10}O_2$ (mol wt 138.17): C, 69.54; H, 7.30. Found: C, 69.28; H, 7.58.

Addition of Methylmagnesium Iodide to 1-Methylbicyclo-[2.2.1]heptane-2,3-dione (11).—An ethereal solution of methylmagnesium iodide was added dropwise to a solution (rapidly stirred) of 0.199 g (0.00129 mol) of **11** in 25 ml of ether until the yellow color vanished. The reaction mixture was poured into 200 ml of water and extracted with three 100-ml portions of ether. The extracts were combined, washed with 5% sodium thiosulfate, dried ($MgSO_4$), and concentrated by slow distillation to give 0.182 g of a yellow oil. Gas–liquid partition chromatography (20% SE-30, 8 ft × 0.25 in., 131°, 100 ml/min He) showed the oil to be a mixture of three components, present in amounts of 55, 41, and *ca.* 4%. The component representing 55% of the product was partially separated into two compounds using a flow rate of 75 ml/min. These two components proved to be **11** and a hydroxy ketone which was presumably the product of Grignard addition at the C-2 carbonyl: ir (CCl_4) 3660, 3430, 1750, 1145, and 1043 cm^{-1}. The component representing 41% of the product mixture was obtained in a like manner and was shown to be **9**. The component representing 4% of the isolated mixture could not be characterized because of lack of material.

Oxidation of *endo*-3-Hydroxy-1-methyl-*anti*-7-methylbicyclo-[2.2.1]heptan-2-one (5) with Potassium Permanganate.—A solution containing 0.140 g (0.000908 mol) of **6** in 20 ml of 4% aqueous potassium permanganate solution was stirred at room temperature for 30 hr. Sodium sulfite (*ca.* 100 mg) was added to destroy excess permanganate and the solution was acidified (*ca.* pH 2) with concentrated hydrochloric acid. The clear aqueous solution was concentrated by distillation (steam bath) at reduced pressure (22–30 Torr) and a gray solid precipitated. The remaining water was decanted and the crude diacid was dried (25–30°) at reduced pressure (0.1 Torr) for 6 hr, giving 0.101 g (60.4%). Two recrystallizations from benzene and subsequent drying (steam bath) at reduced pressure (0.1 Torr) gave a pure sample of santenic acid (**7**): mp 170–171°; mmp 170–171°. Treatment of santenic acid with diazomethane gave dimethyl santenate: ir (CCl_4) 1740 (C=O), 1186, 1166, and 1104 cm^{-1} (CO); nmr (CCl_4) δ 3.61 (s, 6, OCH_3), 1.06 (s, 3, CCH_3), 0.95 (d, 3, J = 6.5 Hz, $CHCH_3$), and 1.88 ppm (m, 6).

Anal. Calcd for $C_{11}H_{18}O_4$ (mol wt 210.23): C, 61.66; H, 8.47. Found: C, 61.94; H, 8.66.

Oxidation of *endo*-3-Hydroxy-1,3-dimethylbicyclo[2.2.1]heptan-2-one (9). A. With Lead Tetraacetate.—A mixture containing 0.119 g (0.773 mmol) of **9** and 0.300 g of lead tetraacetate in 6 ml of 90% acetic acid was stirred for 1 hr at 25° and concentrated *in vacuo* to afford a viscous oil. Water was added to decompose the remaining lead tetraacetate and the resulting suspension was extracted with ether. The crude keto acid **10** obtained upon removal of solvent was esterified with diazomethane. A pure sample was obtained by preparative glpc (20% DEGS, 5 ft × 0.25 in., 120 m./min He): ir (CCl_4) 1735 (ester) and 1720 cm^{-1} (ketone); nmr (CCl_4) δ 1.23 (s, 3, CCH_3), 2.07 (s, 3, O=CCH_3), and 3.59 ppm (s, 3, CO_2CH_3).

Anal. Calcd for $C_{10}H_{16}O_3$ (mol wt 184.23): C, 65.19; H, 8.75. Found: C, 65.11; H, 8.82.

B. With Potassium Permanganate.—Oxidation of 0.340 g (0.221 mmol) of **9** as described above for the oxidation of **6** gave 0.308 g of a colorless oil, a mixture of epimers of **10**.[22] The nmr spectrum exhibits a broad singlet at 7.95 ppm (COOH) and a multiplet extending between 2.75 and 0.80 ppm (relative areas, 1:13). Two similar pairs of singlets are prominent at 2.12 and 2.03 (acetyl) and 1.20 and 1.11 (CCH_3) ppm. The ir spectrum (CCl_4) shows broad OH absorption and bands at 1710 and 1735 cm^{-1}.

Acid-Catalyzed Rearrangement of 6,7-Dimethylbicyclo[3.2.0]-hept-6-en-2-one (5) and 1,7-Dimethylbicyclo[3.2.0]hept-6-en-2-one (8) in Methanolic Hydrochloric Acid.—A solution containing 1.08 g (0.00793 mol) of a mixture of **5** and **8** (ratio 1:2) in 40 ml of 6 *N* methanolic hydrochloric acid was stirred at room temperature for 17.5 hr. The methanolic solution turned very dark as the reaction progressed. This dark solution was poured into 200 ml of water and extracted with ether. The ether extracts were combined, washed with 5% sodium bicarbonate and water, dried ($MgSO_4$), and concentrated by distillation to give 0.750 g of a brown oil. Gas–liquid partition chromatography (20% SE-52, 10 ft × 0.25 in., 130°, 100 ml/min He) showed this oil to consist of five components. Two of these, present in about equal amounts, constituted 83% of the isolated product mixture. Preparative glpc (20% SE-52, 10 ft × 0.25 in., 130°, 100 ml/min He) gave samples of these two components. The compound representing 41% of the product is presumed to be **18**: ir (CCl_4) 2820 (OCH_3), 1740 (weak), 1127, and 1024 cm^{-1} (CO); nmr (CCl_4) δ 3.24 (s, 6, OCH_3) and 1.61 ppm (br s, 6, =CCH_3). The compound isolated as 42% of the product has been assigned the structure **17**: ir (CCl_4) 2820 (OCH_3, 1741 (C=O), 1105, and

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(19) We thank Dr. A. L. Burlingame and Mr. B. R. Simoneit, University of California, Berkeley, for all mass spectra reported here.

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(21) (a) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *ibid.*, **83**, 3998 (1961); (b) J. Meinwald, C. B. Jensen, A. Lewis, and C. Swithenbank, *J. Org. Chem.*, **29**, 3469 (1964)

(22) The *cis* isomer of keto acid **10** has been characterized by Yates: P. Yates and A. G. Fallis, *Tetrahedron Lett.*, 4621 (1967). Comparison of the spectra of our pure ester with those of Yates' pure acid leaves little doubt of the assigned structures (**10**). We are pleased to thank Professor Yates for making the comparison.

1074 cm^{-1} (CO); nmr (CCl_4) δ 3.27 (s, 3, OCH_3), 1.17 (s, 3, CCH_3), 1.05 (s, 3, CCH_3), and 1.42–2.33 ppm (m, 5).

Anal. Calcd for $C_{10}H_{16}O_2$ (mol wt 168.24): C, 71.39; H, 9.59. Found: C, 71.54; H, 9.57.

Acid-Catalyzed Rearrangement of Bicyclo[3.2.0]hept-6-en-2-one (19)[23] in Hydrochloric Acid.—A solution containing 1.335 g (0.01235 mol) of **19** in 100 ml of ether was stirred with 25 ml of 6 *N* hydrochloric acid at room temperature for 148 hr and progress of the reaction was followed by glpc (3% SE-30, 8 ft × 0.125 in., 140°, 25 ml/min He). The reaction mixture was then poured into 100 ml of water and extracted with ether. The extracts were combined, dried ($MgSO_4$), and concentrated at atmospheric pressure leaving a brown oil. The brown color was removed by passing a pentane–ether (1:1) solution of the oil repeatedly through activated charcoal. Removal of the solvent gave a colorless oil which readily crystallized below room temperature and amounted to 1.181 g (66.13%) of *anti*-7-chloro-1-hydroxybicyclo[2.2.1]hept-2-ene (**20**). Preparative glpc (20% SE-52, 10 ft × 0.25 in., 140°, 90 ml/min He) gave a pure sample of **20**: ir (CCl_4) 3580, 3410 (OH), 3055 (CH=CH), and 1195 cm^{-1} (CO); nmr (CCl_4) δ 6.08 (m, 2, HC=CH), 3.54 (s, 1, CHCl), 3.05 (s, 1, COH), 2.64 (s, 1, C-4 bridgehead proton), and 1.67 ppm (m, 4, CH_2CH_2); nmr (DMSO) δ 5.68 (s, 1 COH); mass spectrum (70 eV) *m/e* (rel intensity) 144 (O), 109 (6), 108 (50), 107 (12), 91 (11), 79 (100), 77 (29), 66 (18), and 55 (24).

Anal. Calcd for C_7H_9ClO (mol wt 144.60): C, 58.14; H, 6.27; Cl, 24.52. Found: C, 58.32; H, 6.39; Cl, 24.32.

7-Chloro-1-hydroxybicyclo[2.2.1]heptane (21).—A solution containing 0.296 g (0.00205 mol) of *anti*-7-chloro-1-hydroxybicyclo[2.2.1]hept-2-ene (**20**) and *ca.* 25 mg of platinum dioxide in 10 ml of methanol was hydrogenated (at 49 lb/in.^{2}) for 3.5 hr. The methanolic solution was filtered and carefully concentrated by distillation to give 0.242 g (80.7%) of a colorless oil which crystallized on standing in the cold. Preparative glpc (20% SE-52, 10 ft × 0.25 in., 165°, 25 ml/min He) followed by sublimation (bath temperature 58–60°) at reduced pressure (0.075 Torr) gave a pure sample of 7-chloro-1-hydroxybicyclo[2.2.1]heptane (**21**): mp 113–114°; ir (CCl_4) 3575, 3435 (OH), and 1136 cm^{-1} (CO); nmr (CCl_4) δ 3.72 (s, 1, CHCl), 1.98 (s, 1, COH), and 1.76 ppm (m, 9).

Anal. Calcd for $C_7H_{11}ClO$ (mol wt 146.60): C, 57.34; H, 7.56; Cl, 24.18. Found: C, 57.40; H, 7.61; Cl, 24.13.

1-Hydroxybicyclo[2.2.1]heptane (22).—To a solution containing 0.242 g (0.00165 mol) of 7-chloro-hydroxybicyclo[2.2.1]-heptane (**21**) in 50 ml of freshly condensed ammonia, small pieces of sodium metal were added until the solution remained dark blue. This blue solution was refluxed for 0.5 hr and then the reaction was quenched by the addition of 1 g of ammonium chloride. Evaporation of the ammonia left a salt residue which was dissolved in 10 ml of water and extracted with two 10-ml portions of ether. The extracts were combined, dried ($MgSO_4$), and concentrated to dryness by careful distillation to give 0.157 g (84.9%) of a white, crystalline material. Preparative glpc (20% SE-52, 10 ft × 0.25 in., 150°, 100 ml/min He) indicated the presence of a single compound, which was shown to be 1-hydroxybicyclo-[2.2.1]heptane (**22**):[13] mp 155–156° (sealed tube); ir (CCl_4) 3605, 3310 (OH), and 1133 cm^{-1} (CO); nmr (CCl_4) δ 3.06 (s, 1, COH), 1.98 (m, 1, C-4 bridgehead), and 1.52 ppm (m, 10).

Acid-Catalyzed Rearrangement of Tricyclo[4.3.2.0^{1,6}]undec-10-en-7-one (4)[2] in Hydrochloric Acid.—A solution containing 1.797 g (0.01110 mol) of **4** in 150 ml of ether was stirred with 65 ml of 6 *N* hydrochloric acid at room temperature for 24 hr. The reaction mixture was poured into 150 ml of water and extracted with three 100-ml portions of ether. The extracts were combined, dried ($MgSO_4$), and concentrated to give a light brown oil which solidified on standing in the cold. The solid was dissolved in 5 ml of a pentane–ether (9:1) solution and passed through activated charcoal several times to remove the color. Removal of solvent gave white crystals which were washed with cold pentane and dried (25–30°) at reduced pressure (0.1 Torr) for 24 hr to give 1.143 g (51.95%) of *anti*-11-chloro-8-hydroxytricyclo[6.2.1.0^{1,6}]undec-6(7)-ene (**24**): mp 107–108°; ir (CCl_4) 3560, 3415 (OH), 3035 (CH=C), and 1130 cm^{-1} (CO); nmr (CCl_4) δ 5.34 (s, 1, CH=C), 3.46 (s, 1, CHCl), 2.11 (s, 1, COH), and 1.99 ppm (m, 12); nmr (DMSO) 5.30 ppm (s, 1, COH); mass spectrum (70 eV) *m/e* (rel intensity) 200 (17), 198 (55), 182 (20), 180 (60), 163 (100), 149 (39), 145 (64), and 91 (58).

Anal. Calcd for $C_{11}H_{15}ClO$ (mol wt 198.70): C, 66.49; H, 7.61; Cl, 17.84. Found: C, 66.37; H, 7.49; Cl, 18.00.

Acid-Catalyzed Rearrangement of Tricyclo[6.3.0.0^{1,6}]undec-6(7)-en-9-one (23) in Hydrochloric Acid.—A solution containing 0.125 g (0.000771 mol) of **23** in 20 ml of ether was stirred at room temperature with 10 ml of 6 *N* hydrochloric acid for 26 hr. The reaction mixture was then poured into 50 ml of water and extracted with two 50-ml portions of ether. The extracts were combined, dried (Na_2SO_4), and concentrated to dryness by distillation to give 0.177 g of a colorless oil which appeared to be a single substance (glpc). Preparative glpc (20% SE-52, 10 ft × 0.25 in., 180°, 250 ml/min He) gave 0.032 g of *anti*-11-chloro-8-hydroxytricyclo[6.2.1.0^{1,6}]undec-6(7)-ene (**24**).

Base-Catalyzed Rearrangement of *anti*-11-Chloro-8-hydroxytricyclo[6.2.1.0^{1,6}]undec-6(7)-ene (24).—To a solution prepared from 0.137 g (0.00351 g-atom) of potassium metal in 100 ml of dry *t*-butyl alcohol was added at once 0.403 g (0.00203 mol) of **24** in 10 ml of *t*-butyl alcohol. The resulting solution was refluxed with rapid stirring for 24 hr. The reaction mixture was then poured into 200 ml of water containing 5 g of sodium chloride and extracted with three 100-ml portions of pentane. The extracts were combined, dried ($MgSO_4$), concentrated, and distilled to give 0.238 g (72.3%) of a colorless oil which glpc (3% SE-30, 8 ft × 0.125 in. 180°, 25 ml/min He) showed to be a single compound. Preparative glpc (20% DEGS, 5 ft × 0.25 in., 120°, 120 ml/min He) gave a pure sample of tricyclo[6.3.0.0^{1,6}]undec-6-en-9-one (**23**).

Base-Catalyzed Rearrangement of *anti*-7-Chloro-1-hydroxybicyclo[2.2.1]hept-2-ene (20).—To a solution prepared from 0.250 g (0.00639 g-atom) of potassium metal in 65 ml of dry *t*-butyl alcohol was added at once 0.800 g (0.00553 mol) of **20** in 10 ml of *t*-butyl alcohol. The resulting solution was refluxed with rapid stirring for 10 hr and then stirred for an additional 6 hr at room temperature. The reaction mixture was then poured into 400 ml of water containing 5 g of sodium chloride and extracted with five 100-ml portions of ether. The extracts were combined, dried (Na_2SO_4), and concentrated to give 0.538 g (90.1%) of a colorless oil which glpc (20% SE-52, 10 ft × 0.25 in., 110°, 100 ml/min He) showed to be a single compound. Preparative glpc gave a pure sample of bicyclo[3.2.0]hept-6-en-2-one (**19**).

Solvolyses of Chloro Alcohols 20 and 24.—The solvolyses of **20** and **24** in 50% aqueous ethanol (by volume) were conducted at 55.53 ± 0.05° by the standard ampoule technique.[14] The extent of solvolysis was determined by titration of the ampoule contents with standard base. The half-reaction times were thus determined to be 180 min for **20** and 2.4 min for **24**.

Registry No.—**6**, 22257-23-1; **9**, 22256-24-2; **11**, 1194-35-0; **17**, 22256-25-3; **18**, 22241-66-3; **20**, 22256-26-4; **21**, 22241-67-4; **24**, 22256-27-5.

(23) This ketone is prepared from cyclopentenone as is described for the similar tricyclic compounds in ref 2. See also L. A. Paquette and O. Cox, *J. Amer. Chem. Soc.*, **89**, 5633 (1967).

Spectral Correlations for α,β-Unsaturated Ketones[1a]

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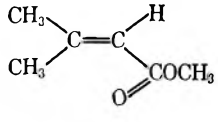
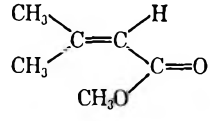
Received March 6, 1969

Preferred conformations of labile alkyl-substituted α,β-unsaturated ketones can be determined quite readily by analysis of nmr and infrared spectra. For the series of ketones studied, correlations of structure with conformation show that the (*S*)-*cis* conformation is favored for those ketones having an α hydrogen and two β-alkyl groups. For methyl ketones with α-methyl and *cis*-β-alkyl groups, steric crowding results in a preferred nonplanar (for C=C and C=O) conformation. For cases where the groups at R and R′ in **25** are as large as a combination of ethyl and methyl, the deviation from planarity is significant, and, where R‴ is also an alkyl group, the data suggest a preferred conformation having the C=O group at or near a 90° angle to the C=C. An attempt is made to approximate the extent of deviation.

It is reported[2] that the COMe group causes a nmr deshielding of the β-methyl group protons in mesityl oxide when they are in the *cis* position. This conclusion was reached on the basis of nmr investigations[3,4] of a series of *cis* and *trans* α,β-unsaturated carboxylic esters. For example, a chemical-shift difference of 0.28 ppm is observed for the two β-methyl groups in methyl β,β-dimethylacrylate. Since this deshielding effect is the average for the three equivalent conformations of the methyl group, it represents a significant shift. To account for a shift of this magnitude, it was suggested that the (*S*)-*cis* conformation (**1a**) is heavily populated. As opposed to the (*S*)-*trans* conformation (**1b**), the (*S*)-*cis* form permits a close approach of the affected protons to the magnetically anisotropic carbonyl group.

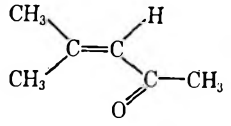


1a



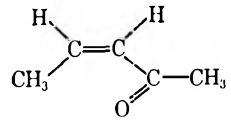
1b

That mesityl oxide (**2**) exists in the (*S*)-*cis* conformation was first demonstrated by dipole-moment measurements[5,6] and subsequently confirmed from infrared,[7,8] Raman,[9] and ultraviolet[5] spectrophotometry. Re-



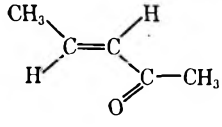
2

δ 2.11 and 1.86 (β CH_3)



3

δ 2.12 (β CH_3)
6.09 (β H)



4

δ 1.90 (β CH_3)
6.71 (β H)

cently, Baldwin[10] has interpreted the nmr spectrum on the basis of the (*S*)-*cis* conformation. He compared the chemical shifts of the β-methyl groups of mesityl oxide with those of *cis*- (**3**) and *trans*-3-penten-2-one (**4**) and assigned the low-field resonance to the β-methyl group which is *cis* to the carbonyl group.

Infrared spectrophotometry differentiates between (*S*)-*cis* and (*S*)-*trans* α,β-unsaturated ketones, since the ratio of the band intensities of the C=O to the C=C stretching vibrations is considerably larger for transoid than for cisoid ketones.[8,9] It was also observed that there is a greater frequency separation between the C=O and the C=C stretching bands of the (*S*)-*cis* conformation than of the (*S*)-*trans*.[9]

The possibility should also be considered that the most stable conformation might be one in which the carbonyl group is rotated out of the carbon–carbon double—plane. The increase in energy due to the decrease in orbital overlap interaction of the two groups might be more than compensated for by a decrease in energy due to a decrease in steric crowding as the two groups rotate away from each other.

In the present work, the preferred conformations of a series of labile (conformationally mobile) α,β-unsaturated ketones have been assigned on the basis of the chemical shifts of hydrogens of β groups. Information from the infrared spectra substantiates the correlations. These results are useful in developing generalizations concerning preferred conformations of α,β-unsaturated ketones from the type of alkyl substituents present.

Nuclear Magnetic Resonance and Infrared Spectroscopy Results.—The chemical shifts observed for the β-methyl, β-methylene, and β-hydrogen moieties for a series of conjugated olefinic ketones are given in Table I, along with the differences in chemical shifts (Δ, ppm) of the protons of a β group *cis* to the carbonyl group relative to a *trans* β group of the same type. With the exception of compound **9**, these chemical-shift differences can be made by direct comparison of identical β groups on the same compound or by comparing *cis* and *trans* isomers. For example, compound **2** has two β-methyl groups. A comparison of the geometric isomers **6** and **7** also permits the determination of chemical-shift differences for *cis* and *trans* β-methyl hydrogens, as well as *cis* and *trans* β-methylene hydrogens. The value for compound **9** is the difference between the observed chemical shift and the average chemical shift (1.84 ppm) of *trans* β-methyl groups (with respect to –COR) in compounds having an α hydrogen. Also listed are the

(1) (a) Supported by U. S. Atomic Energy Commission Contract AT-(40-1)-3234; taken from the Ph.D. dissertation of D. D. F. (b) Texas Eastman Fellow, 1964–1965.

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(10) E. Baldwin, *J. Org. Chem.*, **30**, 2423 (1965).

TABLE I

NMR CHEMICAL SHIFTS OF β SUBSTITUENTS AND THE RATIO OF THE C=O TO C=C STRETCHING BAND INTENSITIES OF CONJUGATED OLEFINIC KETONES

Compd no.	Compd[a]	Chemical shift, δ: cis β CH₃	trans β CH₃	cis β CH₂	trans β CH₂	Δ, ppm: β CH₃	β CH₂	β H	r_i (C=O/C=C)
2	CMe_2=CHCOMe	2.11	1.85	...	...	0.26	...	...	0.60
5	CMe_2=CHCOEt	2.09	1.85	...	...	0.24	...	...	0.70
6	CEtMe=CHCOEt	...	1.85	2.54	...	...	0.40	...	0.88
7	CMeEt=CHCOEt	2.11	...	...	2.14	0.26	...	...	0.66
8	CMe_2=CHCOPr	2.05	1.82	...	...	0.23	...	...	0.89
9	CMePr=CHCOMe	2.05	...	...	2.05	0.21	...	...	0.83
10	CMePr=CHCOPr	2.07	...	...	2.08	0.23	...	...	1.01
11	CPrMe=CHCOPr	...	1.84	2.54	...	...	0.46	...	
12	CMe_2=CEtCOMe	1.74	1.74	...	...	0.00	...	...	5.09
13	CPrMe=CEtCOMe	...	1.70	2.14	...	...	0.00	...	2.94
14	CMePr=CEtCOMe	1.70	...	...	2.14	0.00	...	...	3.05
15	CMe_2=CMeCOEt	1.74	1.74	...	...	0.00	...	...	2.35
16	CEt_2=CMeCOEt	...	...	2.10	2.08	...	0.02	...	2.40
17	CEt_2=CMeCO-*i*-Pr	...	...	2.04	1.95	...	0.09	...	1.71
18	CMe_2=CMeCOMe	1.82	1.76	...	...	0.06	...	...	1.96
19	CEtMe=CMeCOMe	...	1.72	2.25	...	...	0.14	...	1.98
20	CMeEt=CMeCOMe	1.81	...	...	2.11	0.09	...	...	1.69
21	CHEt=CMeCOEt	...	...	2.24	...	...	...	...	5.53
22	CHMe=CMeCOMe	...	1.72	...	...	...	...	...	5.23
23	CH_2=CHCOMe	...	...	...	...	...	...	0.3[b]	~5.0
24	CH_2=CMeCOMe	...	...	...	...	...	...	0.2[c]	9.0[d]

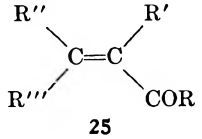
[a] The first alkyl group (or hydrogen) listed is *cis* to the carbonyl group. [b] S. Castellano and J. S. Waugh, *J. Chem. Phys.*, **37**, 1951 (1962). [c] Reference 2, p 123. [d] Reference 8.

ratios (r_i) of the integrated band intensities (determined by cutting and weighing relevant peaks) of the C=O and C=C stretching vibrations.

Discussion

Excluding compounds **21–24**, the α,β-unsaturated ketones in Table I can be divided into three groups: (1) those which show a significant chemical shift of the protons of a β group *cis* to the carbonyl group relative to a *trans* β group of the same type (**2**, **5–11**); (2) those which show an insignificant shift (**12–16**); and (3) those which show a moderate chemical shift (**17–20**).

Consistent with the above discussion, the first group is assigned the (*S*)-*cis* conformation. Infrared data compliment and confirm this assignment, as evidenced by the low ratio of C=O to C=C band intensities. That this ratio would be low for (*S*)-*cis* ketones is well established.[6–8] Considering the general formula **25**,



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for those cases where R′ = H, R″ = alkyl, and R‴ = alkyl, clearly there will be more steric interference between R and R‴ in the (*S*)-*trans* conformation than between R and H in the (*S*)-*cis* conformation, leading to a preference for the (*S*)-*cis* form.

When R′ is a group other than H, steric repulsions would have a tendency to force the molecule out of the (*S*)-*cis* conformation and into a nonplanar conformation. This would be expected to lead to a reduced deshielding effect on the β-carbon protons as the anisotropic carbonyl group turns away. It seems likely that this deshielding effect would become negligible by the time the carbonyl group has turned 90° away from the (*S*)-*cis* conformation. The question arises as to whether the deshielding effect remains negligible or increases as the carbonyl group continues to turn from the 90° out-of-plane position to the (*S*)-*trans* conformation. Considerable evidence suggests that there is a difference in chemical shifts of *cis* and *trans* β protons for compounds with predominant (*S*)-*trans* conformations. For example, a chemical-shift difference of 0.3 ppm is observed for the β protons of methyl vinyl ketone (**23**) (footnote *b*, Table I). Ronayne, Sargent, and Williams[11] indicate that this compound favors the (*S*)-*trans* conformation at room temperature on the basis of a nmr variable-temperature study. Furthermore, the carbonyl stretching band is *ca.* five times as intense as the C=C stretching band, which is consistent with the (*S*)-*trans* conformation. Similar data for 3-methyl-3-buten-2-one (**24**), *i.e.*, a large ratio (9.0)[8] for the integrated band intensities of the C=O and C=C stretching vibrations and a nmr variable-temperature study,[11] indicate an (*S*)-*trans* conformation, and the β hydrogens show a 0.20-ppm difference in chemical shift (see ref 2, p 123).

This β-hydrogen shift difference of 0.2–0.3 ppm for (*S*)-*trans* compounds is considerably less than the corresponding difference for (*S*)-*cis* compounds, *e.g.*, the β-hydrogen Δ = 0.62 for *cis*- (**3**) and *trans*-3-pentanone (**4**). (However, it is not certain that the conformation of **4** is (*S*)-*cis;* so this comparison may be subject to some uncertainty.) At any rate, compounds **12–16**, which show negligible shifts, must be nonplanar with large angles of rotation of the carbonyl group with respect to the carbon–carbon double bond. Compounds **17–20**, which show intermediate chemical shifts, must have conformations between the planar (*S*)-*cis* or (*S*)-*trans* conformations and the 90° nonplanar form. The ratios

(11) J. Ronayne, M. V. Sargent, and D. H. Williams, *J. Amer. Chem. Soc.*, **88**, 5288 (1966).

of the C=O to C=C band intensities for the nonplanar ketones (**12**–**20**) are between the observed values for (*S*)-*cis* ketones (**2**, **5**–**11**) and (*S*)-*trans* ketones (**21**–**24**).

From the available data, the effect of structure on conformational preference can be generalized as follows: (1) labile α,β-unsaturated ketones (**25**) with an α hydrogen and alkyl groups at R″ and R‴ prefer the (*S*)-*cis* conformation; (2) if R and R′ are methyl groups and R‴ is an alkyl group, a slight deviation from the planar conformation occurs in order to relieve the moderate steric repulsions between R and R′; (3) if groups at R and R′ are as large as a combination of an ethyl and a methyl, steric repulsions become large enough to cause significant deviation from the planar conformation. For those cases where there is also an alkyl group at R‴, the data suggest a conformation having the C=O group at or near a 90° angle to the C=C, unless steric repulsions between R and R‴ become large. If steric repulsions among R, R′, and R‴ become large, the molecule assumes a preferred conformation between (*S*)-*cis* or (*S*)-*trans* and 90° out-of-plane. This is well illustrated by 5-ethyl-2,4-dimethyl-4-hepten-3-one (**17**), which has an isopropyl group at R and an ethyl group at R‴. An examination of a molecular model clearly shows that the least sterically hindered conformation has the C=O to C=C angle between 0 and 90° with respect to the planar (*S*)-*cis* conformation The difference in chemical shifts of the β-methylene hydrogens and an intermediate value for the ratio of C=O to C=C stretching vibrations support this proposition. A smaller effect of this type may be present in compound **16**, which has ethyl groups at R and R‴.

Sufficient examples are not available to correlate structure with preferred conformations for ketones with a β hydrogen (**21**–**24**). However, the high ratios of the C=O to C=C stretching bands suggest the (*S*)-*trans* conformation for ketones with a β hydrogen *cis* to the carbonyl group (R‴ = H). As mentioned earlier, Ronayne, Sargent, and Williams[11] classify methyl vinyl ketone (**23**) as predominantly (*S*)-*trans* from a nmr variable temperature study, and Erskine and Waight[8] show 3-methyl-3-buten-2-one (**24**) to be (*S*)-*trans* from infrared data. On the basis of benzene solvent shifts, Timmons[12] classifies 3-methyl-3-buten-2-one (**24**), 3-penten-2-one, 3-methyl-3-penten-2-one (**22**), and 4-phenyl-3-buten-2-one as (*S*)-*trans*.

Owing to interference from groups other than those of interest, there is some uncertainty in some of the assignments. Two unresolved singlets are present in the spectrum of 3,4-dimethyl-3-penten-2-one (**18**) at 1.82 (6 H) and 1.76 ppm (3 H) which represent the α- and β-methyl groups. An unequivocal assignment cannot be made in this case. A singlet representing *ca.* 0.4 H is also present at 2.09 ppm, which may indicate a small population of the (*S*)-*cis* conformer. A similar difficulty is encountered with 4,5-dimethyl-4-hexen-3-one (**15**), which shows two unresolved singlets at 1.74 (6 H) and 1.72 ppm (3 H) representing the α- and β-methyl groups. Even if the assignment of all six hydrogens of the β-methyl groups at 1.74 ppm is in error, there is only a 0.02-ppm chemical shift caused by the anisotropic carbonyl group.

None of the ketones appears to exist as a mixture of conformers at room temperature to a greater extent than described above, and those with α hydrogens and β-alkyl groups are all present in the (*S*)-*cis* form as far as can be determined.

Correlations by Erskine and Waight[8] based on the ratio of the integrated band intensities of the C=O and C=C stretching vibrations agree with these results for ketones having a hydrogen at R′; however, they would classify 3,4-dimethyl-3-penten-2-one (**18**) as (*S*)-*cis*. The present correlations clearly show that this compound prefers a conformation with the C=O rotated somewhat from the planar (*S*)-*cis* conformation. Similarly, from their infrared data, Noack and Jones[9] report that **18** and *trans*-3,4-dimethyl-3-hexen-2-one (**20**) prefer the (*S*)-*cis* conformation; however, the intensities of the C=C stretching bands are between the values shown for fixed (*S*)-*cis* and fixed (*S*)-*trans* compounds shown in their tabulations. These intermediate values, together with the present nmr results, fit better the assignments to nonplanar conformations made here.

For ketones showing intermediate chemical shifts, it appears that there should be a correlation between the chemical shift of β groups and the dihedral angle formed by the carbonyl group and the carbon–carbon double bond. Although an exact angle cannot be calculated from the available data, a function (ϕ) of this angle can be determined as follows.

For (*S*)-*cis* ketones (**2**, **5**–**11**), an average chemical-shift difference (β-*cis* relative to β-*trans*) of 0.24 ppm is observed for β-methyl groups. Then ϕ for ketone **18** is 0.06/0.24 = 0.25. For ketones **19** and **20**, ϕ is 0.09/0.24 = 0.37. Similarly, the average difference in chemical shifts of β-methylene groups is 0.43 for (*S*)-*cis* ketones. Using this value for ketones **19** and **20** leads to the value ϕ = 0.14/0.43 = 0.33. Table II lists values of ϕ for ketones **2** and **5**–**20**. A number near unity indicates a (*S*)-*cis* ketone and a value of zero indicates that the carbonyl group is 90° out of the plane of the carbon–carbon double bond. Although sufficient data are not available to evaluate the Δ value for (*S*)-*trans* β groups, it is conceivable that some of the ketones with intermediate chemical-shift values might have preferred conformations between 90° nonplanar and (*S*)-*trans*.

TABLE II

THE FUNCTION, ϕ, OF α,β-UNSATURATED KETONES LISTED IN TABLE I

Compd	ϕ
2	1.0
5	1.0
6	0.93
7	1.0
8	0.96
9	0.88
10	0.96
11	1.0
12	0.0
13	0.0
14	0.0
15	0.0
16	0.05
17	0.22
18	0.25
19	0.37,[a] 0.33[b]
20	0.37,[a] 0.33[b]

[a] Calculated from β-methyl groups. [b] Calculated from β-methylene groups.

(12) C. J. Timmons, *Chem. Commun.*, 576 (1955).

However, it is probable (see the β-hydrogen discussion above) that Δ will be smaller for fixed (*S*)-*trans* than for fixed (*S*)-*cis* compounds; so only those compounds with small, nonzero values of ϕ suffer from this uncertainty. The relatively low values for the ratios of C=O to C=C stretching frequencies for these compounds indicate that the preferred conformations certainly are not very near (*S*)-*trans*.

Experimental Section

Almost all of the olefinic ketones were separated and purified by preparative gas chromatography, and a Wilkins Model A-700 Autoprep chromatograph was used for this purpose. All of the mass spectra and the nmr spectra of some of the compounds were taken by Mr. H. T. Ford and Dr. P. Flannigan, respectively, of Continental Oil Co., for which assistance the authors are most grateful. The mass spectra were recorded on a CEC 103 mass spectrometer using an ionization voltage of 70 eV. The nmr spectra taken by Dr. Flannigan were recorded at room temperature on a Varian HA-100 spectrometer. The remainder were recorded in this laboratory at room temperature on a Varian A-60 spectrometer.

Infrared spectra were obtained on a Perkin-Elmer Model 337 grating infrared spectrophotometer and a Perkin-Elmer Model 21 spectrophotometer using neat samples between sodium chloride windows.

Ultraviolet spectra for all compounds were obtained in 95% ethanol on a Beckman Model DK-1 recording spectrophotometer. α,β-Unsaturated ketones show a weak R band of the carbonyl group between 300 and 350 mμ and a strong K band of the α,β-conjugated system between 215 and 250 mμ.[13] The empirical generalizations derived by Woodward[14] for the effect of substitution upon the position of the K band were used with excellent results as an aid in assigning the structures of some of the ketones.

Complete details of all syntheses are given in the Ph.D. dissertation of D. D. F.[15]

5-Methyl-4-hexen-3-one (5) and 3,4-Dimethyl-3-penten-2-one (18).[16]—Phosphorus oxychloride (376 g) was distilled into a mixture of 200 g (3.49 mol) of acetone and 251 g (3.49 mol) of butanone contained in a round-bottomed flask. The reaction mixture was left for 48 hr in a water bath cooled by tap water to 28°. The solution was orange at the beginning of the reaction and became progressively darker until a dark brown mixture resulted after 48 hr. The reaction mixture was treated with 1400 ml of water, and the dark brown chloro ketone layer was separated, washed with water, and dried over sodium sulfate. Dehydrochlorination was effected by refluxing with 350 g of dimethylaniline for 30 min. The resulting mixture had two distinct layers. After the mixture was cooled in an ice bath, 235 g of a light brown oil was decanted from the solid dimethylaniline hydrochloride. This crude product was washed with dilute hydrochloric acid followed by sodium bicarbonate solution, and then distilled through a short Vigreux column to give 116 g of colorless product boiling at 130–175°; 116 g of residue remained in the distillation flask. Gc analysis (at 110 and 138°, respectively) of the crude distillate using a 10 ft × 0.25 in. column packed with 20% Carbowax coated on firebrick and a 20 ft × 0.375 in. column packed with 30% SE-30 coated on Chromosorb P showed *ca.* 9.5% mesityl oxide, 48.7% C_7 olefinic ketones, and 41.8% C_8 olefinic ketones.

The desired C_7 homologs could not be separated by preparative gc in a one-step operation [the mixture was complicated by the presence of mesityl oxide, 3,4-dimethyl-4-penten-2-one (**26**), and 4-methyl-4-hexen-2-one (**27**)]. However, at 138°, a 20 ft × 0.375 in. column packed with 30% SE-30 coated on Chromosorb P conveniently separated the desired compounds into groups A and B. Group A was further separated at 80° using a 6 ft × 0.375 in. 20% Carbowax column and was shown to contain 45% **26**, 50% mesityl oxide, and 5% impurities. Similarly, group B contained 12% **5**, 11% **27**, 74% **18**, and 3% impurities. At 115° an 8 ft × 0.375 in., 20% silicone fluid XF-1150 (Varian Aerograph) column achieved resolution sufficient to isolate pure **5** and a mixture of **18** and **27**. The mixture containing 15.7% **27** and 84.3% **18** was separated conveniently at 100° using the 20 ft × 0.375 in., 30% SE-30 column.

Spectral data of compound **5** follow: nmr $\delta_{TMS}^{CCl_4}$ 5.98 [s, fine splitting, 1 H, $CH_3C{=}CH$ (for simplicity, this type of long-range spin–spin coupling between an olefinic proton and protons of an olefinic alkyl group is referred to as a singlet with fine splitting)], 2.34 (q, 2 H, $COCH_2CH_3$), 2.09 (s, fine splitting, *cis* to carbonyl, 3 H, $HC{=}CCH_3$), 1.85 (s, fine splitting, *trans* to carbonyl, 3 H, $HC{=}CCH$)$_3$, and 1.01 (t, 3 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1690 (s, C=O), 1623 (s, C=C), 1413 (m, CH_2 bend of CH_2CO), and 837 cm^{-1} (s, CH bend on trisubstituted double bond); uv λ_{max}^{EtOH} 312 (w, R band) and 237 mμ (s, K band); mass spectrum *m/e* (rel intensity) 112 (16) (parent peak), 83 (100), 57 (51), 55 (82), 43 (15), 41 (19), 39 (43), 29 (93), 28 (25), 27 (63), and 15 (10).

Spectral data of compound **18** follow: nmr $\delta_{TMS}^{CCl_4}$ 2.14 (s, 3 H, $COCH_3$), 1.82 (s, 6 H, *trans* $CH_3C{=}CCH_3$), and 1.76 (s, 3 H, $C{=}CCH_3$ *trans* to carbonyl); ir ν_{max}^{NaCl} 1690 (s, C=O), 1618 (s, C=C), and 1348 cm^{-1} (s, CH_3 bend of a methyl ketone); uv λ_{max}^{EtOH} 305 (w, R band) and 247 mμ (s, K band); mass spectrum *m/e* (rel intensity) 112 (16) (parent peak), 97 (14), 69 (36), 55 (11), 43 (100), 41 (75), 39 (27), 28 (14), 27 (20), and 15 (21).

***cis*-5-Methyl-4-hepten-3-one (6), *trans*-5-Methyl-4-hepten-3-one (7), *cis*-3,4-Dimethyl-3-hexen-2-one (19), and *trans*-3,4-Dimethyl-3-hexen-2-one (20).**—Phosphorus oxychloride (378 g), bp 104°, was distilled into 504 g (7.0 mol) of butanone contained in a round-bottomed flask. The reaction mixture was left in a water bath cooled by tap water to 15–20°. The crude olefinic ketone mixture obtained by the procedure described above was distilled through a short Vigreux column to give 210.8 g of colorless product, bp 52–78° (225 mm), leaving 56 g of high-boiling residue. Gc analysis indicated the presence of 6.5% **6**, 19.9% **7**, 19.8% **19**, 5.3% **20**, and 46.5% 3,4-dimethyl-4-hexen-2-one (**28**) (mixture of *cis* and *trans*). The preparative gc separation of these ketones is described elsewhere.[17]

Spectral data of compound **6** follow: nmr $\delta_{TMS}^{CCl_4}$ 5.96 (s, fine splitting, 1 H, $CH_3C{=}CH$), 2.54 (q, fine splitting, 2 H, $HC{=}CCH_2CH_3$), 2.35 (q, 2 H, $COCH_2CH_3$), 1.85 (s, fine splitting, 3 H, $HC{=}CCH_3$), and 1.04 and 1.02 (overlapping t, 6 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1690 (s, C=O), 1620 (s, C=C), 1413 (m, CH_2 bend of CH_2CO), and 800 cm^{-1} (m, CH bend on trisubstituted double bond); uv λ_{max}^{EtOH} 310–315 (w, R band) and 238 mμ (s, K band); mass spectrum *m/e* (rel intensity) 126 (11) (parent peak), 97 (46), 69 (16), 57 (100), 55 (12), 53 (12), 43 (12), 41 (71), 39 (30), 29 (78), 28 (14), and 27 (43). The compound gave a negative iodoform test; the semicarbazone derivative had a melting point of 127.5–128.5°.

Spectral data of compound **7** follow: nmr $\delta_{TMS}^{CCl_4}$ 5.96 (s, fine splitting, 1 H, $CH_3C{=}CH$), 2.40 (q, 2 H, $COCH_2CH_3$), 2.14 (q, fine splitting, 2 H, $HC{=}CCH_2CH_3$), 2.11 (s, fine splitting, 3 H, $HC{=}CCH_3$), and 1.05 and 1.02 (overlapping t, 6 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1690 (s, C=O), 1618 (s, C=C), 1413 (m, CH_2 bend of CH_2CO), and 803 cm^{-1} (m, CH bend on trisubstituted double bond); uv λ_{max}^{EtOH} 310–315 (w, R band) and 238 mμ (K band); mass spectrum *m/e* (rel intensity) 126 (11) (parent peak), 97 (45), 69 (16), 57 (100), 55 (12), 53 (11), 43 (12), 41 (72), 39 (30), 29 (80), 28 (20), and 27 (44). The compound gave a negative iodoform test; the semicarbazone derivative had a melting point of 155–157°.

Spectral data of compound **19** follow: nmr $\delta_{TMS}^{CCl_4}$ 2.25 (q, 2 H, $C{=}CCH_2CH_3$), 2.13 (s, 3 H, $COCH_3$), 1.81 (s, 3 H, α methyl), 1.72 (s, 3 H, β methyl), and 1.01 (t, 3 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1690 (s, C=O) and 1615 cm^{-1} (m, C=C); uv λ_{max}^{EtOH} 305 (w, R band) and 247 mμ (s, K band); mass spectrum *m/e* (rel intensity) 126 (12) (parent peak), 111 (15), 83 (35), 67 (10), 55 (74), 53 (12), 43 (100), 41 (56), 39 (29), 29 (28), 28 (11), 27 (37), and 15 (23). The compound gave a positive iodoform test.

Spectra data of compound **20** follow: nmr $\delta_{TMS}^{CCl_4}$ 2.15 (s, 3H, $COCH_3$), 2.11 (q, 2 H, $C{=}CCH_2CH_3$), 1.81 (s, 6 H, α and β methyls), and 1.01 (t, 3 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1690 (s, C=O), 1615 (m, C=C), and 1349 cm^{-1} (s, CH_3 bend of $COCH_3$); uv λ_{max}^{EtOH} 305 (w, R band) and 247 mμ (s, K band); mass spectrum *m/e* (rel intensity) 126 (11) (parent peak), 111 (16), 83 (37),

(13) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1963, p 99–100.

(14) R. B. Woodward, *J. Amer. Chem. Soc.*, **63**, 1123 (1941); **64**, 76 (1942).

(15) D. D. Faulk, Ph.D. Dissertation, University of Arkansas, 1966.

(16) J. Colonge and K. Mostafavi, *Bull. Soc. Chim. Fr.*, **5**, 1478 (1938).

(17) D. D. Faulk in "G. C. Preparative Separations," K. P. Dimick, Ed., Varian Aerograph, Palo Alto, Calif., 1966, pp 10–24.

55 (76), 53 (12), 43 (100), 41 (48), 39 (26), 29 (17), 28 (10), 27 (32), and 15 (23). The compound gave a positive iodoform test.

2-Methyl-2-hepten-4-one (8), 4-Methyl-3-hepten-2-one (9), and 3-Ethyl-4-methyl-3-penten-2-one (12).—Analogous to the condensation of a mixture of acetone and butanone by phosphorus oxychloride, 500 g (5.814 mol) of 2-pentanone and 337.2 g (5.814 mol) of acetone were condensed by means of 624.7 g (4.07 mol) of phosphorus oxychloride. After the mixture had stood for 48 hr at room temperature (*ca.* 25°), 790 g (4.85 mol) of crude chloroketone was isolated, which represents 83.4% of the theoretical yield. The chloro ketone was dehydrochlorinated by refluxing for 2 hr with alcoholic potassium hydroxide, which was prepared by dissolving 444.5 g (8.52 mol) of potassium hydroxide in 2000 g of 95% ethanol. After treatment with a large volume of water, the upper ketonic layer was separated and distilled through a short Vigreux column to give a mixture of olefinic ketones boiling at 115–190°.

Gc analysis showed the relative yield of products to be 7.3% mesityl oxide, 47.1% C_8 olefinic ketones, and 45.6% C_{10} ketones. The mixture of C_8 olefinic ketones consists of 21.5% **8**, 12.5% **9**, 45.5% **12**, and 20.5% 3-ethyl-4-methyl-4-penten-2-one (**29**). The C_8 ketones were separated to give **29**, a mixture of **8** and **12**, and pure **9** on a 12 ft × 0.375 in., 30% Carbowax column at 145°. Ketones **8** and **12** were separated on a 20 ft × 0.375 in., 20% polyethylene glycol distearate column at 120°.

Spectral data of compound **8** follow: nmr $\delta_{TMS}^{CCl_4}$ 5.99 (s, fine splitting, 1 H, $CH_3C{=}CH$), 2.26 (t, 2 H, $COCH_2CH_2$), 2.05 (s, fine splitting, *cis* to carbonyl, 3 H, $HC{=}CCH_3$), 1.82 (s, fine splitting, *trans* to carbonyl, 3 H, $HC{=}CCH_3$), *ca.* 1.54 (m, 2 H, $CH_2CH_2CH_3$), and 0.87 (t, 3 H, CH_2CH_3); ir (neat) 1681 (s, C=O), 1613 (s, C=C), and 813 cm^{-1} (w, CH bend on a trisubstituted double bond); uv λ_{max}^{EtOH} 310 (w, R band) and 237 mμ (s, K band); mass spectrum *m/e* (rel intensity) 126 (14) (parent peak), 83 (100), 55 (36), 43 (12), 41 (16), 39 (22), 29 (19), 27 (31), and 15 (10). The compound gave a negative iodoform test.

Spectral data of compound **9** follow: nmr $\delta_{TMS}^{CCl_4}$ 5.95 (s, broad, 1 H, $CH_3C{=}CH$), 2.05 (t, partially obscured, 2 H, $CH_2CH_2C{=}C$), 2.05 (s, fine splitting, 6 H, $COCH_3$ and $COCH{=}CCH_3$ *cis* to carbonyl), 1.47 (sextet 2 H, $CH_3CH_2CH_2$), and 0.90 (t, 3 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1691 (s, C=O), 1620 (s, C=C), 1352 (m, CH_3 bend of $COCH_3$), and 809 cm^{-1} (w, CH bend on a trisubstituted double bond); uv λ_{max}^{EtOH} 310 (w, R band) and 240 mμ (s, K band); mass spectrum *m/e* (rel intensity) 126 (17) (parent peak), 111 (88), 98 (18), 83 (28), 69 (36), 55 (69), 53 (12), 43 (100), 41 (44), 39 (39), 29 (21), 27 (43), and 15 (45). The compound gave a positive iodoform test. This sample contains an impurity with almost identical properties. In the nmr spectrum there is a singlet with an area representing *ca.* 0.7 H at δ 1.82 which shows second-order splitting by the vinyl proton into a doublet. The chemical shift of this absorption is at the correct position to indicate the presence of a small amount of the geometric isomer of **9**; *i.e.*, this impurity has the carbonyl group and the β-methyl group *trans*. A simple calculation indicates that the *cis–trans* mixture contains about 30% the geometric isomer of **9**.

Spectral data of compound **12** follow: nmr $\delta_{TMS}^{CCl_4}$ 2.26 (q, 2 H, $C{=}CCH_2CH_3$), 2.13 (s, 3 H, $COCH_3$), 1.74 (s, 6 H, β methyls), and 0.96 (t, 3 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1688 (s, C=O), 1614 (w, C=C), and 1352 cm^{-1} (m, CH_3 bend of $COCH_3$); uv λ_{max}^{EtOH} 300–305 (w, R band) and 244 mμ (s, K band); mass spectrum *m/e* (rel intensity) 126 (37) (parent peak), 111 (34), 83 (46), 55 (62), 53 (10), 43 (100), 41 (41), 39 (31), 29 (13), 27 (26), and 15 (45). The compound gave a positive iodoform test.

***trans*-6-Methyl-5-nonen-4-one (10).**[18]—2-Pentanone (478 g, 5.56 mol) was added to a solution prepared by dissolving 23 g of sodium in 300 ml of methyl alcohol, and the resulting material was refluxed for 3 hr. The basic solution was neutralized with 20% sulfuric acid and diluted with excess water. The insoluble ketonic layer was separated, washed with water, and dried over potassium carbonate. Distillation through a short Vigreux column under reduced pressure yielded 94 g of colorless product, bp 77–79° (8 mm). It was determined that 2-pentanone condenses only at the methyl carbon in the presence of sodium methoxide by comparing the reaction product with authentic samples of olefinic ketones formed from the acid-catalyzed condensation of 2-pentanone at the methylene carbon.

cis- (**11**) and *trans*-6-methyl-5-nonen-4-one (**10**) are formed along with two other compounds which are probably the nonconjugated isomers, *cis*- (**30**) and *trans*-6-methyl-6-nonen-4-one (**31**). Analytical gc results on a 5% FFAP column show that the mixture contains *ca.* 75.8% conjugated and 24.2% nonconjugated olefinic ketones. A satisfactory gc method to separate the nonconjugated olefinic ketones from the conjugated ones was not accomplished; however, a number of gc columns are suitable for the isolation of **10** from the other three compounds. The 20 ft × 0.375 in., 30% SE-30 column was used at 163° for the isolation of **10**. Interestingly, elution over a 20 ft × 0.375 in., 30% FFAP column causes considerable *trans–cis* (**10** to **11**) isomerization to occur. The fact that the *trans* compound had isomerized to the *cis* isomer is readily detectable from the nmr spectrum owing to the difference in chemical shift of the β-methyl group in the two isomers.

Spectral data of compound **10** follow: nmr $\delta_{TMS}^{CCl_4}$ 5.97 (s, fine splitting, 1 H, $CH_3C{=}CH$), 2.33 (t, 2 H, $COCH_2CH_2$), *ca.* 2.08 (t, partially obscured, 2 H, $C{=}CCH_2CH_2$), 2.07 (s, fine splitting, *cis* to carbonyl, 3 H, $CH{=}CCH_3$), *ca.* 1.56 (m, 4 H, $CH_3CH_2CH_2$), and 0.93 (t, 6 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1691 (s, C=O) and 1623 cm^{-1} (s, C=C); uv λ_{max}^{EtOH} 310 (w, R band) and 240 mμ (s, K band); mass spectrum *m/e* (rel intensity) 154 (13) (parent peak), 111 (100), 71 (39), 69 (23), 43 (64), 41 (47), 39 (26), 29 (18), and 27 (37). The mixture containing the *cis* isomer (**11**) shows a nmr singlet at δ 1.84, which indicates that the β-methyl group is *trans* to the carbonyl function. Also, a partially obscured triplet is found at δ 2.54 indicating that the β methylene is *cis* to the carbonyl function.

***cis*- (13) and *trans*-3-Ethyl-4-methyl-3-hepten-2-one (14).**—2-Pentanone (250 g) was condensed by phosphorus oxychloride in a reaction similar to the ones described above. The reaction mixture was allowed to stand for 48 hr at 20°. The resulting chloroketone was dehydrochlorinated by refluxing for 2 hr with alcoholic potassium hydroxide, prepared by dissolving 168 g (3 mol) of potassium hydroxide in 945 ml of 95% ethanol. Treatment of the product with a large excess of water separated the desired olefinic ketones. Distillation of the crude product gave 42 g of colorless material, bp 55–65° (5–7 mm). This product consisted of a complex mixture of isomeric C_{10} olefinic ketones which could not be completely resolved by any of the gc columns tried. However, 3-ethyl-4-methyl-4-hepten-2-one (**32**) could easily be separated from the other isomers using a 30% SE-30 column at 167°. Analytical gc showed that the mixture contained about 45.9% **32** and 54.1% a mixture of isomeric ketones. Seven grams of **32** was saturated with dry hydrogen chloride and allowed to stand in a refrigerator at 5° for 12 hr. The chloro ketone was dehydrochlorinated by refluxing for 2 hr with alcoholic potassium hydroxide. The recovered olefinic ketones were distilled under reduced pressure to give 5.2 g of a colorless product, bp 57–58° (10 mm). Gc analysis of the mixture obtained in this reaction showed 83.5% **32**, 8.2% **13**, and 8.3% **14**. These ketones were separated using a 20 ft × 0.375 in., 30% FFAP column at 173°.

Spectral data of compound **13** follow: nmr $\delta_{TMS}^{CCl_4}$ 2.14 (m, 4 H, $CH_2CH_2C{=}CCH_2CH_3$), 2.14 (s, 3 H, $COCH_3$), 1.70 (s, 3 H, β methyl), *ca.* 1.47 (m, 2 H, $CH_3CH_2CH_2$), and 1.00 (t, 6 H, CH_2CH_3); ir (neat) 1690 (s, C=O) and 1612 cm^{-1} (m, C=C); uv λ_{max}^{EtOH} 305 (w, R band) and 247 mμ (s, K band); mass spectrum *m/e* (rel intensity) 154 (25) (parent peak), 139 (35), 125 (11), 69 (74), 55 (47), 43 (100), 41 (42), 39 (21), 29 (16), 27 (24), and 15 (16).

The spectral properties of compound **14** are almost identical with those of **13**; therefore, the geometric assignments could be in error.

3-Methyl-3-penten-2-one (23).[19]—A solution of 265 g (3.7 mol) of butanone and 150 g (3.4 mol) of freshly prepared acetaldehyde was placed in a round-bottomed flask and cooled to −5°. This solution was saturated with dry hydrogen chloride and allowed to stand for 12 hr at −5°. The crude product was washed with dilute sodium hydroxide and dried over sodium sulfate. Distillation through a short Vigreux column gave 68 g of colorless product, bp 135–136°. Isolation of **23** from impurities was achieved using a 20% silicon fluid XF-1150 column at 130°.

Spectral data of compound **23** follow: nmr $\delta_{TMS}^{CCl_4}$ 6.67 (q, fine splitting, 1 H, $CH_3C{=}CHCH_3$), 2.22 (s, 3 H, $COCH_3$), 1.86 (d, 3 H, $CHCH_3$, *trans* to carbonyl), and 1.72 (s, fine splitting, 3 H, $CH{=}CCH_3$, α-methyl); ir (neat) ν_{max}^{NaCl} 3055 (w, vinyl H),

(18) J. Colonge, *Bull. Soc. Chim. Fr.*, **49**, 441 (1931).

(19) L. E. Hinkel, E. E. Ayling, J. F. J. Dippy, and T. H. Angel, *J. Chem. Soc.*, 814 (1931).

1677 (s, C=O), 1655 (m, C=C), 1365 (s, CH_3 bend of $COCH_3$), and 822 cm^{-1} (s, CH bend on a trisubstituted double bond); uv λ_{max}^{EtOH} 305 (w, R band) and 228 mμ (s, K band); mass spectrum *m/e* (rel intensity) 98 (33) (parent peak), 83 (25), 55 (100), 43 (55), 39 (22), 29 (29), 27 (32), and 15 (21). The compound gave a positive iodoform test.

4-Methyl-4-hepten-3-one (22).—This compound was prepared by condensation of propionaldehyde and 3-pentanone in a manner similar to the preparation of **23**.

Spectral data of compound **22** follow: nmr $\delta_{TMS}^{CCl_4}$ 6.46 (t, fine splitting, 1 H, $CH_3C{=}CHCH_2$), 2.59 (q, 2 H, $COCH_2CH_3$), 2.24 (quintet, broad, 2 H, CH_3CH_2CH, *trans* to carbonyl), 1.72 (s, fine splitting, 3 H, $CH{=}CCH_3$, α methyl), and 1.08 and 1.04 (2 t, 6 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 3045 (w, vinyl H), 1670 (s, C=O), 1642 (w, C=C), and 802 cm^{-1} (s, CH bend on a trisubstituted double bond); uv λ_{max}^{EtOH} 305 (w, R band) and 224 mμ (s, K band); mass spectrum *m/e* (rel intensity) 126 (15) (parent peak), 97 (80), 69 (77), 57 (13), 41 (100), 39 (27), 29 (38), 28 (12), and 27 (38).

5-Ethyl-4-methyl-4-hepten-3-one (16).—Analogous to the condensations described above, 172 g (2 mol) of 3-pentanone was condensed by means of 108 g (0.66 mol) of phosphorus oxychloride. Twenty grams of zinc chloride was used as a catalyst in this reaction. The usual work-up procedure gave 145 g of crude product. Distillation under reduced pressure gave 85 g of colorless product, bp 75–104° (5 mm). Analysis of the product shows the presence of 7.0% **16** and 93.0% 5-ethyl-4-methyl-5-hepten-3-one (**33**). Separation was accomplished by means of a 20 ft × 0.375 in., 30% FFAP column.

Spectral data of compound **16** follow: nmr $\delta_{TMS}^{CCl_4}$ 2.44 (q, 2 H, $COCH_2CH_3$), 2.10 and 2.08 (pair of quartets, 4 H, CH_3CH_2), 1.79 (s, 3 H, α methyl), and 1.02 (overlapping t, 9 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1689 (s, C=O) and 1615 cm^{-1} (w, C=C); uv λ_{max}^{EtOH} 305 (w, R band) and 247 mμ (s, K band).

4,5-Dimethyl-4-hexen-3-one (15).[20,21]—Propionyl chloride (186 g, 2 mol) was mixed with 210 g (3 mol) of Eastman technical-grade pentene (*ca.* 2:1 ratio of 2-methyl-2-butene and 2-pentene) in a round-bttomed flask fitted with a reflux condenser. Twenty grams of stannic chloride was added slowly through the condenser, causing the temperature to rise to *ca.* 50°. The flask was heated gently for 30 min, at which time the temperature of the reaction mixture had reached *ca.* 100°. The resulting liquid was cooled and then poured into dilute hydrochloric acid prepared with 160 ml of concentrated hydrochloric acid and 600 ml of water. The top ketonic layer was washed with saturated sodium bicarbonate and dried over sodium sulfate. After low-boiling material had been removed, 305 g of crude chloro ketone was refluxed for 2 hr with 90 g of potassium hydroxide dissolved in 405 g of 95% ethanol. Treatment with a large volume of water separated 117 g of olefinic ketone. Although some unidentified products were present, most of the material was a mixture of the condensation products of propionyl chloride and 2-methyl-2-butene. Isolation of the olefinic ketone mixture by preparative gc and subsequent characterization showed the mixture to consist of 84.7% **15** and 15.3% 4,5-dimethyl-5-hexen-3-one (**34**). The two ketones were separated on an 8.5 ft × 0.375 in., 20% TCEP column at 123°.

Spectral data of compound **15** follow: nmr $\delta_{TMS}^{CCl_4}$ 2.42 (q, 2 H, $COCH_2CH_3$), 1.74 (s, 6 H, β methyls), 1.72 (s, 3 H, α methyl), and 0.99 (t, 3 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1695 (s, C=O), 1626 (m, C=C), and 1418 cm^{-1} (w, CH_2 bend of $COCH_2$); λ_{max}^{EtOH} 300–305 (w, R band) and 244 mμ (s, K band); mass spectrum *m/e* (rel intensity) 126 (20) (parent peak), 97 (88), 69 (92), 57 (18), 53 (13), 41 (100), 39 (28), 29 (36), and 27 (34).

5-Ethyl-2,4-dimethyl-4-hepten-3-one (17).—Isobutyryl chloride (7.5 g) and 10.3 g (0.105 mol) of 3-ethyl-2-pentene were condensed in the presence of stannic chloride. The reaction and work-up procedure were similar to that described above. A mixture of **17** and 5-ethyl-2,4-dimethyl-5-hepten-3-one (**35**) was obtained. Separation was accomplished using a 6 ft × 0.375 in., 20% Carbowax column at 155°.

Spectral data of compound **17** follow: nmr $\delta_{TMS}^{CCl_4}$ 2.75 [m, 1 H, $COCH(CH_3)_2$], 2.04 (q, 2 H, $CH_3CH_2C{=}C$, *cis* to carbonyl), 1.95 (q, 2 H, $CH_3CH_2C{=}C$, *trans* to carbonyl), 1.76 (s, 3 H, α methyl), 1.02 [d, 6 H, $CH(CH_3)_2$], and 0.99 (t, 6 H, CH_2CH_3); ir (neat) ν_{max}^{NaCl} 1678 (s, C=O) and 1616 cm^{-1} (w, C=C); uv λ_{max}^{EtOH} 302 (w, R band) and 247 mμ (s, K band); mass spectrum *m/e* (rel intensity) 168 (7) (parent peak), 125 (56), 69 (21), 55 (100), 43 (28), 41 (36), 39 (16), 29 (15), and 27 (25).

Registry No.—**2**, 141-79-7; **5**, 13905-10-7; **6**, 20685-43-2; **7**, 20685-44-3; **8**, 22319-24-0; **9**, 22319-25-1; **10**, 22287-10-1; **11**, 22319-26-2; **12**, 22287-11-2; **13**, 22287-12-3; **14**, 22287-13-4; **15**, 17325-90-5; **16**, 22319-28-4; **17**, 22319-29-5; **18**, 684-94-6; **19**, 20685-45-4; **20**, 20685-46-5; **21**, 22319-31-9; **22**, 565-62-8; **23**, 78-94-4; **24**, 814-78-8.

(20) J. Colonge and K. Mostafavi, *Bull. Soc. Chim. Fr.*, **6**, 335 (1939).
(21) J. Colonge and D. Joly, *Ann. Chem.*, **18**, 286 (1943).

Bicyclo[1.1.1]pentane Derivatives[1]

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Received July 1, 1969

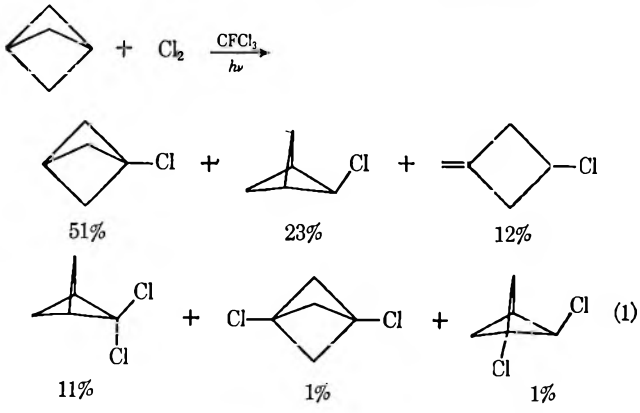
The synthesis of a variety of 1- and 2-substituted bicyclo[1.1.1]pentanes is described. Free-radical substitution occurs primarily at the bridgehead, and both types of hydrogens are markedly deactivated toward free-radical attack. The bridgehead radical opens to the methylenecyclobutyl radical at an appreciable rate. The K_a of the bridgehead acid is higher than that for any other simple saturated carboxylic acid, and the K_b of the bridgehead amine is lower than that of any other simple aliphatic amine. The nmr spectra of the compounds are discussed and the coupling constants and chemical shifts are given.

In the case of bicyclo[1.1.1]pentane, the parent hydrocarbon is more easily obtained than its simple derivatives.[3] Bicyclopentane was originally prepared by the reaction of 3-bromomethylcyclobutyl bromide with lithium amalgam.[4] It has also been obtained by the photolysis of bicyclo[2.1.1]hexan-2-one[5] and of 1,4-pentadiene.[6] The Wurtz reaction has been improved using the naphthalene radical anion as the halogen abstractor to give a 6.5% yield of the hydrocarbon. Recently, Rifi has found that the electrochemical dehalogenation[7] also is successful with 3-bromomethylcyclobutyl bromide and gives over twice the yield obtained using the chemical reagents.[8] This

(1) This investigation was supported by the U. S. Army Research Office (Durham).
(2) Taken from part of the Ph.D. thesis of V. Z. Williams, 1968. Proctor and Gamble Fellow, 1966–1967; Heyl Fellow, 1967–1968.
(3) The only functional bicyclo[1.1.1]pentane derivative which has been obtained from a compound other than the parent hydrocarbon is the 2-phenyl-2-hydroxy compound formed *via* the irradiation of phenyl cyclobutyl ketone [A. Padwa and E. Alexander, *J. Amer. Chem. Soc.*, **89**, 6376 (1967)].
(4) K. B. Wiberg and D. S. Connor, *ibid.*, **88**, 4437 (1966).
(5) J. Meinwald, W. Szkrybalo, and D. R. Dimmel, *Tetrahedron Lett.*, 731 (1967).
(6) R. Srinivasan and K. H. Carlough, *J. Amer. Chem. Soc.*, **89**, 4932 (1967).
(7) M. R. Rifi, *ibid.*, **89**, 4442 (1967).
(8) Dr. M. R. Rifi, personal communication.

appears to be the best way in which to obtain bicyclo[1.1.1]pentane.

One of the simplest methods of obtaining a functional bicyclopentane derivative is free-radical halogenation. We have previously reported on the chlorination using *t*-butyl hypochlorite.[4] We have found it possible to effect direct, photochemically initiated chlorination in Freon 11 (trichlorofluoromethane) as a solvent. Using a limited concentration of chlorine, an 11% yield of a mixture of mono- and dichlorides was obtained with the following distribution (eq 1).



(1)

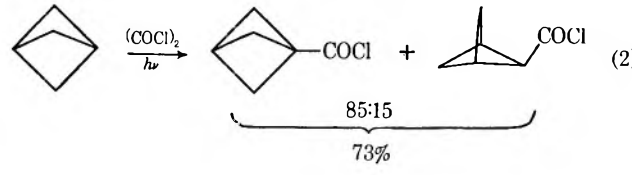
The products were easily identified by their nmr spectra. The majority of the products consisted of polyhalides, and at least part of this was derived from 3-methylenecyclobutyl chloride. It seems probable that the bridgehead radical was formed, and then opened to the 3-methylenecyclobutyl radical before reacting with chlorine. This hypothesis was tested by carrying out the reaction using a relatively high chlorine concentration. The mono- and dichlorides were now obtained in 50% yield and gave the products indicated above in the proportions 62, 15, 0, 14, 2, and 7%, respectively. The amount of ring opening was decreased markedly, suggesting that the 1-bicyclo[1.1.1]-pentyl radical rearranges to the 3-methylenecyclobutyl radical with a significant activation energy.

The ratio of bridgehead to methylene substitution was 2.4:1 (assuming that the 1,2 dichloride was formed from the 1-chloro derivative), giving a relative reactivity per hydrogen of 7:1. The chlorination of other bicyclic hydrocarbons such as norbornane,[9] nortricyclane,[10] bicyclo[2.1.1]hexane,[11] and bicyclo-[2.2.0]hexane[12] has also been studied. In each case, the majority of the products are derived from the unrearranged hydrocarbons, and only in the case of bicyclo[2.2.0]hexane was any bridgehead substitution (15%) found. In the case of bicyclo[2.1.1]hexane, all of the chlorides isolated were substituted at the two-carbon bridge.

Srinivasan and Sonntag[11] found that the rate of chlorination of a methylene group in cyclohexane is only 1.25 times greater than that of the 2 position of bicyclo[2.1.1]hexane. An attempt was made to carry out a competitive chlorination of bicyclo[1.1.1]pentane and cyclohexane. However, cyclohexane reacted essentially instantaneously under conditions which led to a relatively slow reaction with bicyclopentane. It would appear that the relative reactivities must be on the order of 100:1 or greater.

Two factors may contribute to the low reactivity of bicyclo[1.1.1]pentane. First, both the bridgehead and methylene positions incorporate considerable strain, which should result in a marked decrease in reactivity. Second, the secondary hydrogens are sterically not so accessible so in cyclohexane. As a result, the tertiary bridgehead position becomes more reactive than the secondary methylene position.

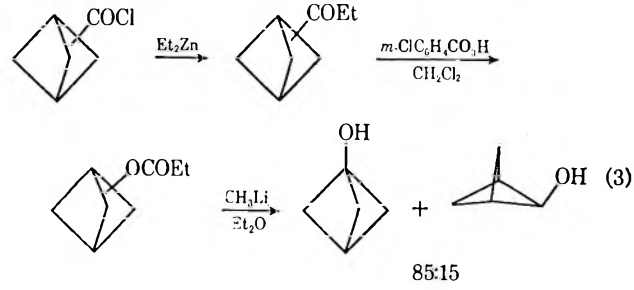
In an effort to introduce conveniently a carbon-containing functional group, the little-used photochemical reaction between a hydrocarbon and oxalyl chloride[13] was tried. The reaction was found to give 73% of a mixture of acid chlorides (eq 2). Some



(2)

disubstitution products also appear to have been formed. Again, bridgehead substitution predominates.

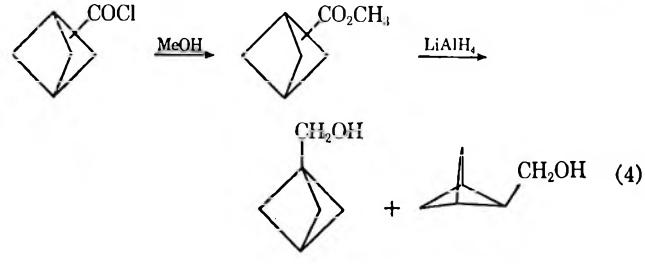
The acid chloride mixture could be converted into a mixture of the 1- and 2-hydroxy compounds by conversion into the ketone and peracid oxidation (eq 3).



(3)

The two alcohols could be separated by vpc, and were obtained in an 85:15 ratio corresponding to the acid chloride mixture. Bicyclo[1.1.1]pentan-1-ol was a solid, mp 61–62°.

Treatment of the acid chloride mixture with methanol gave the methyl esters, which could be reduced to the carbinols with lithium aluminum hydride (eq 4).

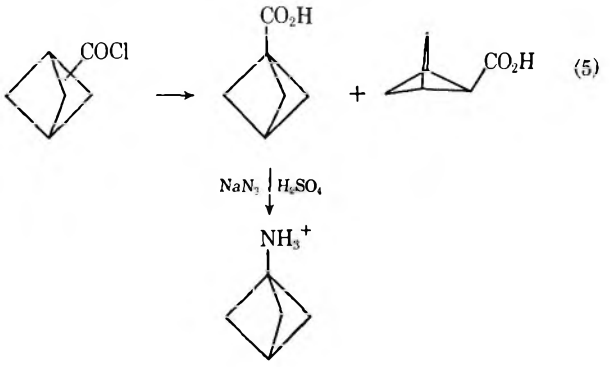


(4)

The carbinol mixture could be separated by vpc. Treatment of the acid chlorides with water gave the carboxylic acids, which could be separated by vpc. The bridgehead acid was a solid, mp 59–59.7°. The

(9) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4**, 382 (1958).
(10) M. L. Poutsma, *J. Amer. Chem. Soc.*, **87**, 4293 (1965).
(11) R. Srinivasan and F. I. Sonntag, *ibid.*, **89**, 407 (1967).
(12) R. Srinivasan and F. I. Sonntag, *Tetrahedron Lett.*, 603 (1967).
(13) M. S. Kharasch and H. C. Brown, *J. Amer. Chem. Soc.*, **64**, 329 (1942). This reaction has recently been applied to a bicyclic system by P. K. Freeman, F. A. Raymond, J. C. Sutton, and W. R. Kindley, *J. Org. Chem.*, **33**, 1448 (1968).

bridgehead acid was converted into the amine *via* the Schmidt reaction (eq 5).

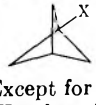


(5)

We have previously noted the effect of hybridization at the bridgehead position on the dissociation constant of carboxylic acids and on the basicity of amines.[14] In order to extend these observations, the compounds obtained in this series were studied. Bicyclo[1.1.1]-pentane-1-carboxylic acid was found to have a K_a of 8.05×10^{-5} in water at 25°, which is the largest value so far noted for a simple saturated carboxylic acid. The corresponding amine was found to have a K_b of 3.8×10^{-6}, and thus is considerably less basic than even ammonia. A summary of some of the available data is recorded in Table I. The 1-bicyclo-

TABLE I

DISSOCIATION CONSTANTS OF CARBOXYLIC ACIDS AND AMINES IN WATER AT 25°

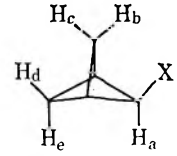
Compd	$K_a \times 10^5$, X = CO_2H[a]	$K_b \times 10^5$, X = NH_2
H–X		1.98
CH_3–X	1.77	42
$(CH_3)_3C$–X	0.89	28
	1.64	11
	3.48	2.0[b]
	8.05	0.38

[a] Except for the bicyclic compounds, the data were taken from M. Kotake, "Constants of Organic Compounds," Asakura Publishing Co., Tokyo, 1963, pp 585 and 615. [b] Reference 14.

[1.1.1]pentanecarboxylic acid is nine times as acidic as pivalic acid, and over twice as acidic as the closely related 1-bicyclo[2.1.1]hexanecarboxylic acid. A similar trend is found with the amines, with 1-bicyclo-[1.1.1]pentylamine being much less basic than even ammonia. The changes in acidity and basicity almost certainly arise primarily from the change in s character in the bridgehead–X bond as the bond angles at the bridgehead are distorted from their normal values.[14] In accord with this, the ^{13}C–H nmr coupling constant at the bridgehead position of bicyclo[1.1.1]-pentane is 160 Hz.[4]

Finally, we may consider the nmr spectra of the bicyclo[1.1.1]pentane derivatives. The 1-substituted derivatives exhibit very simple spectra (two singlets), since there is no coupling between the bridgehead and methylene protons. The chemical shifts are summarized in Table II. The effect of the substituent is remarkably small at the C_3 hydrogen. A larger range of values is found for the C_2 hydrogens, and the difference in values for the two types of hydrogens varies from 0.32 to 0.78 ppm.

Considerably more data may be derived from the spectra of the 2-substituted derivatives (Table III). In each case, the two bridgehead hydrogens lead to a sharp singlet. The methylene protons are all non-equivalent, allowing the observation of both geminal and long-range coupling. The hydroxy and chloro compounds gave essentially first-order splitting patterns and the spectra were easily analyzed. With approximate values of the coupling constants, it was possible to analyze the spectra of the other compounds with the aid of the program LAOCN 3.[15] The designation of the protons is shown below. The long-range cou-



pling constants were *ca.* 10 Hz for the unsubstituted position and *ca.* 7 Hz for the coupling involving H_a. This corresponds to the value found for the parent hydrocarbon.[4] The geminal coupling constants were *ca.* 3 Hz, which is reasonable for this structure.[16]

The magnitudes of the chemical shifts are of interest in connection with development of approaches to calculating these quantities, since the molecules have rigid, well-defined geometries. However, a detailed discussion of this problem will be postponed until other related data may be presented.

Experimental Section

Bicyclo[1.1.1]pentane.—To a 3-l., three-necked flask equipped with an addition funnel with helium inlet, Trubore stirrer with Teflon paddle, and an Allihn condenser attached to a Dry Ice–acetone-cooled trap was added 23 g (1 g-atom) of sodium, 1500 ml of dry glyme, and 128 g (1 mol) of naphthalene. The mixture was stirred under helium at room temperature to allow the deep green radical anion solution to form. The flask was cooled to −30° using a Dry Ice–isopropyl alcohol bath, and a solution of 57 g (0.25 mol) of 3-bromomethylcyclobutyl bromide in 250 ml of dry glyme was added dropwise over a 3-hr period. The addition funnel was replaced by a helium inlet tube which extended below the surface of the solution and the flow of gas was increased to a moderate rate. The solution was allowed to warm slowly and then was heated to reflux for 1.5 hr to distil the products into the trap. The product was bulb-to-bulb distilled into a storage trap for subsequent purification. The excess radical anion in the reaction flask was destroyed with water and the solvent was recovered by centrifugation of the suspended solids and redistillation from sodium.

In a typical run, about 20 ml of volatile material was collected in the trap. Nmr analysis indicated 32% glyme, 55% methyl vinyl ether (from solvent cleavage), and 13% hydrocarbons. The combined crude product from several runs was fractionally distilled in a cold room at 2° using a 25 × 1 cm column with Helipak packing. The condenser was held at −10°. Methyl vinyl ether, bp 8°, was collected, followed by the hydrocarbon fraction, bp 25–45°.

The hydrocarbon fraction was cooled in an ice bath and stirred magnetically. Bromine was added dropwise until the color

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TABLE II

CHEMICAL SHIFTS FOR 1-SUBSTITUTED BICYCLO[1.1.1]PENTANES

R	Registry no.	Chemical shift, δ: Bridgehead	Chemical shift, δ: Methylene	R	Registry no.	Chemical shift, δ: Bridgehead	Chemical shift, δ: Methylene
OH	22287-25-8	2.35	1.92	H	311-75-1	2.45	1.88
CH_3	10555-48-3	2.40	1.67	CH_2OH	22287-32-7	2.48	1.70
CO_2Et	22287-27-0	2.42	2.05	OCOEt	22287-33-8	2.49	2.10
CO_2H	22287-28-1	2.45	2.10	COCl	22287-34-9	2.50	2.18
CH_2OAc	22287-29-2	2.44	1.70	$NH_3^+Cl^-$	22287-35-0	2.61	2.06
COEt	22287-30-5	2.45	2.01	Cl	10555-50-7	2.77	2.27

TABLE III

NMR SPECTRA OF 2-SUBSTITUTED BICYCLO[1.1.1]PENTANES

Substituent	Registry no.	Chemical shift, δ: H_a	H_b	H_c	H_d	H_e	Bridgehead	Coupling constant, Hz: J_{ac}	J_{be}	J_{bc}	J_{de}
Cl	10555-49-4	4.19	2.78	1.91	2.07	1.61	2.62	7.4	10.1	−3.0	−3.0
OH	22287-38-3	4.21	2.81	1.85	1.66	1.25	2.52	6.3	10.1	−2.7	−3.0
$OCOC_2H_5$	22319-33-1	4.58	2.55	1.78	1.75	1.46	2.65	6.9	9.8	−2.7	−3.2
COC_2H_5	22319-34-2	2.85	2.20	1.80	1.74	1.70	2.77	6.7	9.8	−3.0	−2.3
CO_2CH_3	22287-39-4	2.81	2.38	1.85	1.73	1.72	2.73	7.2	9.6	−3.2	−1.9
CO_2H	22287-40-7	2.94	2.49	1.90	1.75	1.76	2.78	7.3	10.0	−3.2	−2.2
CH_2OH	22287-41-8	2.55	2.43	1.88	1.87	1.70	2.49	6.7	10.0	−3.5	−2.5

persisted. The volatile hydrocarbons were bulb-to-bulb distilled into a storage trap. The hydrocarbon mixture was separated by vpc using an 8 ft × 1 in. 30% isoquinoline on 50–60 mesh Anaprep U column. Bicyclo[1.1.1]pentane had a retention time of 15.5 min at room temperature and was isolated in 6.5% yield.

Chlorination of Bicyclo[1.1.1]pentane. A. Low Chlorine Concentration.—To a 25-ml, two-necked flask fitted with a capillary gas inlet tube extending almost to the bottom of the flask, a magnetic stirrer, and a reflux condenser fitted with a drying tube was added 1.5 g (22 mmol) of bicyclo[1.1.1]pentane in 15 ml of Freon 11. The condenser was cooled to −10 to −15° using a circulating bath and the reaction was carried out in a cold room at 2°. Chlorine was bubbled slowly into the stirred mixture while it was irradiated with a 75-W incandescent lamp at a distance of 10 cm. The rate of chlorine addition was such that the solution maintained a light yellow color. The reaction was followed by vpc, and after 8 hr it appeared complete.

The majority of the solvent was removed by cautious distillation through a short-path still. The products were isolated by vpc using a 10 ft × 0.375 in. 20% Carbowax column at 130°. Nine components were found, and six were in sufficient quantity to be isolated and identified. The first component (51% of the volatile material) was 1-chlorobicyclo[1.1.1]pentane, nmr δ 2.27 (s, 6 H) and 2.77 (s, 1 H).

Anal. Calcd for C_5H_7Cl: C, 58.6; H, 6.9; Cl, 34.6. Found: C, 58.5, 58.6; H, 6.7, 6.9; Cl, 34.7, 34.6.

The second component (12%) was shown to be 3-methylenecyclobutyl chloride by its nmr spectrum: δ 2.6–3.6 (m, 4 H), 4.42 (quintuplet, 1H, J = 7.0 Hz), and 4.8–5.0 (m, 2 H).

Anal. Calcd for C_5H_7Cl: C, 58.6; H, 6.7; Cl, 34.6. Found: C, 58.4, 58.4; H, 7.0, 7.0; Cl, 34.5.

The third component (23%) was found to be 2-chlorobicyclo[1.1.1]pentane by its nmr spectrum (Table III).

Anal. Calcd for C_5H_7Cl: C, 58.6; H, 6.9; Cl, 34.6. Found: C, 58.5, 58.4; H, 6.9, 6.9; Cl, 34.7, 34.5.

The fourth and fifth components were too small to be collected. The sixth component (1.4%) was 1,3-dichlorobicyclo[1.1.1]-pentane, mp 72°, nmr δ 2.43 (s). The seventh component (11%) was 2,2-dichlorobicyclo[1.1.1]pentane: nmr δ 1.95 (d, 2H, J = 1.7 Hz), 2.61 (d, 2 H, J = 1.7 Hz), and 3.13 (s, 2 H).

Anal. Calcd for $C_5H_6Cl_2$: C, 43.8; H, 4.4; Cl, 51.8. Found: C, 43.9, 43.8; H, 4.5, 4.5; Cl, 51.7, 51.7.

The eighth component (1.4%) was 1,2-dichlorobicyclo[1.1.1]-pentane. Its nmr spectrum was analogous to that of 2-chlorobicyclo[1.1.1]pentane, with the band for the bridgehead hydrogen integrating for only one proton: δ 1.93 (d of d, 1 H, J = 10.0 and 2.7 Hz), 2.18 (d of d, 1 H, J = 7.2 and 2.5 Hz), 2.37 (d, 1 H, J = 2.7 Hz), 2.94 (s, 1 H), 2.98 (d of d, 1 H, J = 10.0 and 2.5 Hz), and 4.19 (d, 1H, J = 7.2 Hz). The ninth component was not isolated. The total yield of purified mono- and dichlorides was 250 mg (11%).

B. High Chlorine Concentration.—A mixture of 1.0 g of bicyclo[1.1.1]pentane and 2.0 ml of Freon-11 was placed in a 10-ml flask attached to a −5° condenser. An excess of chlorine was bubbled in and the flask was then illuminated. After 3 hr, nitrogen was passed through the solution to sweep out hydrogen chloride. Analysis by vpc indicated the chloride composition to be 62% 1-chlorobicyclo[1.1.1]pentane, 15% 2-chlorobicyclo-[1.1.1]pentane, 2% 1,3-dichlorobicyclo[1.1.1]pentane, 14% 2,2-dichlorobicyclo[1.1.1]pentane, and 7% 1,2-dichlorobicyclo-[1.1.1]pentane. Isolation by preparative vpc gave 0.46 g (31%) of 1-chlorobicyclo[1.1.1]pentane. Some unreacted bicyclo-[1.1.1]pentane also was present.

Bicyclo[1.1.1]pentanecarbonyl Chloride.—A 20 × 1 cm (i.d.) quartz tube was fitted with a long, thin glass stirrer and an efficient condenser with drying tube. The condenser was held at −5° using a circulating bath. Into the reaction vessel was placed 3.0 g (44 mmol) of bicyclo[1.1.1]pentane, 7.6 g (60 mmol) of freshly distilled oxalyl chloride, and 4 ml of Freon 11 as a diluent. The area above the liquid level was covered with aluminum foil. The stirrer was started and the solution was irradiated with two Sylvania G15T8 low-pressure mercury lamps at a distance of 6 in. Irradiation was continued for 10 hr or until the volume of the solution had decreased by about 4 ml. The reaction mixture was transferred to a distillation flask with the aid of a little Freon 11. Distillation gave 4.2 g (73%) of a mixture of 1- and 2-bicyclo[1.1.1]pentanecarbonyl chlorides, bp 34–40° (10 mm). The ratio of the two components was affected by temperature. At 1–2°, the ratio of 1- to 2-substituted derivatives was 78:22 and at 25° it was 85:15.

The pot residue (1.3 g) was treated with methanol and analyzed by nmr and vpc. A complex mixture was found which contained diesters.

Bicyclo[1.1.1]pentyl Ethyl Ketones.—To a 250-ml, three-necked flask fitted with a nitrogen inlet was added 100 ml of dry ether and 2.0 g (16 mmol) of diethylzinc. A nitrogen flow was maintained during the addition to prevent ignition of the diethylzinc. The flask was then equipped with a magnetic stirrer, a reflux condenser with a drying tube, and an addition funnel to which the nitrogen inlet was attached. Under a slow nitrogen flow, 4.08 g (31 mmol) of a mixture of 1- and 2-bicyclo[1.1.1]pentanecarbonyl chlorides in 25 ml of ether was added over 0.5 hr. The solution was stirred for 0.5 hr after addition and cooled in an ice–salt bath, and 20 ml of saturated ammonium chloride solution was added slowly followed by enough 2% hydrochloric acid to dissolve all the solids.

The mixture was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with two 25-ml portions of ether. The combined ether solution was washed with 25-ml portions of saturated sodium bicarbonate solution, water, and saturated salt solution, and dried over magnesium sulfate. The solvent was removed by distillation. The ketones appeared to decompose on distillation and therefore

were used in the following step without purification. The yield was estimated to be 55%.

A sample of the mixture was analyzed by vpc. On a 10 ft × 0.375 in. 20% DEGS column at 110°, the two isomers were separated cleanly. 1-Bicyclo[1.1.1]pentyl ethyl ketone (t_R 12.5 min) had the nmr spectrum summarized in Table II and had an ir carbonyl band at 1705 cm^{-1}. 2-Bicyclo[1.1.1]pentyl ethyl ketone (t_R 15 min) had the nmr spectrum summarized in Table III and had an ir carbonyl band at 1705 cm^{-1}.

Bicyclo[1.1.1]pentyl Propionates.—The crude mixture of bicyclo[1.1.1]pentyl ethyl ketones was mixed with 60 ml of methylene chloride and 5.6 g of *m*-chloroperbenzoic acid. The solution was stirred at room temperature for 4 days. The solution was filtered and then washed with 25 ml of 1.0 *M* sodium sulfate solution, two 25-ml portions of saturated sodium bicarbonate solution, 25 ml of water, and 25 ml of saturated salt solution. The organic layer was dried over sodium sulfate and the solvent was removed using a rotary evaporator. Distillation gave 1.92 g (91%) of a mixture of bicyclo[1.1.1]pentyl propionates, bp 65–67° (23 mm).

The mixture could be separated by vpc using a 20% DEGS column at 110°, giving 74% bridgehead ester (t_R 7.6 min) and 26% secondary ester (t_R 12.5 min).

Bicyclo[1.1.1]pentanols.—Methyllithium was formed from 0.44 g (63 mg-atom) of lithium wire and methyl bromide in 30 ml of dry ether. The flask was cooled in an ice bath and 1.92 g (13.7 mmol) of the mixture of 1- and 2-bicyclo[1.1.1]pentyl propionates in 20 ml of dry ether was added over 1 hr. The solution was allowed to warm at room temperature and was stirred for an additional 1 hr.

The flask was again cooled in an ice bath and a solution of 1.65 g (31.3 mmol) of ammonium chloride in 10 ml of water was added slowly. The solution was transferred to a separatory funnel and enough water was added to dissolve all the solids. The ethereal layer was washed with 20 ml of water and 20 ml of saturated salt solution and dried over sodium sulfate. The majority of the solvent was removed by distillation through a 25 × 1 cm column packed with Helipak. The products were isolated by preparative vpc using a 20% didecyl phthalate column at 110°. 1-Bicyclo[1.1.1]pentanol (t_R 3.4 min) was the first component.

Anal. Calcd for C_5H_8O: C, 71.4; H, 9.5. Found: C, 70.6; H, 9.4.

2-Bicyclo[1.1.1]pentanol (t_R 6.0 min) was the second component.

Anal. Calcd for C_5H_8O: C, 71.4; H, 9.5. Found: C, 70.7, 70.7; H, 9.4, 9.3.

The structures were easily shown from the nmr spectra (Tables II and III).

1-Bicyclo[1.1.1]pentanol was converted into its 3,5-dinitrobenzoate, mp 143.6–144.6° after recrystallization from hexane.

Anal. Calcd for $C_{12}H_{10}N_2O_8$: C, 51.8; H, 3.6; N, 10.1. Found: C, 51.8, 52.0; H, 3.7, 3.8; N, 10.1, 10.1.

2-Bicyclo[1.1.1]pentanol also was converted into its 3,5-dinitrobenzoate, mp 126.4–127.4° after recrystallization from hexane.

Methyl Bicyclo[1.1.1]pentanecarboxylates.—A solution of 2.0 ml of methanol in 25 ml of dry ether was cooled and stirred in an ice bath. A solution of 5.0 g of the 85:15 mixture of bicyclo[1.1.1]pentanecarbonyl chlorides in 15 ml of dry ether was added and the solution was allowed to warm to room temperature over 0.5 hr. The solution was treated with two 15-ml portions of water and two 15-ml portions of sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed through a short Vigreux column, giving 4.4 g (92%) of esters. The esters were separated by vpc using a 10 ft × 0.375 in. Carbowax column at 140°.

Methyl bicyclo[1.1.1]pentane-1-carboxylate (t_R 4.5 min) formed 85% of the mixture.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.7; H, 7.9. Found: C, 66.8; H, 7.8.

Methyl bicyclo[1.1.1]pentane-2-carboxylate formed 15% of the mixture. The nmr spectra of the compounds are summarized in Tables II and III.

Bicyclo[1.1.1]pentanemethanols.—A solution of 5.25 g (42 mmol) of a mixture of 15% methyl bicyclo[1.1.1]pentane-2-carboxylate and 85% methyl bicyclo[1.1.1]pentane-1-carboxylate in 25 ml of dry ether was added over a 1-hr period to 3.8 g of lithium aluminum hydride in 100 ml of ether at 0°. The solution was stirred for 1 hr and treated with 3.8 ml of water, 3.8 ml of 15% potassium hydroxide solution, and 11.4 ml of water. The solution was filtered and dried over magnesium sulfate. The ether was removed by distillation, and the products were isolated by preparative vpc using a 10 ft × 0.375 in. 20% DEGS column at 150°. There was obtained 0.86 g of bicyclo[1.1.1]pentane-1-methanol (t_R 3.0 min) and 0.33 g of bicyclo[1.1.1]pentane-2-methanol (t_R 5.2 min). The nmr spectra are summarized in Tables II and III.

Anal. Calcd for $C_6H_{10}O$: C, 73.4; H, 10.3. Found (1 isomer): C, 72.7, 72.8; H, 9.7, 9.7. Found (2 isomer): C, 73.2, 73.2; H, 10.1, 9.9.

Bicyclo[1.1.1]pentanecarboxylic Acids.—A mixture (1.0 g) of bicyclo[1.1.1]pentanecarbonyl chlorides was dissolved in 25 ml of ether and added dropwise to a stirred salt solution to which 1.0 ml of saturated sodium carbonate solution had been added. The solution was stirred for 3 hr, the aqueous layer was acidified with hydrochloric acid, and the layers were separated. The aqueous layer was extracted with three 25-ml portions of ether, and the combined ether solutions were washed with two 15-ml portions of saturated salt solution and dried over magnesium sulfate. The solvent was removed using a rotary evaporator, giving 0.95 g of crude acid. Separation was effected at 150° using a 10 ft × 0.375 in. 710 silicone column which had been treated with several 0.1-ml injections of acetic acid. The bridgehead isomer (t_R 6.0 min) could be collected in good purity, but, because of tailing, the secondary isomer (t_R 7.2 min) was contaminated with 8–10% bridgehead compound.

Bicyclo[1.1.1]pentane-1-carboxylic acid had a melting point of 59–59.7°.

Anal. Calcd for C_6H_8O: C, 64.1; H, 7.2. Found: C, 63.3, 63.2; H, 6.9, 7.0.

It was converted into a *p*-bromophenacyl ester, mp 104.3–104.6° after recrystallization from methanol.

Anal. Calcd for $C_{14}H_{13}O_3Br$: C, 54.4; H, 4.2; Br, 25.8. Found: C, 54.3, 54.4; H, 4.2, 4.6; Br, 26.0, 26.1.

1-Bicyclo[1.1.1]pentylamine Hydrochloride.—In a 50-ml flask equipped with a stirrer and reflux condenser were placed 13 ml of chloroform, 2.5 ml of concentrated sulfuric acid, and 0.8 g of bicyclo[1.1.1]pentane-1-carboxylic acid. The solution was heated to 35–40° in an oil bath, and 0.95 g (14.5 mmol) of sodium azide was added in small portions over a 1-hr period. The solution was stirred for 1 hr, cooled, made basic with 33% sodium hydroxide solution, and steam distilled into a well-cooled receiver containing 15 ml of 3 *N* hydrochloric acid. The chloroform and excess aqueous acid were removed using a rotary evaporator. The salt was purified by precipitation from 1-propanol, using three times the volume of dry ether. The nmr spectrum is summarized in Table II.

Anal. Calcd for $C_5H_{10}NCl$: C, 50.2; H, 8.4; Cl, 29.7. Found: C, 50.2, 50.3; H, 8.4, 8.3; Cl, 29.5.

Dissociation Constants.—The dissociation constants were determined potentiometrically in water solution, as described previously.[14]

Registry No.—1-Bicyclo[1.1.1]pentanol 3,5-dinitrobenzoate, 22319-35-3; 2-bicyclo[1.1.1]pentanol 3,5-dinitrobenzoate, 22319-36-4; bicyclo[1.1.1]pentane-1-carboxylic acid *p*-bromophenacyl ester, 22319-37-5; 2-bicyclo[1.1.1]pentanecarbonyl chloride, 22319-38-6; 3-methylenecyclobutyl chloride, 22287-42-9; 1,3-dichlorobicyclo[1.1.1]pentane, 22287-43-0; 2,2-dichlorobicyclo[1.1.1]pentane, 22287-44-1; 1,2-dichlorobicyclo[1.1.1]pentane, 22287-45-2.

Reductive Opening of Acyclic Conjugated Cyclopropyl Ketones with Lithium in Liquid Ammonia[1]

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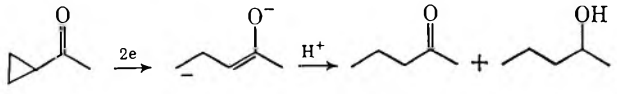
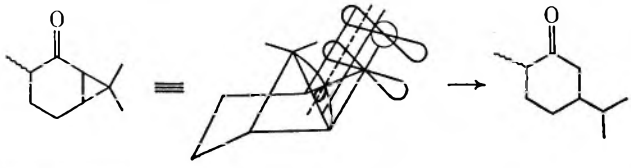
Received June 9, 1969

A series of acyclic 2-methylcyclopropyl alkyl ketones **1** has been reductively cleaved with lithium in liquid ammonia. The selective bond cleavage which occurs depends upon the influence of both steric and electronic factors. The reduction products that predominate in the reaction mixture from the cleavage of 2,2-dimethylcyclopropyl alkyl ketones or *cis*-2-methylcyclopropyl alkyl ketones arise from C-1–C-2 bond breaking. In contrast the *trans*-2-methylcyclopropyl alkyl ketones fragment at the C-1–C-3 bond. The observed ring-opening pattern suggests that steric factors can control the direction of cleavage, presumably through unsymmetrical overlap of the carbonyl π system with one of the cyclopropane bonds. In the absence of these steric elements (as in the *trans*-substituted cyclopropane ring), the bond that cleaves is the one that gives the more thermodynamically stable carbanion intermediate (least substituted carbon).

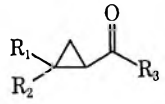
The reduction of organic compounds with metals in liquid ammonia is a well-established synthetic technique.[2-5] Deuteration[6,7] and alkylation[3-10] experiments in the reduction of α,β-unsaturated ketones with lithium in liquid ammonia have shown that the β-carbon atom develops a considerable amount of carbanion character during the reductive process. Cyclopropyl ketones, when reduced with metals in ammonia,[11] undergo reductive cleavage of the cyclopropane ring by a mechanism similar to that described for enones, and thus, the developing carbanionic character of the β carbon could be a controlling factor in a ring opening.



In fused bicyclic systems, however, geometrical factors[12,13] and not electronic factors appear to control the direction of ring opening of the cyclopropane ring, and the bond that cleaves is the one which has the greater overlap with the carbonyl π system. An example of this stereoselective reductive cleavage can be illustrated with the reduction of (+)-carone, which gives only the (−)-carvomenthones upon treatment with lithium in liquid ammonia.[12,13] None of the product which would be derived from the more thermodynamically stable secondary carbanion was found.



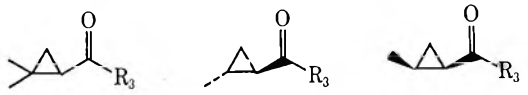
The present study extends this reductive reaction of lithium in liquid ammonia to acyclic conjugated cyclopropyl ketones of the general type **1**, where both



1

$R_1, R_2 = H, CH_3$

bonds of the cyclopropane ring are free to overlap with the carbonyl π system and thus the importance of electronic and steric factors can be evaluated. The six 2-methylcyclopropyl alkyl ketones **2**–**7** were prepared. The ketones **2**, **3**, and **5** were obtained by treating the



2, $R_3 = CH_3$ **4**, $R_3 = CH_3$ **6**, $R_3 = CH_3$

3, $R_3 = C_4H_9$ **5**, $R_3 = C_4H_9$ **7**, $R_3 = C_4H_9$

respective enones with dimethyloxosulfonium ylide,[14] and ketones **4**, **6**, and **7** were prepared from the corresponding cyclopropylcarbinols which, in turn, were prepared from corresponding *cis*- and *trans*-allylic alcohols using methylene iodide and zinc–copper couple.[15,16] The allylic alcohols were prepared from the acetylenic alcohols by hydrogenation.

The lithium in liquid ammonia reduction of an unsymmetrically substituted cyclopropyl ketone can lead to two different ring-opened products. The reduction possibilities are shown in Scheme I. If one presumes that the carbonyl group can rotate to the same extent over both bonds of the cyclopropane ring, thermodynamic considerations of the intermediates formed in the reductive cleavage process should allow one to predict which bond of the cyclopropane ring will preferentially break. Path a in Scheme I shows cleavage of the C-1–C-2 bond, leading to the less stable secondary or tertiary carbanion, whereas path b gives the more stable primary carbanion. Under equal

(1) This work was supported in part by Public Health Service Grant CY-04284, National Cancer Institute, U. S. Public Health Service.

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(11) R. V. Volkenburgh, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Amer. Chem. Soc.*, **71**, 3595 (1949).

(12) T. Norin, *Acta Chem. Scand.*, **19**, 1289 (1965).

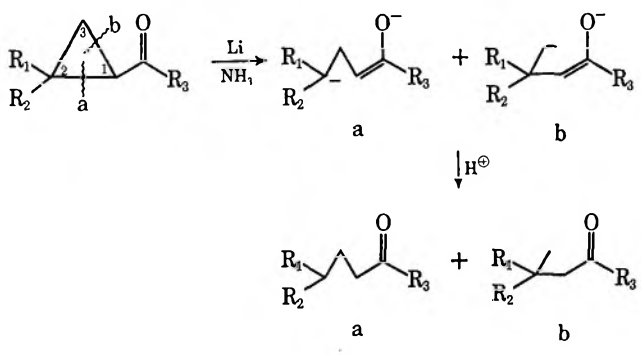
(13) W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).

(14) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965).

(15) H. E. Simmons, E. P. Blanchard, and R. D. Smith, *ibid.*, **86**, 1347 (1964).

(16) W. G. Dauben and G. H. Berezin, *ibid.*, **85**, 468 (1963).

SCHEME I



overlap conditions the product resulting from the more stable primary carbanion intermediate would be expected to predominate in the reduction mixture. The results of the lithium–ammonia reductions are shown in Table I.

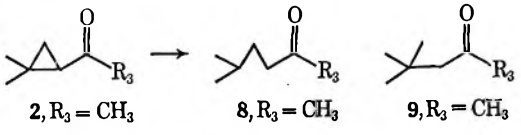
TABLE I

LITHIUM IN LIQUID AMMONIA REDUCTION OF ACYCLIC CONJUGATED CYCLOPROPYL KETONES

Ketone	Starting material, %	Products, path a and b, %	Path a, %	Path b, %
2	10	74[a]	76	24
3	5	87	81	19
4	5	65	6	94
5	5	87	12	88
6	14	53	95	5
7	4	69	91	9

[a] The product ratio remained essentially the same even though the yields ranged from 36 to 84%.

The reduction of 2,2-dimethylcyclopropyl methyl ketone (**2**) with lithium in liquid ammonia afforded two ketonic products, **8** and **9**, and the corresponding alcohols. To simplify product analysis the reduction mixtures were routinely oxidized. The major product from such a work-up was isoamyl methyl ketone (**8**) and the minor component was neopentyl methyl ketone (**9**).

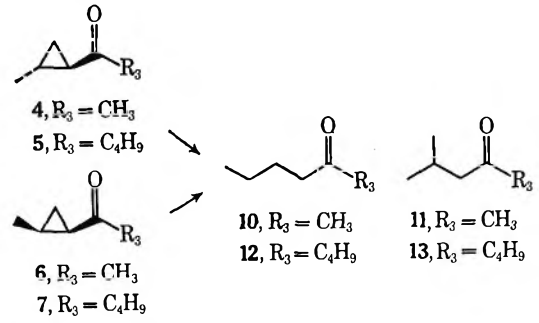


The relative product percentages formed by path a (leading to the less stable tertiary carbanion intermediate) clearly implicated considerations other than simple thermodynamic stabilities of intermediate carbanions in control of the ring-opening process. On the basis of carbanion stabilities, ketone **9** should have been the predominant product. Although the data presented in Table I indicate an 84% recovery of material at the end of the reaction, this result was the best of a series of experiments. The methyl ketones of this series are quite volatile (bp 110–130°), and when attempts were made to isolate the ketonic products the losses were considerable. In order to obviate this difficulty, the *n*-butyl ketone series was studied.

The reductive cleavage of 2,2-dimethylcyclopropyl butyl ketone (**3**) proceeded to give the same ring-opening pattern as ketone **2**. The bond that opened was the one leading to the less thermodynamically stable product, thus suggesting that in this acyclic system a steric control was again controlling the course of the reaction. From molecular models of ketones **2** and **3**, it appeared that the C-1–C-2 bond was in a position to overlap more with the carbonyl π system than the C-1–C-3 bond because of the steric interaction of the *cis*-2-methyl substituent with the carbonyl group.

The reduction of the *trans*-2-methylcyclopropyl ketones **4** and **5** with lithium in liquid ammonia served to substantiate the concept of unsymmetrical overlap in the *cis*-2-methyl-substituted ketones **2** and **3**. When the *cis* substituent was absent, the predominant products were formed by way of the primary carbanion intermediate (path b).[17]

The *cis*-2-methylcyclopropyl ketones **6** and **7** were reduced with lithium in liquid ammonia and the ratio of products **10**/**11** and **12**/**13** were reversed from that observed in the cleavage of the *trans* ketones **4** and **5**. The sharp contrast between the ring opening of the *cis* and *trans* ketones clearly indicated that a steric effect was present in the *cis* ketones and that both steric and electronic factors are involved in the reduction process.



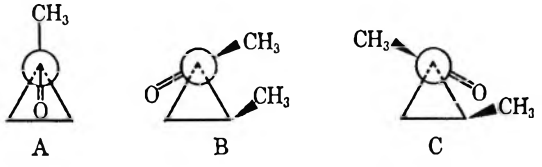
In the case of the *trans*-monomethyl-substituted cyclopropyl ketones **4** and **5**, the free rotation of the carbonyl gives equal π-orbital overlap to either cyclopropane bond. The predominant influence of the course of the reduction is the relative thermodynamic stability of the carbanionic intermediates generated. The *cis*-monomethyl cyclopropyl ketones **6** and **7**, in a thermodynamic sense, provide the same competition between carbanion centers as the *trans* ketones **4** and **5**, but the steric effect is far more important than the relative difference between a primary and secondary carbanion and the ratios are reversed.

The difference in thermodynamic stability of the carbanion is greatest when a tertiary center competes with a primary center, such as in the reduction of the 2,2-dimethylcyclopropyl ketones **2** and **3**. The steric situation in the case of 2,2-dimethyl-substituted cyclopropyl ketones should be the same as it is in the *cis*-2-methylcyclopropyl ketones **6** and **7**. As one can readily see in Table I, the thermodynamic effect changes the *ca.* 4:1 ratio of path a/path b type products in the ketones **2** and **3** to a ratio of *ca.* 10:1 with **6** and **7**. All of these data are consistent with developing carbanion character on a cyclopropyl carbon in the reductive cleavage of cyclopropyl ketones. Recently, similar steric and electronic effects were reported in the reductive cleavage of methyl-substituted phenylcyclo-

(17) After completion of this work, similar results were reported in the literature. See R. Fraisse-Jullien and C. Frejaville, *Bull. Soc. Chim. Fr.*, 4449 (1968). However, their results do not include the *cis*-substituted monomethylcyclopropyl ketones, which are considered necessary to evaluate electronic effects under similar steric conditions.

propanes[18] and, thus, indicate a close relationship between these two series of substituted cyclopropanes.

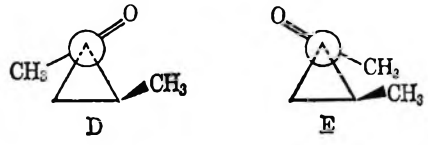
It is of interest to examine the nature of the steric interaction in these reductive cleavages of the *cis*-2-methylcyclopropyl methyl ketones. Electron-diffraction measurements[19] and nmr studies[20] indicate that unsubstituted cyclopropyl methyl ketone exists predominantly as the "bisected" cisoid conformer A. If



A B C

the reductive cleavage proceeds *via* a transition state involving overlap of a bond of the cyclopropane ring and the carbonyl group, then consideration of the two cisoid *gauche* conformations B and C is important. The presence of a substituent on the same side of the cyclopropane ring makes conformation B preferred owing to the unfavorable interaction of the substituent and the carbonyl oxygen in conformation C. In the absence of a substituent on the same side of the cyclopropane, both *gauche* conformations are of equal energy and purely electronic effects control the course of the reaction.

In view of the fact that there is considerable negative character at both the carbonyl oxygen and the β carbon in the transition state, dipolar considerations suggest that a transoid configuration for the transition state most likely would be preferred. The steric interactions in the two *gauche* conformations D and E of the transoid arrangements place the methyl groups in such a position that the steric interactions would lead to the same conclusion as above with the cisoid form.



D E

In view of the sensitivity of the product ratio to the preferred conformations of the starting material, the effect of varying the size of the reducing metal was evaluated. The results, summarized in Table II, show that the metal had no effect on the direction of ring opening. The slight shift in the isomer distribution in the magnesium reduction may be anamolous, for the magnesium did not dissolve appreciably in the ammonia and did not give the typical blue color normally associated with metal in ammonia reduction. The insensitivity of the product ratio to various metals suggests that no change in conformer population occurs. This could be due to the fact that the smallest atom, lithium, is already large enough to establish the preferred conformation or that the conformation of the transition state is predominately transoid in all cases. A similar insensitivity in product ratio with the metal employed has recently been found in the reduction of ketones,[21] a result at variance with earlier reports concerning the effect of metals.[22]

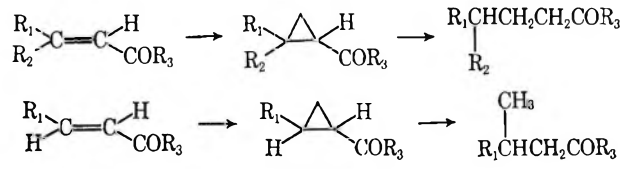
TABLE II

REDUCTION OF 2,2-DIMETHYLCYCLOPROPYL METHYL KETONE (2) WITH VARIOUS METALS IN LIQUID AMMONIA

Metal	Starting material, %	Products,[a] %	Path a, %	Path b, %
Li	10	74	76	24
Ca	28	55	74	26
K	10	73	76	24
Na	17	68	78	22
Mg	57	27	87	13

[a] Determined by internal-standard method using cyclooctane as an internal standard.

These findings of a steric effect in the reduction of conformationally mobile cyclopropyl conjugated ketones call attention to the synthetic utility of the process. In the *cis* series, the overall reaction process is



equivalent to a chain-elongation reaction by insertion of the carbon between the original α and β carbons of the starting material. In the *trans* series, the process is equivalent to a 1,4 addition to the unsaturated system to form a tertiary center β to the carbonyl group.

Experimental Section[23]

Synthesis of Starting Ketones. *cis*- and *trans*-**2-Methylcyclopropyl Methyl Ketones** (6 and 4).—These compounds were prepared as described in an earlier publication.[24]

2,2-Dimethylcyclopropyl Methyl Ketone (2).—Mesityl oxide was allowed to react with dimethyloxosulfonium ylide[14] and 2 was obtained in 56% yield. The spectral properties were in agreement with the reported values.[20,25]

2-Methyl-2-octen-4-one.—Following the general procedure of House and Trost,[26] 10 g of 3,3-dimethylacrylic acid and 138 ml of 1.6 *M* *n*-butyllithium were allowed to react. The reaction mixture, which was composed of the α,β- and β,γ-unsaturated ketone

(18) S. W. Staley and J. J. Rocchio, *J. Amer. Chem. Soc.*, **91**, 1565 (1969).

(19) L. S. Bartell, J. P. Guillory, and A. T. Parks, *J. Phys. Chem.*, **69**, 3043 (1965).

(20) J. L. Pierre and P. Arnaud, *Bull. Soc. Chim. Fr.*, 1690 (1966).

(21) J. W. Huffman and J. T. Charles, *J. Amer. Chem. Soc.*, **90**, 6486 (1968).

(22) G. Ourisson and A. Rassat, *Tetrahedron Lett.*, **21**, 16 (1960); A. Coulombeau and A. Rassat, *Bull. Soc. Chim. Fr.*, 3338 (1965); J.-C. Esprie, A-M. Giroud, and A. Rassat, *ibid.*, 809 (1967); A. Coulombeau and A. Rassat, *Chem. Commun.*, 1587 (1968).

(23) Infrared spectra were recorded on a Perkin-Elmer Model 137 Infracord or a 237 grating spectrophotometer. Ultraviolet spectra were taken with either a Perkin-Elmer ultraviolet–visible or a Beckman DK-2A spectrometer. Nuclear magnetic resonance spectra were determined on a Varian Associates A-60 or HA-100 spectrometer. Mass spectra were recorded with either a Varian Associates M-66 or a modified Consolidated Electronics Corporations Type 21-103C mass spectrometer. An Aerograph A-90 gas chromatograph, equipped with either a 10 ft × 0.375 in., 20% XF-1150 Cyanosilicone or a 10% Carbowax–10% KOH column, was utilized for separation of isomeric compounds. Product percentages were determined from vpc trace analyses using either an Aerograph 204 or a Hewlett-Packard F & M Model 5720 gas chromatograph, both of which were equipped with a flame ionization detector. Column chromatographies were done with neutral Woelm alumina (activity II) unless otherwise indicated. All materials used were either reagent grade or purified technical grades. Combustion analyses were performed by the Microanalytical Department of the University of California, Berkeley.

(24) W. G. Dauben, L. Schutte, and R. E. Wolf, *J. Org. Chem.*, **34**, 1849 (1969).

(25) R. M. Roberts, R. G. Landolt, R. N. Greene, and E. W. Heyer, *J. Amer. Chem. Soc.*, **89**, 1404 (1967).

(26) H. O. House and B. Trost, *J. Org. Chem.*, **30**, 2502 (1965).

as well as a hydrocarbon and a tertiary alcohol, was allowed to stand in aqueous ethanolic potassium carbonate solution for 1 hr and then column chromatographed to yield 3.8 g (27%) of 2-methyl-2-octen-4-one: ir (CCl_4) 3060, 1693, 1625, 1130, and 1040 cm^{-1}; nmr (CCl_4) δ 6.02 (m, 1, C=C**H**), 2.33 (t, 2, J = 6.5 Hz, CH_2CO), 2.08 (d, 3, J = 1.5 Hz, C=CC**H**$_3$, *trans* to CO), 1.83 (d, 3, J = 1.5 Hz, C=CC**H**$_3$, *cis* to CO), 1.48 (m, 4), and 0.9 (t, 3, J = 6.5 Hz, CH_2CH_3).

Anal. Calcd for $C_9H_{16}O$ (mol wt 140.23): C, 77.09; H, 11.50. Found: C, 77.37; H, 11.69.

2,2-Dimethylcyclopropyl Butyl Ketone (3).—Following the procedure described[24,25] for the preparation of 2,2-dimethylcyclopropyl methyl ketone (2), a solution of 3.0 g (17 mmol, 80% pure) of 2-methyl-2-octen-4-one in 8 ml of dimethyl sulfoxide was added to a flask containing 0.42 g (17.4 mmol) of sodium hydride, 3.8 g (17 mmol) of trimethyloxosulfonium iodide, and 17 ml of dimethyl sulfoxide.

The crude product (2.6 g) was column chromatographed to yield 1.6 g (61%) of 2,2-dimethylcyclopropyl butyl ketone (3). A vpc-purified sample gave the following spectral and analytical data: uv max (95% C_2H_5OH) 201.5 mμ (ϵ 5300); ir (CCl_4) 3075, 3010, 1690, 1130, 1090, and 1030 cm^{-1}; nmr (CCl_4) δ 2.42 (t, 2, J = 6.5 Hz, C**H**$_2$CO), 1.74 (d of d, 2, J = 7.5 and 5.5 Hz), 1.6–1.18 (m, 4), 1.18–0.9 [t, 2 s, 9, J = 6.5 Hz, CH_2CH_3 and $\rangle C(CH_3)_2$], and 0.7 (d of d, 1, J = 3.5 and 7.5 Hz, $\rangle CH_2$, H *cis* to carbonyl).

Anal. Calcd for $C_{10}H_{18}O$ (mol wt 154.25): C, 77.87; H, 11.86. Found: C, 78.03; H, 11.59.

***trans*-2-Octen-4-one.**—Following the procedure of Cason,[27] a 41.6-g (0.4 mol) portion of freshly distilled crotonyl chloride (bp 124–125°) and *n*-butylcadmium reagent were allowed to react in the usual manner. The solvent was removed through an 18-in. Vigreux column and the concentrate was distilled under reduced pressure to yield 28.75 g (57%) of *trans*-2-octen-4-one: bp 34–41° (0.5–0.6 mm); uv max (95% C_2H_5OH) 223 mμ (ϵ 11,600); ir (CCl_4) 3020, 1695, 1675, and 970 cm^{-1}; nmr (CCl_4) δ 6.79 (d of q, 1, J = 6.5 and 15 Hz, C=CH), 6.04 (d of q, 1, J = 1.5 and 15 Hz, C=CH), 2.47 (t, 2, J = 6.5 Hz, C**H**$_2$CO), 1.86 (d of d, 3, J = 1.5 and 6.5 Hz, C=CC**H**$_3$), 1.44 (m, 4), and 0.91 (t, 3, J = 6.5 Hz, CH_2CH_3).

Anal. Calcd for $C_8H_{14}O$ (mol wt 126.20): C, 76.14; H, 11.18. Found: C, 76.33; H, 11.07.

***trans*-2-Methylcyclopropyl Butyl Ketone (5).**—A solution of 12.6 g (0.1 mol) of *trans*-2-octen-4-one in 33 ml of dimethyl sulfoxide was added to a flask containing 2.64 g (0.11 mol) of sodium hydride, 22 g (0.1 mol) of trimethyloxosulfonium iodide, and 110 ml of dimethyl sulfoxide according to the procedure described for the preparation of 2,2-dimethylcyclopropyl methyl ketone (2).

After the normal work-up, the crude mixture was dried, concentrated, and distilled under reduced pressure to yield 7.55 g (54%) of *trans*-2-methylcyclopropyl butyl ketone (5): bp 67–68° (15 mm); uv max (95% C_2H_5OH) 195 mμ (ϵ 5,350); ir (CCl_4) 3060, 1695, 1400, and 1080 cm^{-1}; nmr (CCl_4) δ 2.48 (t, 2, J = 6.5 Hz, C**H**$_2$CO), 1.48 (m, 6), 1.15 (distorted s, 3, $\rangle CCH_3$), 0.91 (t over m, J = 6.5 Hz, CH_2CH_3), and 0.65 (m, 1, $\rangle CH_2$, H *cis* to carbonyl).

Anal. Calcd for $C_9H_{16}O$ (mol wt 140.23): C, 77.09; H, 11.50. Found: C, 77.35; H, 11.29.

2-Octyn-4-ol.[28,29]—A flame-dried, three-neck flask was fitted with a mechanical stirrer, a pressure-equalized addition funnel, a Dry Ice–acetone condenser, and an adapter to permit the introduction of gaseous samples. The flask was closed to the atmosphere through a mercury bubbler and flushed with dry nitrogen. An 0.11-mol ethyl Grignard solution in 50 ml of diethyl ether was prepared in the reaction vessel.

A 10-g (0.25 mol) portion of methylacetylene (Farchan Laboratories), which had been precondensed into a Dry Ice–acetone-cooled trap, was allowed to distil into the reaction vessel over a 1-hr period through a Drierite-filled drying tube, which was, in turn, connected to the gas-inlet adapter. The reaction mixture was stirred for 3 hr at room temperature.

The two-phase system (the upper layer was nearly water white and the bottom layer was dark gray) was stirred vigorously and cooled in an ice bath. A solution of 8.6 g (0.10 mol) of freshly distilled valeraldehyde in 75 ml of diethyl ether was added over a 1-hr period to the cold reaction mixture. The Dry Ice–acetone condenser was removed and replaced with a water condenser and the reaction was allowed to stir for 16 hr.

A saturated ammonium chloride solution was added to the mixture until the magnesium salts dissolved. The ethereal layer was separated from the aqueous layer, the aqueous layer was extracted with ether, and the extracts were combined. The ethereal extract was washed with a saturated potassium bicarbonate solution, dried, rotary evaporated, and spinning band distilled to yield 8.9 g (70.5%) of a colorless liquid. The product was identified as 2-octyn-4-ol based on the following data: bp 100–102° (29 mm); ir (CCl_4) 3600, 3440, 2250, 2200, 1100, 1030, 1000, and 885 cm^{-1}; nmr (CCl_4) δ 4.19 (m, 1, C**H**OH), 2.92 (s, 1, O**H**, shifts upfield with dilution), 1.81 (d, 3, J = 2 Hz, $CH_3C{\equiv}C$), 1.46 (m, 6), and 0.93 (t, 3, J = 6 Hz, CH_2CH_3).

Anal. Calcd for $C_8H_{14}O$ (mol wt 126.20): C, 76.14; H, 11.18. Found: C, 76.02; H, 11.03.

***cis*-2-Octen-4-ol.**—The hydrogenation was performed using a Brown[2] apparatus following the external generation procedure.[30] The catalyst was prepared from 1.0 g of Darco G activated charcoal and 1.0 ml of 0.02 *M* palladium(II) chloride solution. To the catalyst suspension was added 2.0 ml of ethylenediamine followed by 6.3 g (50 mmol) of 2-octyn-4-ol. Hydrogen uptake proceeded at a rate of 3.6 mmol/min. The hydrogenation was stopped when 1 molar equiv of hydrogen had been consumed. The hydrogenation mixture, when analyzed on vpc, contained two products in relative amounts of 3.5 and 96.5%.

Spectral and analytical data of the major product were obtained from a vpc-purified sample: bp 63–65° (20 mm); ir (CCl_4) 3600, 3330, 3010, 1660, 965, and 725 cm^{-1}; nmr (CCl_4) δ 5.32 (m, 2, HC=CH), 4.03 (m, 1, C**H**OH), 3.14 (s, 1, O**H**), 1.63 (d, 3, J = 5.5 Hz, C**H**$_3$C=C), 1.32 (m, 6), and 0.91 (t, 3, J = 6.5 Hz, CH_2CH_3).

Anal. Calcd for $C_8H_{16}O$ (mol wt 128.22): C, 75.00; H, 12.50. Found: C, 74.74; H, 12.37.

The minor product was not collected. It was assumed to be the saturated carbinol.

***trans*-2-Octen-4-ol.**—A mixture of 630 mg (5 mmol) of *trans*-2-octen-4-one, 100 mg (2.5 mmol) of lithium aluminum hydride, and 15 ml of dry diethyl ether was allowed to stir overnight at room temperature. An additional 47.5 mg (1.25 mmol) of lithium aluminum hydride was added and the mixture was allowed to stir under reflux for 1 hr.

The reaction mixture was treated with a saturated ammonium chloride solution, cautiously, until the dense salts precipitated. The liquid layer was decanted and the salts were washed with ether.

The ethereal extracts were combined, dried, and rotary evaporated, and the concentrate was bulb-to-bulb distilled to yield 104 mg (16%) of a clear liquid.

The spectral data were taken on a sample judged to be 80% pure on the basis of vpc analysis and contaminant peaks in the nmr: ir (CCl_4) 3600, 3350, 1670, and 965 cm^{-1}; nmr (CCl_4) δ 5.45 (m, 1.5), 3.9 (m, 0.8), 3.5 (m, 0.4), 2.83 (s, 1, O**H**), 1.67 (d, 2.8, J = 5 Hz, C=CC**H**$_3$), 1.36 (m, 6.2), and 0.9 (t, 3.2, J = 6 Hz, CH_2CH_3).

The minor product was assumed to be the saturated carbinol based on the position of contaminant peaks in the nmr of the mixed sample. No attempt was made to further purify the sample.

A vpc coinjection of *trans*-2-octen-4-ol and *cis*-2-octen-4-ol gave one peak on a 20% XF-1150 Cyanosilicone column (150°, 60 psi).

***cis*-2-Methylcyclopropylbutylcarbinol.**—A solution of 3.78 g (30 mmol) of *cis*-2-octen-4-ol in 15 ml of dry diethyl ether was added to a mixture of 5.49 g (84.2 mmol) of zinc–copper couple (Metal Hydrides LPO 100), 17.67 g (66 mmol) of methylene iodide, and 40 ml of diethyl ether, and the resulting mixture was allowed to react according to a literature procedure.[16]

Methylene iodide contaminated the product mixture even after sodium methoxide treatment,[16] but it was effectively removed by column chromatography (silica gel) using pentane as the eluting solvent. The more polar product was eluted with blends of pentane–diethyl ether to yield 3.16 g (74%) of a colorless liquid, which was identified as *cis*-2-methylcyclopropylbutylcarbinol by the following spectral characteristics: ir (CCl_4) 3600, 3060,

(27) J. Cason and F. S. Prout, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 601.

(28) I. A. Favorskaia, E. M. Auvinen, and J. P. Artsybashev, *J. Gen. Chem. USSR*, **28**, 1832 (1958); *Zh. Obshch. Khim.*, **28**, 1785 (1958).

(29) I. M. Heilbron, E. R. H. Jones, and R. A. Raphael, *J Chem. Soc.*, 264 (1943).

(30) C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3989 (1966). The authors wish to thank Dr. C. A. Brown for his assistance in this hydrogenation.

TABLE III

REDUCTION OF 2,2-DIMETHYLCYCLOPROPYL METHYL KETONE (2) WITH LITHIUM IN LIQUID AMMONIA

Run	Reagents: Ammonia, ml	Reagents: Ketone 2, g	Reagents: Lithium, g	Reaction time, hr	Ketones after oxidation, %	Ketone product distribution, %: 9	2	8	14	Ring-opening ratio of 8/9
1	200[a]	2.24	2.8	1	36[b]	19	15	66	..	3.4
2	200[a]	2.24	0.31	2	48[b]	14	40	46	..	3.3
3	200	2.24	1.4	6	51[c]	20	21	51	8	2.5
4	400	2.24	2.8	2	70[c]	17	19	59	5	3.4
5	400	2.24	2.8	2	53[c]	17	22	55	6	3.2
6	60	0.114	0.14	2	...[c,d]	21	8	69	..	3.3
7	60	0.112	0.14	2	84[c]	21	12	67	..	3.2

[a] Ammonia was dried over sodium before use. [b] Products were determined by actual isolation. The work-up varied from the standard procedure in that the ammonium chloride was added before the ammonia was evaporated. [c] Products were determined by comparison with an internal standard on vpc. [d] Cyclooctane was included as an internal standard at the start of the reaction. Preferential loss of the standard was noted. The yield was >100%.

3000, and 1015 cm^{-1}; nmr (CCl_4) δ 3.09 (m, 1, CHOH), 2.67 (s, 1, OH), and 1.7–0.7 (m, 16; at 1.43, m, CH_2; at 1.04, d, $\rangle CCH_3$; at 0.92, t, CH_2CH_3; at 0.8–0.6, m, $\rangle CH$).

The alcohol was not characterized further and was used without further purification in the next step.

cis-2-**Methylcyclopropyl Butyl Ketone** (7).—To a rapidly stirred solution of *cis*-2-methylcyclopropylbutylcarbinol in 100 ml of freshly distilled acetone (from potassium permanganate) was added 6.4 ml (17 mmol) of Jones reagent[31] (prepared from 26.72 g of chromium trioxide and 23 ml of concentrated sulfuric acid diluted with 100 ml of water). After 5 min the excess chromic acid was decomposed with 5 ml of methanol.

The liquid layer was decanted and the salts were washed with three 50-ml portions of acetone. The extracts were combined and rotary evaporated. The concentrate was taken up in ether and the ethereal solution was washed with a saturated sodium chloride solution, dried, and rotary evaporated to yield 1.26 g (69%) of a colorless liquid, which gave one peak on vpc and was identified as *cis*-2-methylcyclopropyl butyl ketone (7) based on the following spectral and analytical data: ir (CCl_4) 3075, 3010, 1695, 1385, 1125, 1068, 1032, and 855 cm^{-1}; nmr (CCl_4) δ 2.44 (t, 2, J = 7 Hz, CH_2CO), a 1.95 (m, 1, $\rangle CHCO$), and 1.7–0.7 [m, 13; at 1.4, m, $(CH_2)_2$; at 1.06, a sharp spike, $\rangle CCH_3$; at 0.91, t, J = 6.5 Hz, CH_2CH_3]. Upon vpc coinjection (20% XF-1150 Cyanosilicone, 150°), the *cis* ketone preceded the *trans* ketone (relative retention time 0.96:1.0).

Anal. Calcd for $C_9H_{16}O$ (mol wt 140.23): C, 77.09; H, 11.50. Found: C, 76.92; H, 11.34.

General Reduction Procedure.—The entire reaction sequence, including drying of the ammonia, was conducted as described previously.[13] The work-up procedure was changed owing to the volatility of the products, and the modified procedure is as follows.

After the reaction had stirred for the stated time, the ammonia was allowed to evaporate. To the enolate salts were added a 100% excess of a saturated ammonium chloride solution followed by portions of diethyl ether.

The two layers were separated; the aqueous layer was saturated with sodium chloride and extracted with ether. The ethereal extracts were combined, washed with saturated sodium carbonate, and dried. The ethereal solutions were analyzed by vpc and, in all cases, alcohols as well as ketones were observed in the product mixture. The ethereal solution was routinely oxidized with the Brown oxidant solution[32] [prepared from 41 g (137 mmol) of sodium dichromate dihydrate, 200 ml of distilled water, and 30.8 ml of 96% sulfuric acid].

Except where indicated, the yield of volatile ketones was determined by mixing a weighed portion of the ethereal solution with a known weight of an internal standard (cyclopentanone, cyclohexanone, or cyclooctane) and relating the relative areas to the amounts of each ketone present.

Reduction of 2,2-Dimethylcyclopropyl Methyl Ketone (2).—Several reductions were carried out using ketone **2** as a substrate. The variations employed and the results obtained are listed in Table III.

Vpc analysis of the oxidized product mixture showed three peaks. On occasion a fourth peak was observed, which was shown to be 2-methyl-1-hexen-5-one (14) by comparison of retention times and ir spectra with those of an authentic sample. This product was assumed to be thermally produced[26] (cracking on vpc?) and not the result of the lithium in ammonia reduction. The products were collected by preparative vpc (20% XF-1150 Cyanosilicone, 10 ft × 0.375 in., 150°, 60 psi).

The minor product (8.5 min) was identified as neopentyl methyl ketone (9) on the basis of the following spectral characteristics: ir (CCl_4) 1718, 1360, 1350, 1220, and 1150 cm^{-1}; nmr (CCl_4) δ 2.27 (s, 2, CH_2CO), 2.05 (s, 3, CH_3CO), and 1.0 [s, 9, $(CH_3)_3C$]. The structure was later confirmed by independent synthesis.

The second product eluted (11 min) was identified as the starting ketone **2** by ir and retention time.

The major product (13.5 min) was identified as isoamyl methyl ketone (8) based on the following spectral characteristics: ir (CCl_4) 1715, 1365, and 1160 cm^{-1}; nmr (CCl_4) δ 2.35 (t, 2, J = 7 Hz, CH_2CH_2CO), 2.02 (s, 3, CH_3CO), 1.44 (m, 3), and 0.89 [d, 6, J = 5.5 Hz, $(CH_3)_2CH$]. The ir and mass spectra were identical with those of an authentic sample.

Reduction of 2,2-Dimethylcyclopropyl Butyl Ketone (3).—From 1.33 g (8.5 mmol) of 2,2-dimethylcyclopropyl butyl ketone (**3**), 1.18 g (170 mg-atoms) of lithium, and 200 ml of ammonia was obtained 1.3 g (96.4%) of a clear oil. The oil was oxidized with the Brown oxidant solution[33] to yield 1.21 g (91%) of product ketones which, when analyzed on vpc, gave the following product distribution: neopentyl butyl ketone (t_R 19.25 min, 17.3%); starting ketone (t_R 26 min, 4.9%); isoamyl butyl ketone (t_R 32.25 min, 76.6%); and 2-methyl-1-nonen-5-one (t_R 42.25 min, 1.2%).

The first eluted product (t_R 19.25 min) was identified as neopentyl butyl ketone based on spectral data: ir (CCl_4) 1715, 1465, 1365, and 1250 cm^{-1}; nmr (CCl_4) δ 2.21 [s over t, 4, $(CH_3)_3CCH_2CO$ and CH_2CH_2CO], 1.9–1.15 (m, 4), and 0.98 [s over t, 12, $(CH_3)_3C$ and CH_3CH_2].

The vpc retention time, ir, and nmr of the second product (26 min) were identical with those of starting ketone **3**.

The structure of isoamyl *n*-butyl ketone (t_R 32.25 min) was assigned on the basis of the following spectral data: ir (CCl_4) 1715, 1380, 1365, 1250, 1130 and 1040 cm^{-1}; nmr (CCl_4) δ 2.31 (t, 4, J = 6.5 Hz, CH_2COCH_2), 1.41 (m, 7), and 0.87 [d over t, 9, doublet J = 7 Hz, $(CH_3)_2CHCH_2$]; mol wt, 156 (mass spectrum).

The final product eluted (t_R 42.25 min) was assigned the structure of 2-methyl-1-nonen-5-one on the basis of the following data: ir (CCl_4) 3060 (C=CH), 1715 (C=O), 1645 (C=C), and 890 cm^{-1} (CH_2=C); mol wt 154 (mass spectrum of an enriched sample).

Reduction of *trans*-2-**Methylcyclopropyl Methyl Ketone** (4).—From 0.98 g (10 mmol) of *trans*-2-methylcyclopropyl methyl ketone (4), 1.39 g (200 mg-atoms) of lithium, and 200 ml of ammonia was obtained a calculated yield (by vpc) of 0.48 g (48%) with the following product distribution: methyl isobutyl ketone (11, t_R 10 min, 86.7%); methyl *n*-butyl ketone (10, t_R 13.25 min, 5.9%); and *trans*-2-methylcyclopropyl methyl ketone (4, t_R 15 min, 7.4%).

Methyl isobutyl ketone (11) was identified by comparison of ir, nmr, and vpc retention time with those of an authentic sample.

Methyl *n*-butyl ketone (10) was independently prepared from the oxidation of 2-hexanol, and spectral data were identical with those of the sample from the reduction.

The final product was identified as starting material 4 by spectral and retention-time comparisons with an authentic sample.

(31) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(32) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **83**, 2952 (1961).

A second reduction of 98 mg of *trans*-2-methylcyclopropyl methyl ketone (**4**) gave a calculated yield of 70.5 mg (70.5%) and was composed of 91.6% **11**, 2.5% **10**, and 5.9% starting material **4**.

Reduction of *trans*-2-Methylcyclopropyl Butyl Ketone (5).—From 1.4 g (10 mmol) of *trans*-2-methylcyclopropyl butyl ketone (**5**), 1.38 g (200 mg-atoms) of lithium, and 200 ml of ammonia was obtained 1.3 g (91.8%) of product ketones. Vpc analysis of the product mixture indicated the following distribution: an unidentified component (t_R 5.5–9.0 min, 10.2%); isobutyl *n*-butyl ketone (**13**, t_R 19.5 min, 75.3%); di-*n*-butyl ketone (**12**, t_R 26.0 min, 9.8%); and *trans*-2-methylcyclopropyl butyl ketone (**5**, t_R 28.0 min, 4.7%).

The first two peaks (t_R 5.5–9.0 min) appeared to be low molecular weight ketones and hydrocarbons on the basis of spectral properties: ir (CCl_4) 1712 (C=O), 1640 (C=C), and 890 cm^{-1} (CH=C); nmr (CCl_4) complex absorptions at δ 5.32–4.15 (C=CH), 2.41–0.83, and 0.25–0. No attempt was made to further purify the mixture.

The major product (t_R 19.5 min) was identified as isobutyl *n*-butyl ketone (**13**) based on the following spectral data: ir (CCl_4) 1715, 1380, 1365 [$(CH_3)_2CH$], 1170, and 1145 cm^{-1}; nmr (CCl_4) δ 2.28 and 2.17 (t over d, 4, J = 6.5 Hz, CH_2CH_2CO); J = 2 Hz, $CHCH_2CO$), 2.05–1.05 (m, 5), and 0.90 and 0.89 [t over d, 9, J = 6.5 Hz, CH_3CH_2; J = 6 Hz, $(CH_3)_2CH$].

The third product eluted (t_R 26 min) was enriched by vpc purification (85%) and was assigned the structure of di-*n*-butyl ketone (**12**) based on the spectral characteristics of the impure sample: nmr (CCl_4) δ 2.30 (t, 4, J = 6.5 Hz, CH_2COCH_2), 1.40 (m, 8), and 0.94 (t, 6, J = 6.5 Hz, CH_3CH_2). The vpc retention time corresponded to that of the major ring-opened product **12** obtained from *cis*-2-methylcyclopropyl *n*-butyl ketone (**7**).

The final product eluted corresponded with the starting cyclopropyl ketone (**5**).

Reduction of *cis*-2-Methylcyclopropyl Methyl Ketone (6).—Following the usual procedure, 0.98 g (9.3 mmol) of *cis*-2-methylcyclopropyl methyl ketone (**6**), 93% pure by vpc, in 5 ml of ether was allowed to react for 2 hr with 1.39 g (200 mg-atoms) of lithium in 200 ml of ammonia. The calculated volatile yield was 52%. The product mixture was composed of 6.1% methyl isobutyl ketone (**11**), 79.3% methyl *n*-butyl ketone (**10**), and 14.6% *cis*-2-methyleyclopropyl methyl ketone (**6**).

In a second run, 98 mg of ketone **6** provided 69 mg (69%, calculated by internal standard) of which the compoisition was 3.3% **11**, 73.1% **10**, and 21.2% **6**.

Product assignments for methyl isobutyl ketone (**11**) and methyl *n*-butyl ketone (**10**) were based on identical vpc retention times, ir spectra, and nmr spectra with those of an authentic sample and an independently prepared sample, respectively.

Reduction of *cis*-2-Methylcyclopropyl Butyl Ketone (7).—A solution of 800 mg (5.7 mmol) of *cis*-2-methylcyclopropyl butyl ketone (**7**) in 5 ml of ether was allowed to react for 2.5 hr with 790 mg (114 mg-atoms) of lithium in 125 ml of ammonia. The product mixture was concentrated after oxidation to yield 0.58 g (73%) of an oil which, when analyzed on vpc, was composed of 8.5% isobutyl *n*-butyl ketone (**13**) and 9.15% di-*n*-butyl ketone (**12**).

The first product eluted was assigned the structure isobutyl butyl ketone (**13**) on the basis of identical vpc retention times and nmr spectra with those of the major ketone from the reductive cleavage of *trans*-2-methylcyclopropyl butyl ketone (**5**).

The major product was assigned the structure di-*n*-butyl ketone (**12**) from the following spectral data: ir (CCl_4) 1718 and 1260 cm^{-1}; nmr (CCl_4) δ 2.30 (t, 4, J = 6.5 Hz, CH_2COCH_2), 1.40 (m, 8), and 0.94 (t, 6, J = 6 Hz, CH_3CH_2). The vpc retention time was identical with that of the minor ketone **12** obtained from the reductive cleavage of *trans*-2-methylcyclopropyl butyl ketone (**5**).

Metal Reduction of 2,2-Dimethylcyclopropyl Methyl Ketone (2). **A. With Calcium.**—The same procedure as described for run 7 (Table III) was employed to reduce 114 mg of ketone **2** with 0.08 g (21 mg-atoms) of pentane-washed calcium metal. The calculated yield was 97 mg (93%) and the product mixture was composed of 17% neopentyl methyl ketone (**9**), 34% starting ketone (**2**), and 49% isoamyl methyl ketone (**8**). The normalized percentage of **8**/**9** was 74:26.

B. With Potassium.—From 112 mg of ketone **2** and 0.08 g of potassium metal was obtained 95 mg (83%) of a product mixture composed of 21% ketone **9**, 12% ketone **2**, and 67% ketone **8**. The normalized percentage of **8**/**9** was 76:24.

C. With Sodium.—From 114 mg of ketone **2** and 0.46 g of hexane-washed sodium metal was obtained 99 mg (85%) of a product mixture containing 18% ketone **9**, 20% ketone **2**, and 62% ketone **8**. The normalized percentage of **8**/**9** was 78:22.

D. With Magnesium.—To an ammonia solution of 0.49 g of magnesium turnings was added 112 mg of ketone **2** as before. The typical blue color did not develop with the addition of magnesium to liquid ammonia, and throughout the reaction the metal did not appear to be dissolving. The sequence of reduction–oxidation was carried out as with the other metals. The calculated yield was 96 mg (84%), and the composition was 4% ketone **9**, 68% ketone **2**, and 28% ketone **8**. The normalized percentage of **8**/**9** was 87:13.

Registry No.—**3**, 22286-91-5; **5**, 22286-92-6; **7**, 22286-93-7; **8**, 110-12-3; **9**, 590-50-1; **12**, 502-56-7; **13**, 7492-38-8; 2-methyl-2-octen-4-one, 19860-71-0; *trans*-2-octan-4-one, 22286-99-3; 2-octyn-4-ol, 22286-98-2; *cis*-2-octen-4-ol, 22287-00-9; *trans*-2-octen-4-ol, 20125-81-9; *cis*-2-methylcyclopropylbutylcarbinol, 22287-01-0; neopentyl butyl ketone, 22319-52-4; isoamyl *n*-butyl ketone, 22287-02-1; 2-methyl-1-nonen-5-one, 22319-53-5.

A Nuclear Magnetic Resonance Evaluation of Cyclopropyl Participation in Rigid, Tricyclic Cyclopropyl Ketones

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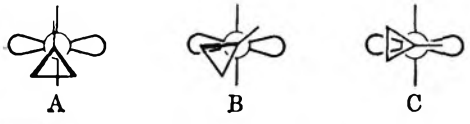
Received June 9, 1969

The geometric requirements for ground-state cyclopropyl ketone delocalization were probed by comparing the chemical-shift behavior of the H_β cyclopropyl protons in conformationally defined, rigid ketones and the corresponding hydrocarbons. The tricyclo[2.2.1.$0^{2,6}$]heptan-7-yl (**2**) and the tetracyclo[2.2.1.$0^{2,6}0^{3,5}$]heptan-7-yl (**3**) skeletons were used as models for the bisected conformation (A). Tricyclo[3.3.0.$0^{2,8}$]octan-3-yl (**8**) derivatives served as models for the unsymmetrical, "bicyclobutonium ion" conformation (B). Nonconjugative carbonyl group contributions to the cyclopropyl proton shifts were estimated using appropriate bicyclic models. These effects as well as ring strain effects were found to be minimal. The downfield shifts observed for the bisected systems follow: **2**, 1.1 ppm; **3**, 0.8 ppm. For the unsymmetrical model **8**, the shift was 0.1–0.5 ppm. These data provide direct support for the hypothesis of maximum delocalization in the bisected conformation. Delocalization in B did not involve preferential conjugation of the cyclopropane carbon–carbon bond "geometrically disposed for overlap."

The presence or absence of specific geometric requirements for conjugative interaction of a cyclopropane ring with an adjacent chromophore constitutes an area of active interest.[2] Three distinct conformations have been considered: the bisected species A, the unsymmetrical or bicyclobutonium ion geometry B, and the symmetrical arrangement C. Recent structural studies on freely rotating systems containing a cyclopropyl moiety adjacent to an electron-deficient center (carbonyl group[3] or carbonium ion[4,5]) have established that the bisected conformer A represents a conformational energy minimum.[6] These data, in turn, have been interpreted as evidence supporting the hypothesis of maximum overlap in conformation A.[4-7] With respect to conformer C, this conclusion seems justified. Studies in hindered systems[5] have shown that interaction between a cyclopropane ring and an adjacent cationic center is reduced considerably[5a] (or becomes negligible[5b]) when the system is constrained to geometry C.[6b] The analogous comparison between conformers A and B, however, is less firmly established. While the cumulative evidence suggests clearly that A provides the optimum geometry for interaction, an independent, direct determination of the ground-state delocalization *possible* in B would provide a more rigorous test of this hypothesis.

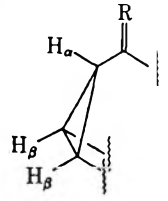


A B C

Since conformationally mobile systems are not suited for such an investigation, an examination of cyclopropyl ketone participation in geometrically defined, rigid systems was undertaken. In this way the conjugative participation possible in each conformation, A and B, could be evaluated individually using proton nmr. The results described provide support for the hypothesis of maximum delocalization in conformation A (compared with B), and they qualitatively define the nature of delocalization in conformation B.

Methods and Results

The ground-state participation in each tricyclic cyclopropyl ketone was probed by comparing the chemical shift behavior of the more remote H_β proton (see part structure **1** for notation) in the ketone (**1c**) with that in the reference hydrocarbon (**1h**). In order



1h, R = H_2
c, R = O

to interpret these data in terms of cyclopropyl ketone resonance, however, the contribution of several nonconjugative effects to the chemical-shift behavior of the H_β protons required evaluation. These include carbonyl group anisotropy and inductive effects, ring strain effects within a given system, and the effect of strain differences in the series of systems examined. The transoid relationship of the carbonyl group and the H_β protons (see **1c**) tentatively suggested that the carbonyl group effects should be relatively unimportant. Verification of this assumption was obtained in the following way. The steric and spacial relationships of the H_β protons and the carbonyl group were approximated by means of bicyclic systems. Since these systems do not contain a cyclopropyl group and consequently conjugation is not possible, a comparison of

(1) Partial financial support from the University of Texas Research Institute is gratefully acknowledged.

(2) Reviews: (a) R. Breslow in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y. 1963, Chapter 3; (b) J. P. Pete, *Bull. Soc. Chim. Fr.*, 357 (1967); (c) M. Hanack and H. J. Schneider, *Angew. Chem., Intern. Ed. Engl.*, **6**, 666 (1967).

(3) L. S. Bartell and J. P. Guillory, *J. Chem. Phys.*, **43**, 647, 654 (1965); L. S. Bartell, J. P. Guillory, and A. P. Parks, *J. Phys. Chem.*, **69**, 3043 (1965).

(4) N. C. Deno, H. G. Richey, Jr., J. S. Liu, D. N. Lincoln, and J. O. Turner, *J. Amer. Chem. Soc.*, **87**, 4533 (1965); C. U. Pittman, Jr., and G. A. Olah, *ibid.*, **87**, 5123 (1965); P. von R. Schleyer and G. W. VanDine, *ibid.*, **88**, 2321 (1966); H. G. Richey, Jr., and J. M. Richey, *ibid.*, **88**, 4971 (1966).

(5) (a) T. Sharpe and J. C. Martin, *ibid.*, **88**, 1815 (1966); (b) H. C. Brown and J. D. Cleveland, *ibid.*, **88**, 2051 (1966).

(6) For similar studies, also see (a) G. L. Closs and H. B. Klinger, *ibid.*, **87**, 3265 (1965); W. G. Dauben and G. H. Berezin, *ibid.*, **89**, 3449 (1967); C. H. Heathcock and S. R. Poulter, *ibid.*, **90**, 3766 (1968); M. J. Jorgenson and T. Leung, *ibid.*, **90**, 3769 (1968); G. R. De Mare and J. S. Martin, *ibid.*, **88**, 5033 (1966); G. A. Russell and J. Malkus, *ibid.*, **89**, 160 (1967); A. H. Cowley and T. A. Furtsch, *ibid.*, **91**, 39 (1969). (b) Conformation C is preferred, however, for cyclopropyl interaction with an adjacent electron-rich center; *cf.* N. L. Bauld, R. Gordon, and J. Zoeller, *ibid.*, **89**, 3948 (1967).

(7) R. Hoffmann, *Tetrahedron Lett.*, 3819 (1965); K. Shimizu, H. Kato and T. Yonezawa, *Nippon Kagaku Zasshi*, **88**, 1050 (1967); *Chem. Abstr.*, **68**, 77601 (1968).

the chemical-shift parameters for the appropriate H_β proton models in the ketone and the hydrocarbon provided an estimate of the nonconjugative carbonyl group effects. These bicyclic systems also provide a crude estimate of the strain effects due to the introduction of a sp^2-hybridized carbon atom in a given system. As discussed below in detail for each specific system, the introduction of a carbonyl group has a negligible influence on the relative H_β proton chemical shifts. The internal ring strain contributions to the H_β proton shifts were minimized by restricting chemical shift comparisons to a given system.

In addition to differences in the relative geometries of the cyclopropane ring and the carbonyl group, the series examined differ in ring strain. The possibility that these changes in strain make a significant, nonconjugative contribution to the comparative results obtained seems unlikely, however, since both unstrained, acyclic cyclopropyl ketones[3-5] and the more strained of the systems examined in the present work (*i.e.*, **2** and **3**; *vide infra*) show qualitatively the same interaction.

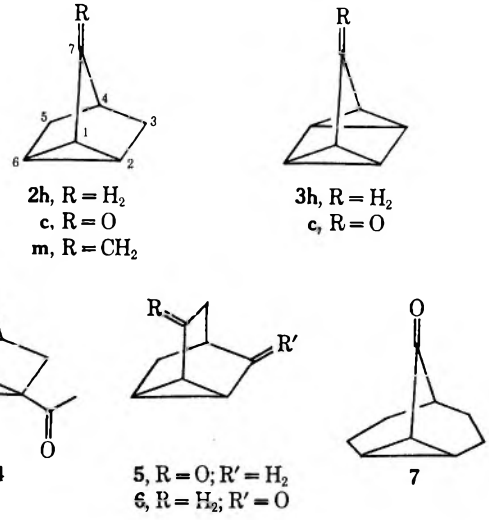
As models for cyclopropyl ketone delocalization in the rigid, bisected conformation A, tricyclo[2.2.1.$0^{2,6}$]-heptan-7-one (**2c**)[8,9] (nortricyclanone) and tetracyclo-[2.2.1.0.^{2,6}0^{3,5}]heptan-7-one (**3c**)[10] (quadricyclanone) were used. These nmr data, together with those for related systems and for the nonrigid 1-acetylnortricyclanone (**4**),[11] are given in Table I. A preliminary

TABLE I
100-MHz NMR DATA FOR SOME BISECTED CYCLOPROPYL KETONES[a]

	H_α	H_β	H_4	$-CH_2-$
2h	0.95	0.95	1.90	1.18
2c	1.10	2.07	1.80	1.65, 1.97
2m	1.4	1.4	2.10	1.4
3h[b]	1.4	1.4		2.0
3c[c]	1.02	2.21		
4		1.83	2.08	1.38 (4H), 1.47 (2H)

[a] Chemical shifts determined in this work are reported for 10–20% carbon tetrachloride solutions, in parts per million downfield from internal tetramethylsilane. Using **2c** as a model, the cyclopropyl proton chemical shifts were shown to be independent of concentration (see Experimental Section for details). [b] Values from W. G. Dauben and R. L. Cargill, *Tetrahedron*, **15**, 197 (1961), carbon tetrachloride solution, concentration not specified. [c] Values from P. R. Story and S. R. Fahrenholtz, ref 10, carbon tetrachloride solution, concentration not specified.

examination of two less strained models for A, namely tricyclo[3.2.1.$0^{2,7}$]octan-3-one (**5**)[12] and tricyclo-[3.3.1.$0^{2,8}$]nonan-9-one (**7**),[13] as well as the slightly skewed tricyclo[3.2.1.$0^{2,7}$]octan-8-one (**6**),[13] was made. Unfortunately, a coalescence of all protons in the nmr spectra of these ketones precluded precise assignments for the H_β protons.



Tricyclo[3.3.0.$0^{2,8}$]octan-3-one (**8c**)[14] was used as a model for cyclopropyl ketone participation fixed in the unsymmetrical geometry B. An inspection of stereomodels shows that the system is quite rigid and that the C_2–C_8 σ-cyclopropane carbon–carbon bond forms a dihedral angle of *ca.* 25° with the π bond of the carbonyl group. Thus this cyclopropane bond is preferentially oriented for overlap with the adjacent carbonyl group. The chemical-shift data for this ketone and the related hydrocarbon (**8h**) are given in Table II. In addition, tentative assignments for the published nmr spectrum[15] of the vinylcyclopropane **9** are included in Table II.

TABLE II
100-MHz NMR DATA FOR THE TRICYCLO[3.3.0.$0^{2,8}$]OCTAN-3-YL SKELETON[a]

		H_β		H_4			
	H_α	C_1	C_8	*exo*	*endo*	H_5	$-CH_2-$
8h	1.4[b]	1.8[c]	1.4[b]			2.55	1.4, 1.8
8c[d]	1.80	2.65	1.96	2.38	1.56	2.90	1.56, 2.05
9[e]	1.92	2.42	1.7[f]			3.04	1.7[f]

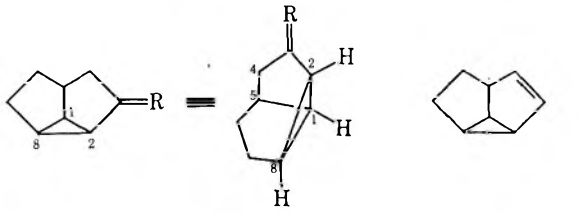
[a] See Table I. [b] Range of 1.17–1.65 ppm. [c] Range of 1.65–2.05 ppm. [d] Data from ref 14, 20% carbon tetrachloride solution. [e] See text and ref 15, degassed deuteriochloroform solution, concentration not specified. [f] Range of 1.45–1.90 ppm.

These assignments are based on the analysis presented by Chapman and coworkers[15] and on analogy with the presence of a low-field, one-proton quartet in both **8c** and **9**.

The nonconjugative effects of introducing a carbonyl group into a bisected framework, (*i.e.*, skeleton **2** or **3**) were estimated with the bicyclo[2.2.1]heptan-2-yl system (**10**). Stereomodels show that the C_4-bridgehead proton in ketone **10c** reasonably approximates the spacial arrangement of the H_β proton in ketones **2c** and **3c** with respect to the carbonyl group. The increase in strain accompanying the introduction of an sp^2 carbon, however, is only qualitatively the same for **2**, **3**, and **10**. Since conjugation is not possible in **10c**, a comparison of the chemical-shift behavior of the C_4 H in hydrocarbon **10h** with that in the ketone **10c** will give an estimate of the composite nonconjugative carbonyl group effects.

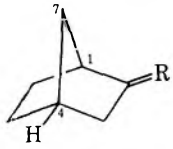
(8) J. Meinwald and J. K. Crandall, *J. Amer. Chem. Soc.*, **88**, 1292 (1966); *Org. Syn.*, **45**, 74 (1965).
(9) R. R. Sauers and P. E. Sonnet, *Chem. Ind.* (London), 786 (1963).
(10) P. R. Story and S. R. Fahrenholtz, *J. Amer. Chem. Soc.*, **86**, 1270 (1964).
(11) Kindly provided by Professor H. Hart: H. Hart and R. A. Martin, *J. Org. Chem.*, **24**, 1267 (1959).
(12) W. R. Moore, W. R. Moser, and J. E. LaPrade, *ibid.*, **28**, 2200 (1963).
(13) W. von E. Doering, E. T. Fossel and R. L. Kaye, *Tetrahedron*, **21**, 25 (1965).
(14) S. A. Monti, D. J. Bucheck, and J. C. Shepard, *J. Org. Chem.*, **34**, 3080 (1969).
(15) O. L. Chapman, G. W. Borden, R. W. King, and B. Winkler, *J. Amer. Chem. Soc.*, **86**, 2660 (1964).

In norbornane (**10h**) this proton appears at 2.2 ppm.[16] The chemical shift of this proton in camphor (**10c**, 1,7,7-trimethyl) is *ca.* 2.2 ppm.[17] Thus the nonconjugative effects in these ring systems appear negligible.

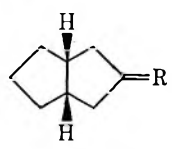


8h, R = H_2
c, R = O

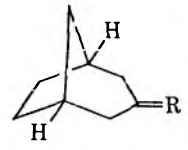
9



10h, R = H_2
c, R = O



11h, R = H_2
c, R = O



12h, R = H_2
c, R = O

In the unsymmetric ketone **8c**, the H_β protons are nonequivalent. As a model for the H_1 proton in **8c**, the tertiary protons in the *cis*-tricyclo[3.3.0]octan-3-yl skeleton (**11**) were used. Once again, stereomodels confirm the appropriateness of this model. In hydrocarbon **11h**, this proton resonates at 2.4 ppm[18] and in the ketone **11c** at 2.6 ppm.[14] Thus a *ca.* 0.2-ppm *downfield* shift results from nonconjugative carbonyl effects at H_1. In a similar way, the bridgehead protons in the bicyclo[3.2.1]octan-3-yl system (**12**) were used as a model for the H_8 proton in **8c**. Although two conformations are possible for **12c**, stereomodels show that this system constitutes a reasonable model. In ketone **12c**, the bridgehead proton appears at 2.5 ppm.[14] Literature data for the hydrocarbon **12h** are unavailable, but an estimate of 2.2–2.4 ppm for this tertiary proton seems reasonable on comparison with **10h** and **11h**. Thus, a *downfield* shift of *ca.* 0.1–0.3 ppm would also be expected for H_8 in **8c**. This is in the same direction and of approximately the same magnitude as that estimated for H_1. Consequently these nonconjugative carbonyl effects essentially cancel one another when a relative comparison of the H_1 and H_8 chemical shifts is made.

Discussion

In the bisected conformation A, charge delocalization in the cyclopropyl ketone system is postulated to involve equal participation of two cyclopropane σ bonds (bonds darkened in A). Since nonconjugative effects associated with the introduction of a carbonyl group into the bisected skeleton were shown to be minimal, any resonance effects would be reflected in a downfield shift for the H_β protons. An inspection of the data in Table I clearly verifies the presence of such charge delocalization in this conformation. In the nortricyclene skeleton **2**, a paramagnetic shift of 1.12 ppm for the magnetically identical H_β protons results on going from nortricyclene (**2h**) to nortricyclanone (**2c**). A further indication of the charge delocalization to the C_2 and C_6 carbon atoms of **2c** is provided by a comparison of the methylene proton chemical shifts in **2h** and **2c**. Both the *exo* and *endo* methylene protons of **2c** are shifted downfield by *ca.* 0.5–0.8 ppm. Since the *exo* protons are located in the *shielding* cone of the carbonyl group, they are assigned to the 1.65-ppm resonance and the *endo* protons to the 1.97-ppm signal. The paramagnetic shift of both sets of methylene protons strongly supports the presence of two electron-deficient cyclopropyl carbon atoms in **2c**.

A similar examination of the data for the cross-conjugated quadricyclene system (**3**) shows that the H_β protons of **3c** are shifted downfield by 0.8 ppm. Both the cross-conjugated nature of **3c** and the electrostatic consequences of the vicinal relationship of the two sets of H_β carbon atoms could account for the diminished participation qualitatively suggested by the relative magnitudes of the H_β proton shifts for **3c** (0.8 ppm) *vs.* **2c** (1.12 ppm). A more quantitative interpretation of this difference seems unwarranted, however, since the effect of subtle nonconjugative environmental differences between the two system cannot be evaluated accurately.

If one assumes that the nonconjugative anisotropy and strain effects of a methylene group are similar to those of a carbonyl group, the data in Table I for the exocyclic methylene derivative **2m** support vinylcyclopropane conjugation in the bisected conformation A. The magnitude of the H_β proton shift (*ca.* 0.45 ppm) suggests less charge delocalization than observed for the carbonyl group, as expected. Once again these data support only general trends and should not be interpreted quantitatively.

By way of comparison, the magnetically equivalent H_β protons of the nonrigid 1-acetylnortricyclene (**4**)[11] appear *ca.* 0.9 ppm lower field than in the reference hydrocarbon **2h**. Since this molecule can adopt both a cisoid and a transoid bisected conformation, the observed shift most probably reflects charge delocalization as well as carbonyl group anisotropy effects.

In the unsymmetrical geometry B, participation is postulated to involve preferential overlap of only *one* cyclopropane σ bond with the adjacent carbonyl group (bond darkened in B). As a consequence of this selective overlap, delocalization in a conformationally rigid system would result in nonequivalent chemical-shift behavior for the two H_β protons. In terms of the tricyclo[3.3.0.$0^{2,8}$]octan-3-yl skeleton **8**, this hypothesis requires that the C_8 H_β proton experience a greater downfield shift than the C_1 H_β proton upon introduction of a carbonyl group. As seen in Table II, the data for this system are at variance with this postulate. The C_1 H_β proton is shifted downfield *ca.* 0.7 ppm in ketone **8c** and the C_8 H_β proton *ca.* 0.4 ppm. If one corrects for the nonconjugative carbonyl group effects, *ca.* 0.2 ppm for the C_1 H position and *ca.* 0.1–0.3p pm for the C_8 H position, the C_1 H_β proton experiences a greater paramagnetic shift (*ca.* 0.5 ppm) than the C_8 H_β proton (*ca.* 0.1–0.3 ppm).

These results suggest that for rigid tricyclic systems, cyclopropyl ketone delocalization in the unsymmetrical geometry B does not involve preferential conjugation of the cyclopropane carbon–carbon bond "geometrically disposed for overlap" (bond darkened in B). Com-

(16) MIT Seminars in Organic Chemistry, Fall semester, 1961, Spectrum No. 52.
(17) Sadtler NMR Spectra Catalogue, Spectrum No. 30.
(18) W. B. Moniz and J. A. Dixon, *J. Amer. Chem. Soc.*, **83**, 1671 (1961).

parison of the downfield shifts observed in the bisected geometry A (2, 1.1, and 3, 0.8 ppm) and in the unsymmetrical geometry B (8, 0.1–0.5 ppm) provides direct support for the proposition that ground-state cyclopropyl ketone delocalization is maximized in the bisected conformation.

An examination of the relevant data for the unsymmetrical vinylcyclopropane 9 (see Table II) leads to conclusions analogous to those obtained for carbonyl group conjugation. There is no evidence to support selective overlap of the C_2–C_8 σ bond. Since an accurate estimate of the carbon–carbon double-bond anisotropy and other nonconjugative effects on the H_β proton resonances due to the presence of two sp^2-hydridized carbons in 9 is more tenuous, these tentative conclusions concerning the geometric parameters for vinylcyclopropane participation require further support.

Experimental Section

Nmr spectra were obtained on a Varian Associates Model HA-100 spectrometer; infrared spectra were measured on a Perkin-Elmer Model 237 or 257 grating infrared spectrometer.

Nortricyclene (2h) was prepared by the method of Schleyer.[19] The cyclopropyl hydrogen–carbon-13 coupling constant of $^1J_{^{13}CH} = 175$ Hz was measured.[20]

Nortricyclanone (2c) was prepared by the method of Meinwald.[8] The $^1J_{^{13}CH}$ for the H_α position was 184 Hz and for the H_β position 185 Hz.[20] The chemical shifts of the H_α, H_β, and *exo*-CH_2– (1.65 ppm) protons remained constant (±1 Hz) on going from a neat sample to a 2.5% CCl_4 solution. The C_4 H^9 and the *endo*-CH_2– (1.97 ppm) protons were shifted *ca.* 8 and 4 Hz, respectively, upon dilution.

3-Methylenetricyclo[2.2.1.0^{2,6}]heptane (2m) was prepared from nortricyclanone (2c) using the Corey[21] modification of the Wittig reaction. The crude product was purified by chromatography on silica gel using pentane. Distillation furnished pure 2m: bp 113–114°; average yield of three runs *ca.* 16%; ir (CCl_4) 1684 cm^{-1}; nmr (CCl_4), 4.48, 1 H (singlet), 4.60 ppm, 1 H (d, $J \sim 1$ Hz) (see Table I).

Tricyclo[3.3.0.0^{2,8}]octane (8h) was prepared from ketone 8c[14] using the Huang-Minlon adaptation of the Wolff–Kishner reduction.[22] The crude product was purified by preparative vpc to give hydrocarbon 8h:[23] mol wt (mass spectrum) 108; nmr (CCl_4), 1.17–1.65 (6 H, complex), 1.65–2.05 ppm (5 H, complex) (see Table II).

Registry No.—2c, 279-19-6; 2h, 695-05-6; 2m, 1974-87-4; 4, 22482-71-9; 8h, 2401-89-0.

(19) P. von R. Schleyer, *J. Amer. Chem. Soc.*, **80**, 1700 (1958).

(20) The generous assistance of Dr. M. Gordon in obtaining these data is gratefully acknowledged.

(21) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(22) *Cf.* N. A. LeBel and R. M. Liesemer, *J. Amer. Chem. Soc.*, **87**, 4301 (1965).

(23) Alternate preparations: J. Zirner and S. Winstein, *Proc. Chem. Soc.* (London), 235 (1964); M. Schwarz, A. Besold, and E. R. Nelson, *J. Org. Chem.*, **30**, 2425 (1965).

Condensation–Cyclization of Diketones and Keto Esters with Electron-Deficient Aromatics. I. Formation and Structure of Some Stable Delocalized Anions Containing the Bicyclo[3.3.1]nonane Skeleton

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Received May 10, 1969

A series of new bicyclic anions containing the bicyclo[3.3.1]nonane skeleton have been prepared from *sym*-trinitrobenzene, 3,5-dinitrobenzonitrile, and methyl 3,5-dinitrobenzoate. The electron-deficient aromatics are bridged across the *ortho* and *para* positions with various ketones and keto esters such as acetone, dicarbomethoxyacetone, ethyl acetoacetate, α-acetylbutyrolactone, and acetylacetone. The condensation–cyclizations are initiated with primary, secondary, and tertiary amines. Two distinct mechanistic routes are indicated. With acetone and secondary amines, an enamine intermediate is proposed as a precursor to the bicyclic anion. With more acidic ketones and keto esters (*i.e.*, acetylacetone and ethyl acetoacetate) a delocalized carbanion intermediate is involved.

The chemistry of σ complexes arising from the interaction of electron-deficient aromatics and bases has received considerable attention during the past five years and has recently been reviewed.[2,3] We have reported preliminary investigations of a new type of extremely stable bicyclic anion which results from internal cyclization in certain σ complexes.[4,5] The bicyclic structure 1 was observed to form upon addition of diethylamine to a solution of *sym*-trinitrobenzene in acetone,[4] whereas 2 was formed upon addition of triethylamine to a mull of *sym*-trinitrobenzene and dibenzyl ketone.[5] The total stereochemistry of 2 has not yet been determined, but isomers with the phenyl groups *cis* and *trans* have been isolated.[6] It was originally supposed that formation of such bicyclic anions occurred only with *sym*-trinitrobenzene and specific ketones. We have since discovered that the reaction is quite general and occurs with a variety of structurally different diketones and keto esters with various electron-deficient benzenes in the presence of primary, secondary, and tertiary amines. We report here results of investigations carried out with *sym*-trinitrobenzene, 3,5-dinitrobenzonitrile, and methyl 3,5-dinitrobenzoate. Acetone, ethyl acetoacetate, acetylacetone, α-acetylbutyrolactone, and 1,3-dicarbomethoxyacetone all were utilized as ketonic addends. Piperidine, *t*-butylamine, diethylamine, and triethylamine all were effective in promoting reaction, but the triethylammonium salts crystallized particularly well (see Experimental Section). The mechanistic routes leading to the bicyclic anions are discussed and two different reaction paths are proposed.

(1) To whom all inquiries should be addressed.

(2) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).

(3) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev.* (London), 123 (1968).

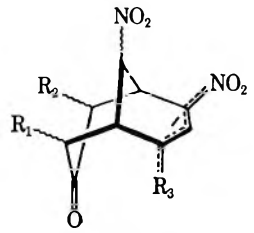
(4) M. J. Strauss and H. Schran, *J. Amer. Chem. Soc.*, **91**, 3974 (1969).

(5) R. Foster, M. I. Foreman, and M. J. Strauss, *Tetrahedron Lett.*, 4949 (1968).

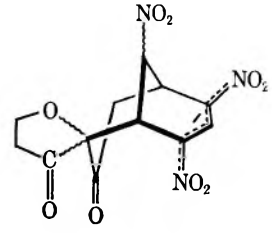
(6) M. I. Foreman, R. Foster, and M. J. Strauss, *J. Chem. Soc.*, in press.

TABLE I

TRINITRO, CYANODINITRO, AND CARBOMETHOXYDINITRO ANIONS



1–7 and 9–13



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Compd	Aromatic compd	Amine	Ketone or keto ester	Product
1	*sym*-Trinitrobenzene	$HN(CH_2CH_3)_2$	Acetone	$R_1 = R_2 = H$; $R_3 = NO_2$
2	*sym*-Trinitrobenzene	$N(CH_2CH_3)_3$	Dibenzyl ketone	$R_1 = R_2 = C_6H_5$; $R_3 = NO_2$
3	*sym*-Trinitrobenzene	$HN(CH_2CH_3)_2$	Acetylacetone	$R_1 = COCH_3$; $R_2 = H$; $R_3 = NO_2$
4	*sym*-Trinitrobenzene	$N(CH_2CH_3)_3$	Acetylacetone	$R_1 = COCH_3$; $R_2 = H$; $R_3 = NO_2$
5	*sym*-Trinitrobenzene	*t*-$BuNH_2$	Acetylacetone	$R_1 = COCH_3$; $R_2 = H$; $R_3 = NO_2$
6	*sym*-Trinitrobenzene	Piperidine	Acetylacetone	$R_1 = COCH_3$; $R_2 = H$; $R_3 = NO_2$
7	*sym*-Trinitrobenzene	$N(CH_2CH_3)_3$	Ethyl acetoacetate	$R_1 = CO_2CH_2CH_3$; $R_2 = H$; $R_3 = NO_2$
8	*sym*-Trinitrobenzene	$N(CH_2CH_3)_3$	α-Acetylbutyrolactone	
9	*sym*-Trinitrobenzene	$N(CH_2CH_3)_3$	1,3-Dicarbomethoxyacetone	$R_1 = R_2 = CO_2CH_3$; $R_3 = NO_2$
10	3,5-Dinitrobenzonitrile	$N(CH_2CH_3)_3$	Ethyl acetoacetate	R_1 or $R_2 = CO_2CH_2CH_3$; R_2 or $R_1 = H$; $R_3 = CN$
11	3,5-Dinitrobenzonitrile	$N(CH_2CH_3)_3$	1,3-Dicarbomethoxyacetone	$R_1 = R_2 = CO_2CH_3$; $R_3 = CN$
12	Methyl 3,5-dinitrobenzoate	$N(CH_2CH_3)_3$	1,3-Dicarbomethoxyacetone	$R_1 = R_2 = CO_2CH_3$; $R_3 = CO_2CH_3$
13	Methyl 3,5-dinitrobenzoate	$HN(CH_2CH_3)_2$	Acetone	$R_1 = R_2 = H$; $R_3 = CO_2CH_3$

The various complexes investigated are summarized in Table I.

Nmr Spectra.—The adducts **1–13** are moderately soluble in polar organic solvents such as acetone and methanol. They are also slightly soluble in water and in some cases chloroform. Nmr spectra were obtained from solutions prepared by dissolving recrystallized adduct in acetone-d_6, DMSO-d_6, chloroform-d_1, or a mixture of the latter two. In many cases the resulting products are a mixture of stereoisomers. Unsuccessful attempts at separation were made by fractional crystallization and column chromatography. The resulting nmr spectra of the crude adducts are consequently difficult to interpret in certain instances. The spectra were run on a Varian A-60 instrument with TMS as an internal reference. Some pertinent spectral data are summarized in Table II.

Visible Spectra.—The trinitro complexes **1–9** are brilliant red-orange crystals. Substitution of a cyano or carbomethoxy group on the delocalized anionic portion of the structure results in bright yellow crystals of **10–13**. These qualitative color characteristics result from changes in the delocalized propenide portion of the molecule and are illustrated in a more quantitative fashion by the visible absorption maxima in acetone and methanol solution. For the complexes **1–9**, λ_{max} is 505 ± 10 mμ and ϵ_{max} is 30,000–50,000, and for **10–13**, λ_{max} is 377 ± 5 mμ and ϵ_{max} is 18,000–22,000. The absorption maxima are summarized in the Experimental Section. The visible spectra were run on a Perkin-Elmer 202 UV-Visible spectrophotometer.

Discussion

The Acetone and Acetylacetone Adducts.—The nmr spectrum of the bicyclic anion **1** formed from *sym*-trinitrobenzene, acetone, and diethylamine has previously been described.[4] The dinitropropenide proton appears as a singlet at δ 8.52. The bridging $HCNO_2$ proton appears as a triplet centered at δ 5.72 and probably lies over the bridging carbonyl function. This stereochemistry has been assigned on the basis of chemical-shift comparisons with other aliphatic nitro compounds in acetone solution.[4] The two bridgehead protons appear as a poorly resolved doublet at δ 4.53. When methyl 3,5-dinitrobenzoate is used as the electron-difficient aromatic compound, the nmr spectrum of the adduct **13** is consistent with a structure in which the CO_2CH_3 group is part of the delocalized anionic function. Although a small quantity of DMSO-d_6 was added to aid dissolution of **13**, the major chemical-shift differences between this adduct and **1** are most likely due to structural changes and not solvent effects. The bridging $HCNO_2$ proton appears at essentially the same frequency as in **1**. The propenide proton in **13** appears 0.55 ppm upfield from that in **1**. This would be expected if the CO_2CH_3 function is attached to the delocalized propenide portion of the molecule. Since this group is much less electronegative than NO_2, electron density should then be higher on the carbon framework in **13** and result in greater shielding of the propenide proton. The bridgehead positions in **13** are not equivalent and appear as two broad absorptions at δ 4.45 and 3.98. This

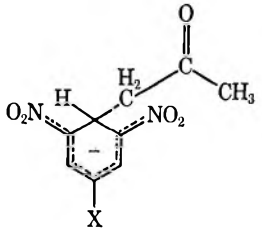
TABLE II

CHEMICAL SHIFTS (δ VALUES) AND SPLITTING[a] OF PROTONS IN THE BICYCLIC ANIONS 1–3, 8, 10, AND 13 (MEASURED AT 60 MHz)

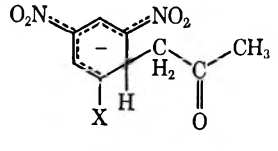
	Protons					
Adduct	Propenide	Bridgehead	Bridging $HCNO_2$	α to keto bridge	Other	Solvent
1[b]	8.52 (s, 1 H)	4.53 (m, 2 H)	5.72 (t, 1 H, J = 3 cps)	2.3–3.0 (m, 4 H)		Acetone-d_6
2[c]	8.59 (s, 1 H)	4.62 (m, 2 H)	5.97 (t, 1 H, J = 3 cps)	4.42 (m, 2 H)	7.13 (m, 10 H, aromatic H)	DMSO-d_6
3	8.40 (s, 1 H)	5.18 (m, 1 H) 4.20 (m, 1 H)	5.31 (m, 1 H)	Under acetyl group and cation absorptions	2.50 (s, 3 H, CH_3CO)	DMSO-d_6
8	8.50 (s, 1 H)	4.88 (t, 1 H, J = 3 cps) 4.4 (m, 1 H), under lactone OCH_2	6.18 (t, 1 H, J = 3 cps)	2.58 (m, 2 H), overlaps cation and CH_2C of lactone	4.4 (m, 2 H, OCH_2 of lactone) 2.58 (m, 2 H, CCH_2 of lactone)	$CDCl_3$–DMSO-d_6 (1:1)
10	7.43 (s, 1 H)	4.05 (br, 2 H), overlaps CH_2 of CO_2Et	5.11 (t, 1 H, J = 3 cps)	2.67 (m, 2 H), overlaps cation absorptions; $CHCO_2$ Et not observed (rapid exchange)[d]	4.27 (q, 2 H) 1.32 (t, 3 H) (both CO_2Et)	DMSO-d_6
13	7.97 (s, 1 H)	4.45 (br, 1 H) 3.98 (br, 1 H)	5.68 (t, 1 H, J = 3 cps)	Obscured by cation absorption	3.59 (s, 3 H, CO_2CH_3)	DMSO-d_6

[a] s = singlet; t = triplet, q = quartet; m = multiplet; br = broad. [b] Reference 4. [c] Reference 5. [d] Exchange with DMSO-d_6 solvent catalyzed by free amine should diminish the intensity of this absorption considerably.

difference cannot be explained on the basis of electronegativity effects, as other interactions might be quite important in this rigid structure. The CO_2CH_3 singlet in **13** appears at δ 3.59, 0.6 ppm upfield from that in the starting methyl 3,5-dinitrobenzoate, supporting the conclusion that the CO_2CH_3 function is part of the delocalized propenide system. The protons α to the carbonyl in **13** are obscured by partially protonated DMSO-d_5 solvent and the diethylammonium cation quartet. We have previously proposed[4] that **1** arises from an enamine σ complex as shown in Scheme I. A more direct path to **1**, through internal cyclization of a σ complex formed by attack of acetonate anion on *sym*-trinitrobenzene, is less likely, for reasons to be discussed shortly. A route involving an enamine σ-complex intermediate might also lead to **13**. Foreman and Foster have shown[7] that formation of σ complexes from 1-substituted 3,5-dinitrobenzenes, acetone, and triethylamine (which cannot form an enamine intermediate) occurs to give a mixture of both possible isomers, **14** and **15**, where X = CN or CF_3. If both



14



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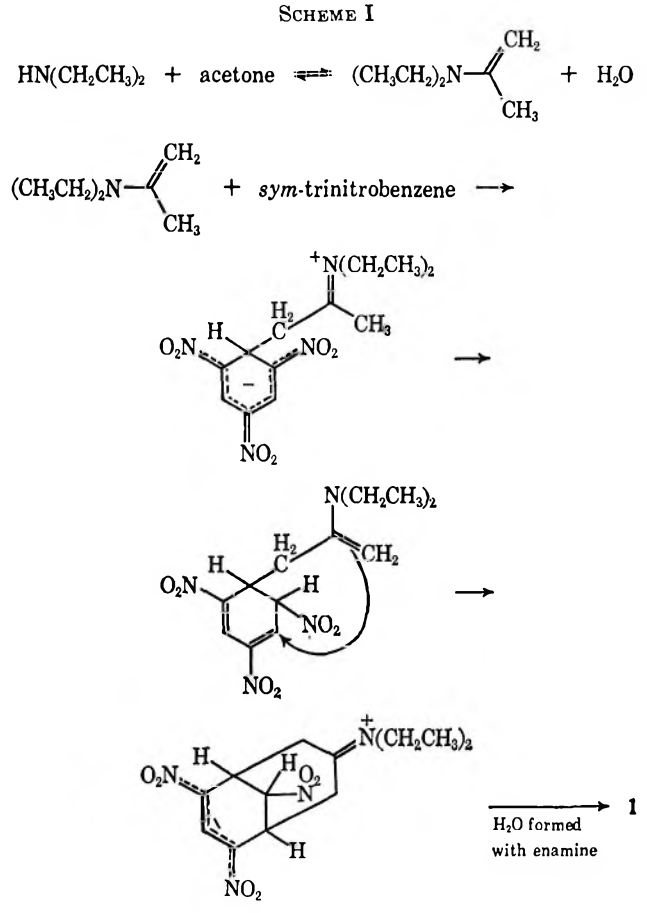
isomeric enamine σ complexes **16** and **17** are formed from methyl 3,5-dinitrobenzoate, acetone, and diethylamine either one could lead directly to **13** (Scheme II). Although both **16** and **17** are probably in rapid equilibrium, since only **13** and not **18** is obtained as the final product, either **17** proceeds solely to **13** or the conversion of **16** into **13** is kinetically or thermodynamically favored.

SCHEME I

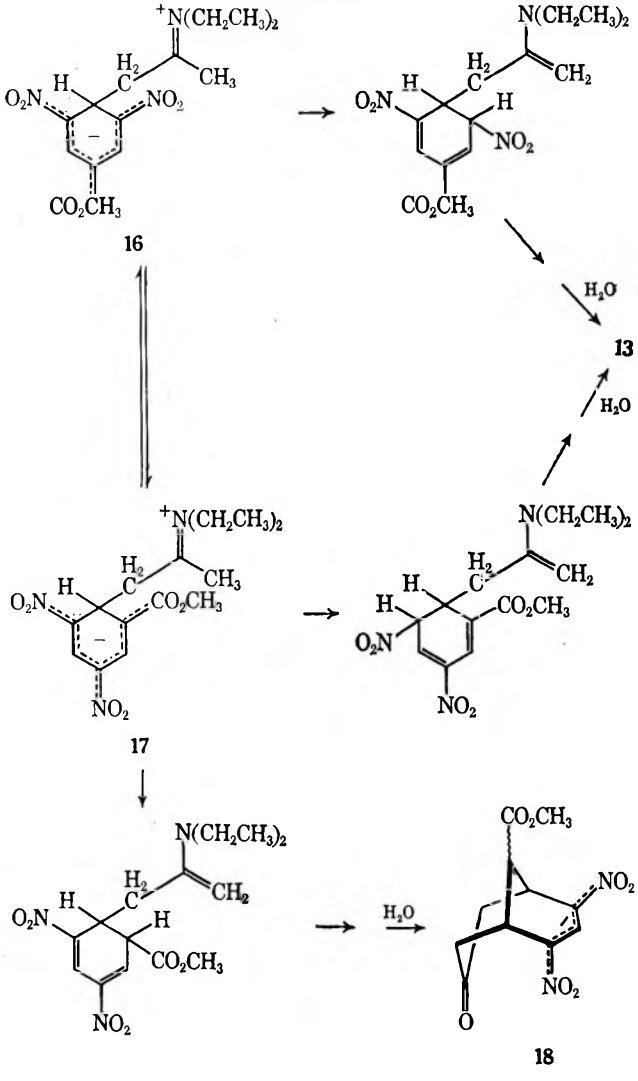


An alternative mechanistic pathway can be formulated which does not involve enamine intermediates (Scheme III). If triethylamine is used instead of diethylamine, the reaction with *sym*-trinitrobenzene and acetone stops at the σ-complex state and **19** can be isolated as the crystalline triethylammonium salt.[8]

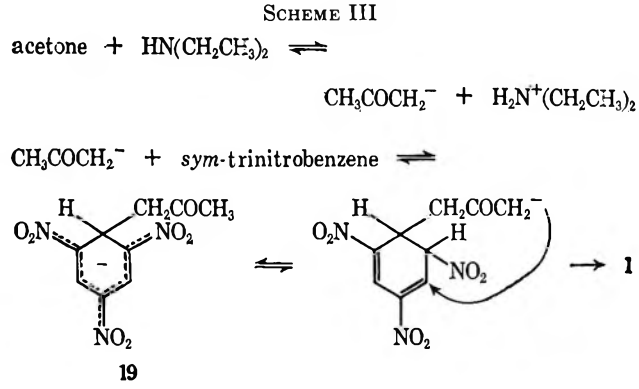
(7) M. I. Foreman and R. Foster, *Can. J. Chem.*, **47**, 729 (1969).

(8) R. Foster and C. A. Fyfe, *J. Chem. Soc., B*, 53 (1966).

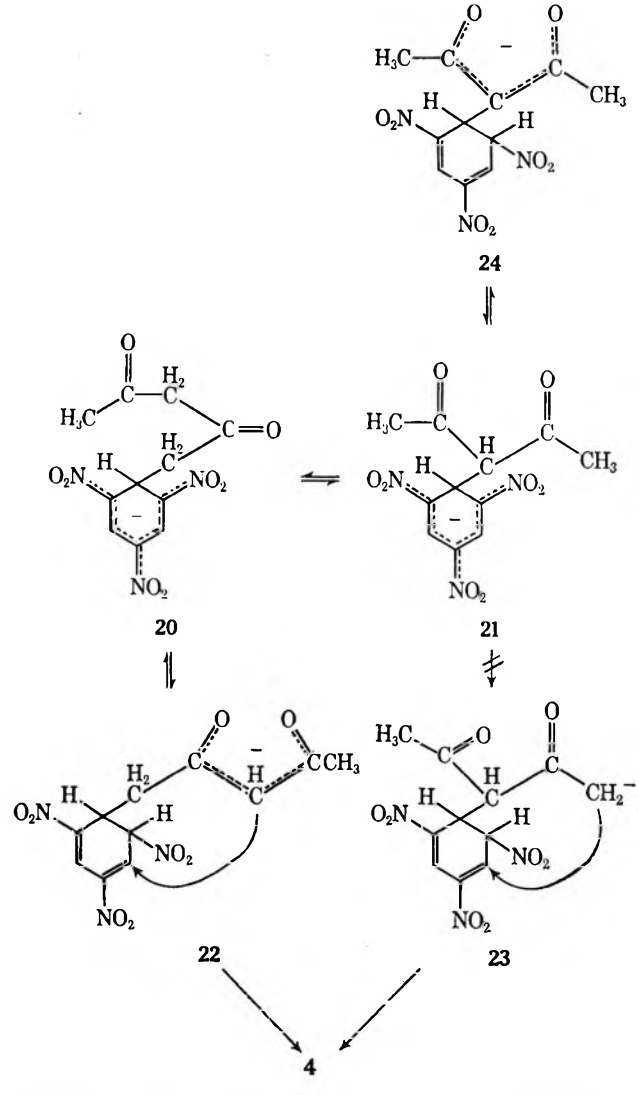
SCHEME II



SCHEME III



from the most acidic hydrogen available on the acetylacetonate moiety. In the case of **20** this would yield **22**, which is conformationally able to undergo intramolecular cyclization to **4**. With **21**, the result might be **24**, in which intramolecular cyclization cannot occur (except for unobserved intramolecular oxygen attack). Proton abstraction from the terminal methyl group in **21** is not favored even though the resultant **23** could



proceed directly to the bicyclic anion **4**. This is confirmed by the observation that with acetylacetone the reaction stops at the σ-complex stage. These observations are consistent with the fact that diethylamine and triethylamine are effective in producing bicyclic structures like **2**–**12** with acidic ketones and

We have observed similar behavior with methyl 3,5-dinitrobenzoate, acetone, and triethylamine. If these reagents are mixed and left standing for 4 days, a purple solution results with a visible spectrum characteristic of anionic σ complexes.[2] In this case the complex cannot be isolated, presumably because the equilibrium lies far on the side of the reactants. With more acidic ketones and keto esters (*i.e.*, acetylacetone, ethyl acetoacetate), bicyclic structures like **2**–**12** are formed with both triethylamine and diethylamine, presumably by a route analogous to Scheme III. The enamines formed from such acidic species should be much less reactive than the enamine of acetone and diethylamine. In addition, σ complexes resulting from reaction of acetylacetone, triethylamine, and *sym*-trinitrobenzene, while they are detectable in the visible spectrum of the reaction solution, cannot be isolated. The bicyclic product **4** precipitates soon after the reagents are mixed. This is in marked contrast to the behavior of acetone itself, where the only isolable product is the σ complex **19**.

There are two possible initial complexes, **20** and **21**, which may form from acetylacetone, *sym*-trinitrobenzene, and triethylamine. Probably **20** and **21** would be in equilibrium and further intramolecular cyclization would favor that route which involves proton abstraction (intramolecularly or by solvent)

keto esters, but only diethylamine is effective with acetone, yielding **1** and **13**, where an enamine intermediate is probably involved.

The adducts formed from diethylamine and triethylamine with acetylacetone, **3** and **4**, are much less soluble in acetone than **1**. To obtain sufficiently resolved nmr spectra of the acetylacetone adducts, solutions were prepared with DMSO-d_6. These adducts are a mixture of stereoisomers, due to asymmetric centers at the $HCNO_2$ bridge and adjacent to the keto bridge, and exhibit complex nmr spectra. Similar isomerism has previously been observed in **2** where the phenyl groups can be *cis* or *trans*, and in that case the isomers were separated.[6] All the adducts **3–7** and **9–12** probably exist as a keto–enol equilibrium mixture containing a greater amount of the enolic structure. This point is further supported by the infrared spectra (*vide infra*). Since exchange with DMSO-d_6 catalyzed by traces of free amine is also a complicating factor, it is not surprising that the enolic and ammonium cation absorptions are difficult to detect in the nmr spectra determined in this solvent. Similar exchange resulting in a diminished $^+$NH absorption and increasing protonated solvent absorption has previously been observed in related systems.[4] The quadrupole moment of nitrogen also contributes to broadening of the $^+$NH signal.

The Ethyl Acetoacetate Adducts.—Ethyl acetoacetate condenses with *sym*-trinitrobenzene and with 3,5-dinitrobenzonitrile in the presence of triethylamine to yield the anions **7** and **10**, respectively. A number of isomers are possible in each case, resulting in complex nmr spectra. The propenide proton in **7** appears as a broad singlet at δ 8.33 (1 H), almost the same value observed for the propenide proton(s) in **4**. Evidently, the chemical shift of this kind of proton is very similar in the various isomers of **7**, a conclusion supported by the slight variation in shift of the propenide protons in all the trinitro adducts (Table III). Using

TABLE III

CHEMICAL SHIFT OF PROPENIDE PROTON(S) (δ VALUES) IN THE BICYCLIC ANIONS 1–9

Anion	Shift
1	8.52
2	8.59
3	8.40
4	8.36
5	8.40
6	8.40
7	8.33
8	8.50
9	8.52

3,5-dinitrobenzonitrile as the aromatic substrate, the resulting adduct **10** shows a propenide absorption at δ 7.43 (1 H), 0.9 ppm upfield from that in the trinitro adduct **7**. This is definitive evidence for the conclusion that the less electronegative cyano group is part of the delocalized anionic portion of the molecule. Further corroborating evidence for this point results from the visible spectrum of **10** which, like **11**, has an absorption at *ca.* 380 mμ characteristic of the cyanonitropropenide function, and not at *ca.* 500 mμ, which characterizes **1–9**.

The infrared spectra of **7** and **10** are also of interest. The CN stretch in **10** appears at 2180 cm^{-1}, about 45 cm^{-1} lower in frequency than conjugated nitriles and 70 cm^{-1} lower than unconjugated nitriles. This in indicative of charge delocalization onto this function. The carbonyl region is broad at 1620–1670 cm^{-1} in both **7** and **10**. In considering the carbonyl region of the infrared for all the acetylacetone, ethyl acetoacetate, and α-acetylbutyrolactone adducts, it should be noted that in the former two cases there is no appreciable absorption above 1690 cm^{-1}, presumably because the β-diketo function in each exists to a considerable extent in the enol form (a very small absorption above 1700 cm^{-1} probably does result from the diketo structure). In the spiro cyclic adduct **8**, where the carbon atom joining the two carbonylic functions has no hydrogen (*i.e.*, the spiro carbon atom), both the lactone and bridging carbonyls are clearly observed at 1760 and 1755 cm^{-1}.

The 1,3-Dicarbomethoxyacetone Adducts.—1,3-Dicarbomethoxyacetone condenses with *sym*-trinitrobenzene, 3,5-dinitrobenzonitrile, and methyl 3,5-dinitrobenzoate in the presence of triethylamine to yield the corresponding bicyclic anions **9**, **11**, and **12**. The nmr spectra of these adducts are quite complex owing to the isomeric mixtures. 1,3-Dicarbomethoxyacetone appears to be the most reactive of all the keto esters used, as the characteristic orange and yellow colors of the adducts developed very soon after mixing the reagents. Some difficulty was encountered in recrystallizing these products. A 9:1 mixture of ether–methanol was found to be a reasonably effective solvent for recrystallization. The 1600–1800-cm^{-1} region of the infrared spectra of **9**, **11**, and **12** is quite interesting. In **9** and **11** this region is characterized by three peaks at 1610, 1645, and 1730 cm^{-1}. In **12** an added peak appears at 1685 cm^{-1}. This must be due to the CO_2CH_3 on the delocalized propenide function of **12**. In the starting ester, the CO_2CH_3 carbonyl absorbs at 1725 cm^{-1}. The shift to lower frequency in **12** is consistent with attachment to the delocalized anionic system.

The α-Acetylbutyrolactone Adduct.—A spiro bicyclic structure should form when the starting keto ester is part of a ring. Thus, reaction of *sym*-trinitrobenzene with α-acetylbutyrolactone yields orange crystals of what might be the spiro adduct **8**. A definite structural assignment must wait the difficult task of isomer separation.

Experimental Section

All the adducts **1–13** were prepared by dissolving a maximum amount of electron-deficient aromatic compound in about 2 ml of the ketonic substrate. The solution was gently warmed to about 30–35° to aid dissolution, and a two- to threefold excess of amine was then added (based on a limiting amount of aromatic). The intensely colored solution was kept at 30–40° and agitated occasionally. After 4–12 hr, *ca.* 100 ml of cold anhydrous ether was added. In most cases, an orange-yellow solid precipitated immediately from solution. This solid was filtered, washed with cold anhydrous ether, redissolved in 150–250 ml of boiling ether with just enough methanol added to effect dissolution, and kept at 0–10° for 3 days. The resulting crystals were filtered and dried under vacuum at 30–40°. In some instances, the initial product did not precipitate from solution on addition of ether but deposited as a highly colored oil on the bottom of the flask. In these cases, the oil was washed with copious amounts of anhydrous ether and redissolved in an ether–methanol solution, which after standing for 3 days at 0–10° deposited crystals of the adduct.

TABLE IV
CHARACTERIZATION OF THE BICYCLIC ANIONS

Adduct	Mp, °C	λ_{max}, mμ	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1[a]	171–172	510[b]	45.35	5.85	16.27	45.40	5.78	16.25
2[c]	190–191	500[b]	61.82	6.15	10.68	61.72	6.18	10.80
3	157–158	515[b]	46.63	5.74	14.50	46.89	6.00	14.80
4	152–153	506[d]	49.27	6.57	13.52	49.46	6.33	13.38
5	144–160[e]	507[b]	46.63	5.74	14.50	46.76	5.62	14.22
6	180–181	504[d]	48.24	5.57	14.06	48.44	5.86	13.86
7	147–148	504[d]	48.64	6.35	12.60	48.60	6.43	12.50
8	157–164	504[d]	48.86	5.92	12.66	48.58	6.00	12.90
9	119–122	500[b]	46.71	5.78	11.47	46.84	5.83	11.36
10	146–151[e]	374[d]	53.76	6.65	13.20	53.91	6.80	13.24
11	126–127	382[d]	51.27	6.03	11.96	50.93	5.92	12.09
12	118–119	375[d]	50.30	6.23	8.38	50.55	6.35	8.33
13	140–150[e]	372[d]	50.39	6.49	11.76	50.40	6.59	11.54

[a] Reference 3. [b] In acetone. [c] Reference 4. [d] In methanol. [e] Melts with decomposition.

A typical example is outlined below. The elemental analyses, melting points, and visible maxima of **1**–**13** are summarized in Table IV.

1,3-Dicarbomethoxyacetone-1,3,5-trinitrobenzene (9).—A mixture of 1.3 ml of 1,3-dicarbomethoxyacetone and 2.13 g (0.01 mol) of trinitrobenzene 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°.

Registry No.—**1**, 12379-55-4; **2**,**12** 379-64-5; **3**–**6**, mixture, 12379-56-5; **7**, 12379-59-8; **8**, 12379-58-7; **9**, 12379-61-2; **10**, 12379-60-1; **11**, 12379-62-3; **12**, 12379-63-4; **13**, 12379-57-6.

Acknowledgment.—The authors acknowledge partial support by the Army Research Office at Durham (Grant DAHCO4 69 C), the National Aeronautics and Space Administration (Grant NGR 46-001-008 S2 68-19), the National Science Foundation (Institutional Grant 69-87), the Research Corporation, and the University of Vermont. T. C. Jensen is further indebted to the Department of Health, Education and Welfare for an National Defense Education Act Fellowship.

Conformational Equilibria for 2- and 3-Bicyclo[3.3.1]nonanols[1]

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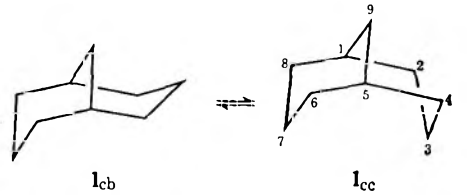
Received April 22, 1969

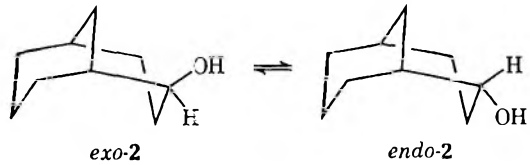
Equilibration of either the *exo*- or *endo*-3-bicyclo[3.3.1]nonanols with aluminum isoproxide in isopropyl alcohol at 94° gave 96.9% *exo* isomer. The ΔG^0 of −2.5 kcal/mol obtained is a reasonable approximation of the energy difference between the chair–boat and double-chair conformers of bicyclo[3.3.1]nonane. Equilibration of either of the two isomers of 2-bicyclo[3.3.1]nonanol under the same conditions gave 68.7% *endo* isomer (equatorial hydroxyl). In this protic solvent, $\Delta G^0_{OH} = -0.56$ kcal/mol. Equilibration over Raney nickel in cyclohexane gives a ΔG^0_{OH} of −0.25 kcal/mol for an aprotic solvent.

Bicyclo[3.3.1]nonane provides an interesting vehicle for the study of conformational effects. Thus it has been established,[2] contrary to most expectations,[3] that the molecule adopts preferentially the double-chair rather than the chair–boat conformation. No estimate of the energy difference between these two conformations was available when the study reported here was made.[4] X-Ray studies[2] showed that the ring distorts readily parallel to the plane of symmetry through C_3, C_7, and C_9, but is resistant to distortions which destroy this as a symmetry element. Little has been done to ascertain the influence of these ring distortions on the conformational preferences of ring substituents.



1_{cb} 1_{cc}

Equilibration of 2-Bicyclo[3.3.1]nonanols.—The two epimeric 2-bicyclo[3.3.1]nonanols, *exo*-**2** and *endo*-**2**,



exo-**2** *endo*-**2**

(1) The authors are pleased to make acknowledgment to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. A preliminary account of this work was given at the Northwest Regional Meeting of the American Chemical Society, Richland, Wash., June 1967.

(2) M. Dobler and J. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); W. A. C. Brown, J. Martin, and G. A. Sim *J. Chem. Soc.* 1844 (1965).

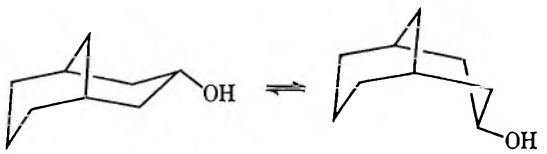
(3) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 295–296.

(4) See, however, R. A. Appleton, C. Egan, J. M. Evans, S. H. Graham, and J. Dixon, *J. Chem. Soc., C*, 1110 (1968).

were prepared according to known procedures.[5-7] Pure samples were collected by preparative gas chromatography, and these had physical and spectral properties in excellent agreement with published values. The equilibrium mixtures were analyzed directly by glpc. Equilibration over aluminum isopropoxide in isopropyl alcohol at 94° was carried out from both pure epimers. The equilibrium mixture contained 31.0% *exo*-**2** and 69.0% *endo*-**2**. Equilibration over Raney nickel catalyst in isopropyl alcohol[8] gave an equilibrium mixture containing 31.3% *exo*-**2** and 68.7% *endo*-**2**. Thus in isopropyl alcohol $\Delta G^0_{OH} = -0.56$ kcal/mol. Our value is in excellent agreement with the value of −0.559 kcal/mol obtained by Baggeley, *et al.*,[9] and published after our work was nearly completed.

The equilibration of *exo*-**2** and *endo*-**2** was also carried out in cyclohexane using Raney nickel as catalyst.[8] The equilibrium mixture contained 40.5% *exo*-**2** and 59.5% *endo*-**2** with $K = 1.47$ and $\Delta G^0_{OH} = -0.25$ kcal/mol.

Equilibration of 3-Bicyclo[3.3.1]nonanols.—Both the *exo*- and *endo*-3-bicyclo[3.3.1]nonanols (**3**) were prepared by established procedures[5] and purified by preparative gas chromatography. Our sample of *exo*-**3** showed a high-frequency methylene stretch at 2968 ± 2 cm^{-1}, whereas Hartmann and Gräfe[10] report 2980 cm^{-1}. However, our sample has an nmr spectrum which duplicates that reproduced in Schaefer's paper.[5] Direct glpc analysis of the isomers of **3** was not possible; so mixtures were converted into the acetates, which were analyzed *via* glpc. Check runs on known mixtures showed that the method was reliable and accurate to at least 1 part in 100.



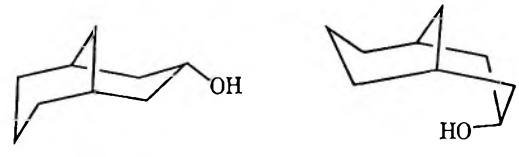
endo-**3** *exo*-**3**

Each of the epimers was equilibrated over aluminum isopropoxide according to the procedure of Eliel and Ro.[11] When equilibration was made in boiling isopropyl alcohol, the mixture obtained from *endo*-**3** consisted of 4.3% *endo*-**3** and 95.7% *exo*-**3**, while the mixture from *exo*-**3** contained 3.6% *endo*-**3**. Difficulty was experienced with sublimation of the alcohols from the reaction mixture; so all later runs were made in sealed tubes. Duplicate runs at 94.1° starting with either epimer gave 3.1% *endo*-**3** and 96.9% *exo*-**3**. Thus the equilibrium constant for the *endo*–*exo* conversion is 31.3 and $\Delta G^0_{94} = -2.51$ kcal/mol. An attempt to repeat the studies using Raney nickel gave only 2-bicyclo[3.3.1]nonanone.

(5) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).
(6) R. A. Appleton, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 805 (1967).
(7) E. N. Marvell, G. J. Gleicher, D. Sturmer, and K. Salisbury, *J. Org. Chem.*, **33**, 3393 (1968).
(8) E. L. Eliel and S. M. Schroeter, *J. Amer. Chem. Soc.*, **87**, 5031 (1965).
(9) K. H. Baggeley, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 299 (1967).
(10) M. Hartmann and U. Gräfe, *Angew. Chem.*, 305 (1967).
(11) E. L. Eliel and R. S. Ro, *J. Amer. Chem. Soc.*, **79**, 5992 (1957).

Discussion

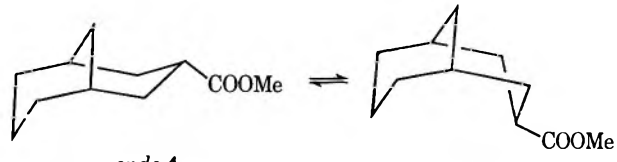
The ΔG^0 for the *endo*-**3** to *exo*-**3** equilibrium represents a reasonable value for the $\mathbf{1}_{cb}$–$\mathbf{1}_{cc}$ equilibrium. The ΔG^0 values for the substituted isomers and the unsubstituted conformers will correspond accurately only when (a) the *exo* isomer exists predominantly in the double chair and the *endo* in the chair–boat conformations; and (b) the substituents alter the energies of the conformations in parallel fashion. Both conditions appear to be satisfied here. The double-chair conformation for *exo*-**3** is supported by the spectral data.[12] While a double-chair conformation has been suggested[13] for *endo*-**3**, the case for the chair–boat conformation has been argued effectively[4,12] and will not be repeated here. There are two possible chair–boat conformers for *endo*-**3**, *endo*-$\mathbf{3}_{bc}$ and *endo*-$\mathbf{3}_{cb}$. The



endo-$\mathbf{3}_{cb}$ *endo*-$\mathbf{3}_{bc}$

former is excluded because it possesses two 1,3-diaxial methylene–hydroxyl interactions not present in the latter.[14] Thus the first condition is satisfied. Since the hydroxyl group is effectively in an equatorial position in each isomer, the second condition is also satisfied.

Our conclusion that the ΔG^0 for the $\mathbf{1}_{cb}$–$\mathbf{1}_{cc}$ equilibrium is 2.5 kcal/mol (at 94°) is supported by the report[4] that $\Delta G^0_{25°}$ for the *endo*-**4**–*exo*-**4** equilibrium is 2.7 kcal/mol. That the ΔG^0 value is thus independent of the nature of the substituent indicates clearly that the energy difference is that for the skeletal change only. If $\mathbf{1}_{cb}$ and $\mathbf{1}_{cc}$ are assumed to be of equal entropy except for that due to the higher symmetry of $\mathbf{1}_{cc}$, the $\Delta H = 2.9$–3.2 kcal/mol can be compared with a calculated potential-energy difference for the two conformers. Using a modified Wiberg program.[16,17] we have calculated[7] that this value is 3.7 kcal/mol. The agreement is reasonably satisfactory.



endo-**4** *exo*-**4**

The total strain energy for $\mathbf{1}_{cc}$ compared with chair cyclohexane as a strain-free model can now be estimated. The lateral rigidity of the bicyclo[3.3.1]-nonane ring[2] ensures that $\mathbf{1}_{cb}$ will possess a C_{2v} boat form. Thus the strain energy of $\mathbf{1}_{cb}$ is the sum of a chair cyclohexane (0.0 kcal/mol) and a C_{2v} boat cyclohexane (6.9 kcal/mol).[18] Since $\mathbf{1}_{cc}$ has *ca.* 2.9 kcal/

(12) W. O. K. Macrosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, 2589 (1965).
(13) C.-Y. Chen and R. J. W. Le Fevre, *ibid.* 737 (1965).
(14) For a cyclohexane ring a methyl–hydroxyl diaxial interaction is unfavorably by 2.4 kcal/mol,[15] and two somewhat smaller but similar interactions seems quite sufficient to eliminate *endo*-$\mathbf{3}_{bc}$.
(15) E. L. Eliel and H. Haubenstock *J. Org. Chem.*, **26**, 3504 (1961).
(16) K. B. Wiberg, *J. Amer. Chem. Soc.*, **87**, 1070 (1965).
(17) G. J. Gleicher and P. von R Schleyer, *ibid.*, **89**, 582 (1967).
(18) J. B. Kendrickson, *ibid.*, **83**, 4537 (1961).

mol less strain than $\mathbf{1}_{cb}$, the total strain energy for $\mathbf{1}_{cc}$ must be close to 4.0 kcal/mol. Clearly the calculated[17] value of 11.7 kcal/mol is much too large.

Our results for the *endo*-2–*exo*-2 equilibrium provide two ΔG^0_{OH} values, 0.25 kcal/mol in an aprotic solvent and 0.56 kcal/mol for protic solvents. Two values for ΔG^0_{OH} have been found for cyclohexane,[3] 0.6–0.7 for aprotic media and 0.90 for protic media. In view of the general uncertainties associated with conformational ΔG^0 values in general and for the hydroxyl group particularly,[8] the values for the bicyclic molecule can be said to be about half of those found for cyclohexane. This relation can be readily accounted for, and it suggests that the distortions of a normal cyclohexane ring present in $\mathbf{1}_{cc}$ do not materially influence the ΔG^0 (see below).

The equatorial (*endo*) position at C_2 in $\mathbf{1}_{cc}$ differs from a normal equatorial position in a cyclohexane ring by having a diaxial interaction with the *endo* hydrogen at C_8.[7] Assuming that 1,3-diaxial interactions are additive, the *exo* position at C_2 has two of these while the *endo* has one. For cyclohexane the axial position has two and the equatorial none. Hence the ΔG^0 for C_2 on the bicyclic system should be half that for a cyclohexane ΔG^0. The experimental results are in accord with this simple analysis. It must be noted, however, that the C_1–C_2–C_3 angle in the bicyclic ring is *ca.* 114°, which tilts the *exo* bond outward from the threefold axis of a cyclohexane ring by about 9°. This distortion, which is about one-third of that required to produce a planar cyclohexane ring, would be expected to reduce the interactions in the *exo* position, and hence to reduce the ΔG^0 at C_2 to considerably less than half the normal value. The results indicate that this distortion has little if any influence on the relative ΔG^0 values. We attribute this to the distortions made in the more flexible cyclohexane ring to minimize axial interactions, which reduce the normal ΔG^0 for cyclohexane in a manner not accessible to the more rigid bicyclic system.

The computed geometry[7] and the van der Waals parametrization of Hill[19] were used to calculate the nonbonded interaction energy difference for *exo*-2 and *endo*-2. The calculated ΔG^0 of 0.1 kcal/mol treats the hydroxyl as a spherical oxygen only and ignores the hydrogen. This value, which would be expected to equate more nearly to the ΔG^0 in an aprotic solvent, is in reasonable agreement with the experimental value of 0.25 kcal/mol.

Experimental Section

***exo*-2-Bicyclo[3.3.1]nonanol (*exo*-2).**—2-Bicyclo[3.3.1]nonen-9-one[20] (20.0 g, 0.15 mol) was dissolved in 200 ml of diethylene glycol containing 15 ml (0.31 mol) of 99% hydrazine hydrate and 14 g of potassium hydroxide. The mixture was heated slowly to 200° under nitrogen and heating was continued until no further water collected in the Dean–Stark trap (6–8 hr). The mixture was cooled, diluted with ice–water, and extracted with pentane. Material which had sublimed into the condenser was washed out with pentane, the combined pentane solutions were dried ($MgSO_4$), and the solvent was removed by evaporation to give 14.2 g (79%) of white solid. A sample purified by sublimation melted at 93–96° (lit.[5] mp 96–97°).

The above olefin was converted into *exo*-2,3-epoxybicyclo[3.3.1]nonane by the method of Payne.[21] A solution containing 1 equiv of bicyclo[3.3.1]nonene, 1 equiv of benzonitrile, a 50% molar excess of 30% hydrogen peroxide, and *ca.* 2 molar equiv of potassium bicarbonate in methanol was stirred at room temperature for 48 hr. Water was added and the organic products were taken up in pentane and dried ($MgSO_4$). The solvent was removed *in vacuo*, and glpc analysis (15 ft × 1/4 in. 5% FFAP on Chromosorb G at 118°) showed the product to consist of a mixture of epoxide and unreacted benzonitrile and olefin. This was separated *via* preparative thin layer chromatography (Merck PF_{254} silica gel, benzene; olefin R_f 0.7, benzonitrile R_f 0.4, epoxide R_f 0.25) and the epoxide was purified by sublimation *in vacuo*, mp 182–183°, yield 25–30%.

Anal. Calculated for $C_9H_{14}O$: C, 78.22; H, 10.21. Found: C, 78.04; H, 9.98.

A mixture of 13 g (0.094 mol) of crude *exo*-2,3-epoxybicyclo[3.3.1]nonane and 27 g (0.074 mol) of lithium aluminum hydride in 800 ml of tetrahydrofuran was heated at 50° for 24 hr. Excess hydride was destroyed by careful addition of water, and the organic layer was decanted. Precipitated solids were washed with ether and the extracts were combined with the decanted solution. The solvent was removed *in vacuo* and the crude alcohol was purified by sublimation: mp 175–178° (lit.[5] mp 176–177°); ir (CCl_4) 3600, 3400, 2980 (sh), 1480, and 1030 cm^{-1}; nmr (CCl_4) δ 3.80 (m, 1 H), 3.20 (s, 1 H), and 0.9–2.4 (m, 14 H). Analysis *via* glpc (12 ft × 0.125 in. 5% FFAP on Chromosorb G at 118°) showed 9.9% *endo* epimer present as an impurity. Samples for use in the equilibration were purified by preparative gas chromatography.

A *p*-nitrobenzoate was prepared by heating 50 mg of the alcohol with a 10% excess of *p*-nitrobenzoyl chloride in 1 ml of pyridine at 80° for 3 hr. Water (5 ml) was added and the mixture was extracted with ether. The ether extracts were washed with sodium bicarbonate solution and dried over sodium sulfate, and the solvent was removed by distillation. The product was recrystallized from hexane, mp 110–112° (lit.[5] mp 111–112°).

***endo*-2-Bicyclo[3.3.1]nonanol (*endo*-2).**—A solution of 2-bicyclo[3.3.1]nonanone[22] (4.5 g, 33 mmol) in 16 ml of methanol was added dropwise to a solution of 2.45 g (64 mmol) of sodium borohydride in 32 ml of methanol. The reaction mixture was kept at 15° until addition had been completed and was then stirred overnight at room temperature. Excess hydride was destroyed, 700 ml of water was added, and the solution was extracted with pentane. The pentane extracts were dried (K_2CO_3) and the solvent was removed. The product was purified by sublimation, mp 178–182° (lit.[5] mp 177–178°), yield 3.6 g (80%). Analysis by glpc (12 ft × 0.125 in. 5% FFAP on Chromosorb G at 120°) indicated the presence of 2% *exo*-2 as an impurity. Samples for equilibration were purified by preparative gas chromatography.

A *p*-nitrobenzoate was prepared as described under *exo*-2, mp 103–105° (lit.[5] mp 101–102°).

***exo*-3-Bicyclo[3.3.1]nonanol (*exo*-3).**—This alcohol was prepared on a 0.25-mol scale from 2-bicyclo[3.3.1]nonene according to the procedure of Schaefer, *et al.*[5] The crude product was purified by sublimation to give a white solid, mp 118–125°, in 50% yield. Analysis on a 100-ft capillary column (MBMA at 128°) showed 83% *exo*-3. This was further purified by preparative glpc (15 ft × 0.375 in. Carbowax 20M on firebrick) to give a solid, mp 100–102° (lit.[5] mp 100–101°), which analyzed as better than 99% *exo*-3. The nmr spectrum was identical with that reproduced in the literature.[5]

A *p*-nitrobenzoate was prepared as described for *exo*-2, mp 148–151° (lit.[10] mp 150–151°).

***endo*-3-Bicyclo[3.3.1]nonanol (*endo*-3).**—To a solution of 3.5 g (25 mmol) of *exo*-3 in 30 ml of anhydrous pyridine was added over a 2-hr period a mixture of 7.5 g (75 mmol) of chromium trioxide in 75 ml of anhydrous pyridine. The reaction mixture was stirred at 45° for 48 hr. A solution containing 9 g of sodium bisulfite in 25 ml of water was then added to the reaction mixture, and the solution was acidified with concentrated hydrochloric acid. The product was extracted with pentane, and the extracts were washed with water and dried ($MgSO_4$). Removal of the solvent by distillation gave 2.7 g (78%) of crude ketone. Sublimation gave 2.5 g of product, mp 172–177° (lit.[5] mp 170–176°).

The above product was reduced with sodium borohydride according to the procedure of Schaefer, *et al.*[5] Compound *endo*-3

(19) T. L. Hill, *J. Chem. Phys.* **16**, 399 (1948).

(20) S. Brewis and P. R. Hughes, *Chem. Commun.*, 6 (1966). We are deeply indebted to Dr. S. Brewis for a generous gift of this compound.

(21) G. B. Payne, *Tetrahedron*, **18**, 763 (1962).

(22) E. N. Marvell, D. Sturmer, and C. Rowell, *ibid.*, **22**, 861 (1966).

was obtained in 71% yield after purification by sublimation, mp 120–123° (lit.[5] mp 121.5–124°). The nmr spectrum is in good agreement with that published.[5]

A *p*-nitrobenzoate was prepared according to the procedure given under *endo*-**2**, mp 101–103° (lit.[10] mp 106–107°).

3-Bicyclo[3.3.1]nonyl Acetates.—For the glpc analysis the *exo*- and *endo*-**3** mixtures were converted into the acetates. The alcohol mixture (*ca.* 100 mg) was mixed with 20 mg of anhydrous sodium acetate and 200 mg of acetic anhydride and the reaction mixture was heated for 2 hr at 100°. Ice (5 g) was added to the mixture and the product was taken up in pentane. The solution was dried ($MgSO_4$) and concentrated. Analysis was made *via* glpc as described below. Four independent runs on a sample containing 5.9% *endo*-**3** and 94.1% *exo*-**3** by weight gave 5.5 94.5, 5.6:94.4, 5.7:94.3, and 5.7:94.3%.

exo-**3-Bicyclo[3.3.1]nonyl Acetate.**—A sample of pure *exo*-**3** was acetylated as described above. The acetate was recovered by removal of the pentane: ir (neat) 1730, 1360, 1240, 1090 and 1030 cm^{-1}; nmr (CCl_4) δ 5.4 (m), 1.95 (s), and 0.8–2.4 (m).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 72.49; H, 9.95. Found: C, 72.70; H, 10.06.

endo-**3-Bicyclo[3.3.1]nonyl Acetate.**—A sample of the *endo* acetate prepared as above showed ir (neat) 1735, 1370, 1240, 1080, and 1010 cm^{-1}; nmr (CCl_4) δ 4.9 (m) and 0.7–2.5 (m).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 72.49; H, 9.95. Found: C, 72.57; H, 10.06.

Equilibration.—Those equilibrations using Raney nickel as a catalyst used solvents and catalyst prepared as described by Eliel and Schroeter.[8] A solution containing *ca.* 100 mg of the appropriate alcohol in 2–3 ml of solvent was mixed, with the catalyst (1–3 g) and sealed in a glass tube. The tube was suspended in a constant-temperature bath until equilibration (as determined from a series of check samples) was complete. The reaction was terminated by removal of the sample from the bath and after opening of the tube by removal of the catalyst by filtration. The catalyst was washed thoroughly and the solvent was removed by distillation. Analysis was made by glpc, and in most cases at least two runs were made from each side of the equilibrium. In the case of the 3-bicyclo[3.3.1]nonanols, the crude mixture was converted into the acetates prior to analysis as described above.

Reagents and solvents for equilibrations using aluminum isopropoxide were prepared as described by Eliel and Schroeter.[8] Equilibrations were carried out on 100 mg of the alcohol with 110 mg of aluminum isopropoxide in 1–2 ml of isopropyl alcohol containing 10–20 μl of acetone. A sealed-tube technique was used as described above. After equilibration had been completed, the contents of the reaction tube were poured into 5 ml of 0.7 *N* hydrochloric acid and the product was taken up in pentane. The pentane solution was dried (K_2CO_3) and used for analysis.

Analyses.—All analyses were carried out on an Aerograph 204B equipped with flame ionization detector and an L & N type W recorder with a Disc integrator. Mixtures of *exo*- and *endo*-**2** were analyzed directly using a 12 ft × 0.125 in. 5% FFAP on Chromosorb G column at 125°. The *exo*- and *endo*-**3** were converted into the acetates as described above and analyzed on a 100-ft capillary column with MBMA as a liquid phase at 125°. Peak areas indicated by the Disc integrator were checked by counting squares on the graph. All analyses were made in duplicate and the value reported is an average of the two (Table I).

TABLE I
RESULTS OF EQUILIBRATION STUDIES

Run	Reactant	Catalyst	Solvent	Time, days	Equilibrium mixture, *exo*/*endo*
1	*endo*-**3**	Al-*i*-PrO	*i*-PrOH	20	96.8:3.2
2	*endo*-**3**	Al-*i*-PrO	*i*-PrOH	20	96.9:3.1
3	*exo*-**3**	Al-*i*-PrO	*i*-PrOH	20	97.1:2.9
4	*exo*-**3**	Al-*i*-PrO	*i*-PrOH	23	96.7:3.4
5	*exo*-**2**	Al-*i*-PrO	*i*-PrOH	20	30.8:69.2
6	*endo*-**2**	Al-*i*-PrO	*i*-PrOH	20	31.3:68.7
7	*exo*-**2**	Raney Ni	*i*-PrOH	8	32.1:67.9
8	*endo*-**2**	Raney Ni	*i*-PrOH	8	31.2:68.8
9	*exo*-**2**	Raney Ni	C_6H_{12}[a]	10	41.0:59.0
10	*exo*-**2**	Raney Ni	C_6H_{12}	10	41.0:59.0
11	*exo*-**2**	Raney Ni	C_6H_{12}	10	39.6:60.4
12	*endo*-**2**	Raney Ni	C_6H_{12}	10	42.0:58.0
13	*endo*-**2**	Raney Ni	C_6H_{12}	10	39.8:60.2
14	*b*	Raney Ni	*i*-PrOH	2	30.6:69.4
15	*b*	Raney Ni	C_6H_{12}	3.5	32.0:68.0

[a] Cyclohexane. [b] 2-Bicyclo[3.3.1]nonanone.

Registry No.—*exo*-**2**, 22485-97-8; *endo*-**2**, 10036-25-6; *exo*-**3**, 10036-10-9; *endo*-**3**, 10036-08-5.

Synthesis of Bicyclo[3.3.1]nonanes. Products of the Friedel–Crafts Reaction of 3-(3-Cyclohexen-1-yl)propionyl Chloride[1]

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Received April 22, 1969

A series of bicyclo[3.3.1]nonane derivatives can be prepared by a Friedel–Crafts reaction of 3-(3-cyclohexen-1-yl)propionyl chloride (**2**) under various conditions. Stannic chloride in chloroform gives 7-bicyclo[3.3.1]nonen-2-one (**3**) and 8-chloro-2-bicyclo[3.3.1]nonanone (**4**). Aluminum chloride in 1,2-dichloroethane leads to 6-chloro-2-bicyclo [3.3.1]nonanone (**7**), which can be converted into 6-bicyclo[3.3.1]nonen-2-one (**8**). With aluminum chloride in boiling cyclohexane, **2** gives 2-bicyclo[3.3.1]nonanone (**6**). Finally, 3-(3-cyclohexen-1-yl)propionic acid (**1**) gives 2,3,4,5,6,7-hexahydro-1-indenone (**9**) when treated with polyphosphoric acid.

Interest in the bicyclo[3.3.1]nonane ring system has been revived recently, in part because it is of importance in the synthesis of some complex natural products,[4] and in part because it presents an interesting skeleton for mechanistic studies.[5] This interest has promoted development of some novel and useful syntheses of the ring system,[6] but most of these are best adapted to the preparation of molecules substituted in a single ring. The preparation of bicyclo[3.3.1]nonanes with

(1) The authors are pleased to make acknowledgement to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) Petroleum Research Fund Fellow, 1966–1968.

(3) Petroleum Research Fund Fellow, 1963–1964.

(4) J. Martin, W. Parker, and R. A. Raphael, *Chem. Commun.*, 633 (1965); R. O. H. Murray, W. Parker, and R. A. Raphael, *Tetrahedron*, **16**, 74 (1961).

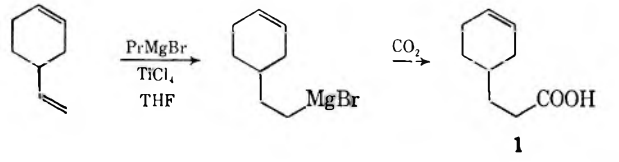
(5) See, for example, the following papers and preceding papers in each series: (a) J. M. Davies and S. H. Graham, *J. Chem. Soc.*, 2040 (1968); (b) M. A. Eakin, J. Martin, and W. Parker, *Chem. Commun.*, 298 (1968); (c) J. P. Schaefer and C. A. Flegal, *J. Amer. Chem. Soc.*, **89**, 5729 (1967); (d) E. N. Marvell, G. J. Gleicher, D. Sturmer, and K. Salisbury, *J. Org. Chem.*, **33**, 3393 (1968).

(6) G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.*, **78**, 5129 (1956); S. Brewis and P. R. Hughes, *Chem. Commun.*, 6 (1966); E. F. Knights and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 5283 (1968).

substituents in both rings is still dominated[7] by the classic synthesis of Meerwein.[8] We have now developed an economical and versatile synthesis for bicyclo[3.3.1]nonanes bearing different functionality in each of the rings.

Earlier work[9] had shown that the "ene participation" route to bicyclo[3.3.1]nonanes is not synthetically useful. However, the great simplicity and potential versatility of the route prompted us to examine further variants which might prove effective. One reasonable possibility was internal acylation, a process used successfully for the formation of bicyclic ketones,[10] albeit normally for *ortho*-fused rings. After the present work had been completed, Erman and Kretschmer[11] showed that 4-cyclooctenecarbonyl chloride gives 2-chlorobicyclo[3.3.1]nonan-9-one.

The synthesis of 3-(3-cyclohexen-1-yl)propionic acid (**1**) was accomplished initially by conventional elaboration of the side chain in 3-cyclohexene-1-carboxaldehyde. However, the elegant procedure of Finkbeiner and Cooper[12] was modified to provide a single-step path to the desired acid in *ca.* 50% yield from 4-vinylcyclohexene.



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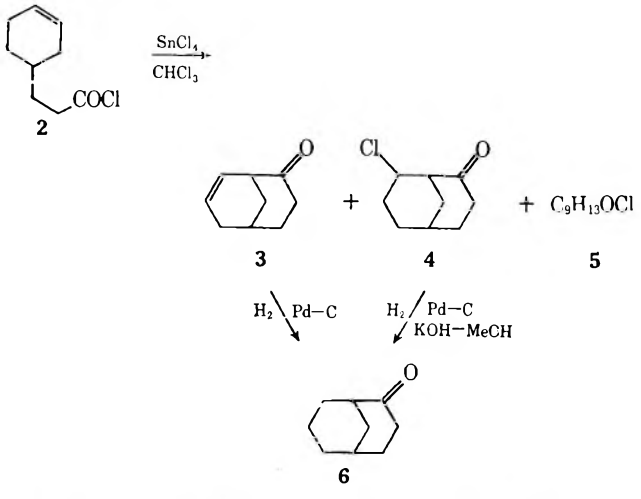
Acylation with Stannic Chloride.—The first attempts to induce 3-(3-cyclohexen-1-yl)propionyl chloride (**2**) to undergo an internal acylation were carried out with stannic chloride in chloroform. Three products were isolated from the reaction: an unsaturated ketone (**3**) and two monochloro ketones (**4** and **5**). Enone **3**, mp



2 3 4 5 6

66–68°, was characterized spectrally: uv, λ_{max} 298 nm (ϵ 180) and 202 (2100); ir, 1710 cm^{-1} (ketone); nmr, two olefinic protons at 5.5–6.2 ppm and particularly a single-proton resonance centered at 2.8 ppm.[5d] Cyclization would be expected to lead to 7-bicyclo[3.3.1]-nonen-2-one (**3**) or to 6-bicyclo[3.2.2]nonen-2-one, a known substance.[13] The latter was eliminated, since it has λ_{max} 288 and 214 nm and nmr and mass spectra clearly different from the product isolated in our reaction. The assignment of a bicyclo[3.3.1]nonane skeleton to our product was confirmed by reduction of **3** to the known ketone **6**.[14] However, the position of the double bond is not necessarily as shown despite the synthetic route, since Colvin and Parker[15] have shown that double bonds in the bicyclo[3.3.1]nonane system may migrate under acid conditions. The presence of a proton resonance at 2.8 ppm in the nmr spectrum of **3**, which can be assigned to the bridgehead proton at C_1, suggested that the 7 position was correct. This was confirmed by the synthesis of 6-bicyclo[3.3.1]-nonen-2-one (**8**) (see below), which has no bands in this region. Despite its apparent purity, **2** could contain small amounts of **8**, since we would probably be unable to detect 5–10% **8** in our sample.

Of the two monochloro ketones, one has been tentatively identified as 8-chlorobicyclo[3.3.1]nonan-2-one (**4**). Catalytic reduction of **4** under basic conditions gave **6** which delineates the carbon skeleton. The synthetic scheme suggests that the chlorine should be at C_8, but later results (see below) showed that chlorine migration occurs readily. Dehydrohalogenation should provide an unequivocal assignment, since an 8 Cl should give exclusively **3**, while a 7 Cl should give a mixture of **3** and **8**. Dehydrohalogenation proved difficult. Tertiary amines gave poor yields of complex mixtures, and silver ion led to a mixture of **3** and a second product having ν_{CO} at 1755 cm^{-1}. We have been unable to separate the mixture, but the presence of **3** can be confirmed spectrally. Furthermore, the CHCl resonance in the nmr spectrum of **4** is markedly different from those of a CHOH at C_3. Thus we consider that the chlorine is attached to C_8, but whether it is *exo* or *endo* is not yet established.

The third product (**5**) is characterized by a carbonyl band at 1710 cm^{-1} and a proton resonance at 4.4 ppm, suggesting the presence of a CHCl unit. The compound analyzes correctly for $C_9H_{13}OCl$ and is monomeric (mass spectrum). However, all attempts to remove the halogen reductively in order to determine the nature of the carbon skeleton have been unsuccessful. Thus no structural assignment can be made at present.

Influence of Conditions on Yields.—In order to improve the yield of **3**, a relatively comprehensive study of the influence of catalyst and solvent on the Friedel–Crafts reaction of 2 was made. The results of glpc analysis of the products obtained are shown in Table I. The data disclose a remarkable sensitivity of the nature of the product to both catalyst and solvent. Since the bicyclic products are generally difficult to isolate and purify, only those conditions which lead to relatively simple mixtures were selected for further study. Aside from the stannic chloride–chloroform

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(8) H. Meerwein, F. Kiel, G. Klosgen, and E. Schoh, *J. Prakt. Chem.*, [2] **104**, 161 (1922).
(9) E. N. Marvell, D. Sturmer, and R. S. Knutson *J. Org. Chem.*, **33**, 2991 (1968).
(10) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 1637 (1938); J. C. Bardhan and K. C. Bhattacharyya, *Chem. Ind.* (London), 800 (1953); D. W. Mathieson, *J. Chem. Soc.*, 3251 (1953); P. A. Plattner and G. Büchi, *Helv. Chim. Acta*, **29**, 1608 (1946).
(11) W. F. Erman and H. C. Kretschmer, *J. Org. Chem.*, **33**, 1545 (1968).
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(14) E. N. Marvell, D. Sturmer, and C. Rowell, *Tetrahedron*, **22**, 861 (1966), and references cited therein.
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TABLE I

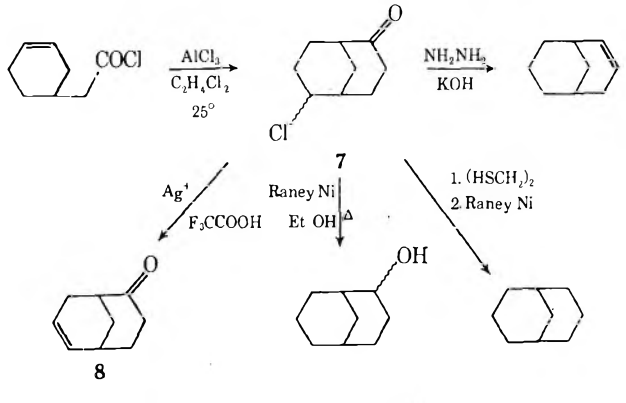
RESULTS OF THE ANALYSIS OF FRIEDEL–CRAFTS PRODUCTS FROM 2 UNDER VARIOUS CONDITIONS

		Per cent area under peak[a]								
Catalyst	Solvent	A[b]	B[c]	C[b]	D[b]	E[b]	F[d]	G[b]	H[e]	I[b]
$SnCl_4$	$ClCH_2CH_2Cl$		40			5	29		13	14
	$CHCl_3$		48			5	17	4		26
	CH_2Cl_2		43			5	28		9	16
	CS_2		33			7	42		10	8
$AlCl_3$	$ClCH_2CH_2Cl$		3	2	2	6	21		63	4
	CCl_4		6	6	28	16	17		19	2
	$CHCl_3$		6		5	12	44		27	6
	CS_2		7	7	28	20	18		19	2
	C_6H_{12}	37	52[f]			2	4	2		4
$ZnCl_2$[g]	$CHCl_3$		50			11		30		7
	CH_2Cl_2		36					57		7
$FeCl_3$	$ClCH_2CH_2Cl$		29				14	20	42	6
	$CHCl_3$		17				56		17	10
	CS_2		5	3			22	22	44	4
$TiCl_4$	CCl_4		7	←	10	→	61		10	6
	CS_2		15	←	13	→	56		5	12

[a] The peaks are lettered in order of elution. [b] The substance responsible for this peak has not been identified. [c] This component is 7-bicyclo[3.3.1]nonen-2-one (**3**). [d] This component is 8-chlorobicyclo[3.3.1]nonan-2-one (**4**). [e] This component is 6-chlorobicyclo[3.3.1]-nonen-2-one (**7**). [f] This component is 2-bicyclo[3.3.1]nonanone (**6**). [g] Reactions with $ZnCl_2$ were slow and these results represent incomplete reaction.

system already considered for the preparation of **3**, the use of aluminum chloride–dichloroethane for the preparation of the compound responsible for peak H, of aluminum chloride–cyclohexane for the synthesis of **6**, and of titanium chloride–dichloroethane for formation of **4** were examined further.

Acylation with Aluminum Chloride–Dichloroethane.—As is indicated in Table I, the use of aluminum chloride in dichloroethane converts **2** mainly into one compound elected as peak H. This product is another monochloro ketone, $C_9H_{13}OCl$, which has been assigned the structure of 6-chloro-2-bicyclo[3.3.1]nonanone (**7**) on the basis of the data described below. It was



isolated routinely in yields of 40% on a preparative scale. Removal of the chlorine atom by reductive means proved difficult, but was ultimately accomplished in two ways. Wolff–Kishner reduction gave a crystalline hydrocarbon which proved identical with 2-bicyclo[3.3.1]nonene.[16] Raney nickel desulfurization of the ethylene dithioketal of **7** gave bicyclo[3.3.1]-nonane. These show that the carbon skeleton is once again bicyclo[3.3.1]nonane, and the second reaction suggests that reductive dechlorination should be possible. This proved correct, since, when **7** was treated with a large excess of W-2 Raney nickel, 2-bicyclo-[3.3.1]nonanol was obtained as an equilibrium mixture[17] of the two epimers.

The position of the chlorine relative to the carbonyl group was established by dehydrohalogenation to 6-bicyclo[3.3.1]nonen-2-one (**8**), a ketone previously isolated by Rogers.[18] Since the nmr spectrum of **8** shows no deflection of the base line at 2.5–3.0 ppm, we can state that the dehydrohalogenation product must contain less than 5% **3**. Thus the position of the chlorine at C_6 is clearly established, but its orientation is uncertain. Allinger and Liang[19] have shown that the orientation of a chlorine on a cyclohexane ring can be deduced from the position of the C–Cl stretch in the infrared. Thus ν_{C-Cl} for axial chlorine should be 661–678 cm^{-1} and ν_{C-Cl} for equatorial chlorine should be 749–758 cm^{-1}. Ketone **7** has two bands, one at 768 cm^{-1} and a second of lesser intensity at 715 cm^{-1}. These suggest that **7** is a mixture of epimers.

Migration of a chlorine during internal acylation is not without precedent. Nenitzescu and coworkers[20] have studied this phenomenon with some care, and have shown that the main product normally obtained has the chlorine atom on that carbon atom most distant from the carbonyl group which permits formation of a secondary chloride. Our results agree with this generalization. That the chlorine migration can indeed occur under the conditions of the reaction was confirmed by treating **4** with aluminum chloride in dichloroethane. A good yield of **7** was obtained.

Synthesis of 2-Bicyclo[3.3.1]nonanone (6).—Since the occurrence of hydride transfers in carbonium ion reactions and particularly in Friedel–Crafts reactions[21] is well established, it seemed that the use of an ap-

(16) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

(17) E. N. Marvell and R. S. Knutson *ibid.* **35**, 388 (1970); K. H. Baggeley, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 299 (1967).

(18) We are indebted to Professor N. A. J. Rogers of the University of Lancaster for spectral data.

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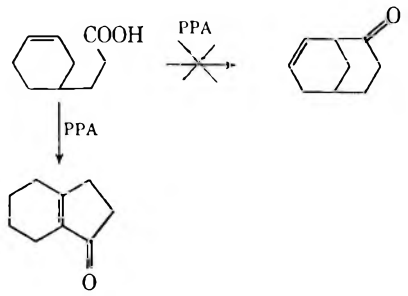
(21) C. D. Nenitzescu, *Chem. Ber.*, **69**, 1820 (1963).

propriate solvent might permit synthesis of **6**. This aim was realized when a hydrocarbon solvent was employed. Studies with pentane, 3-methylpentane, cyclohexane, and methylcyclohexane at temperatures ranging from 0° to solvent reflux showed that the use of cyclohexane at reflux was most effective. The main by-product was isolated by preparative glpc and spectral examination showed that it was a hydrocarbon. Presumably, it is derived from the solvent carbonium ion formed in the hydride-transfer process, but it was not examined further. Since this hydrocarbon is easily separated from the desired **6** by column chromatography, this route constitutes a very economical synthesis for **6** from 4-vinylcyclohexene in three steps with an overall yield of *ca.* 20%.

Synthesis of 8-Chlorobicyclo[3.3.1]nonan-2-one (4).—As the data of Table I suggest, the most effective conditions for the preparation of **4** involve the use of titanium tetrachloride in 1,2-dichloroethane. Isolation of **4** from the product mixture was most conveniently accomplished by distillation followed by low-temperature crystallization. Despite the inefficiency of this process, yields of *ca.* 30% pure **4** can be obtained routinely.

Cyclization of 1 in Polyphosphoric Acid.—Finally, an attempt to simplify the synthesis of **3** was made by treating 3-(3-cyclohexen-1-yl)propionic acid with polyphosphoric acid (PPA). No **3** was formed in this



9

process, which gave an excellent yield of 2,3,4,5,6,7-hexahydro-1-indenone (**9**). Presumably, a shift of the double bond precedes the ring-closure step. Thus by appropriate control of catalyst, solvent, and substrate, this general synthetic route can be used to convert 4-vinylcyclohexene into **3**, **4**, **6**, **7**, or **9** in reasonable yields by a process involving no more than three steps in any case.

Experimental Section

Diethyl 2-(3-Cyclohexen-1-yl)ethane-1,1-dicarboxylate.—A tosylate was prepared in 96% yield from 485 g (4.34 mol) of 3-cyclohexen-1-ylmethanol[9] according to the method of Tipson.[22] The crude tosylate, ir (neat) 1590, 1500, 1350, and 1180 cm^{-1}, was used directly in the second step. To a solution containing 0.61 mol of sodium diethyl malonate in 450 ml of anhydrous ethanol was added over a 5-hr period 154 g (0.60 mol of crude tosylate). The reaction mixture was heated under reflux for 36 hr. To this was added 250 ml of water, and most of the ethanol was removed under reduced pressure. The residue was acidified with dilute hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ether. The desired product was isolated by fractional distillation: bp 95–99° (2 mm); yield 102.6 g (70%); $n^{20}D$ 1.4620; ir 1740, 1650, 1465 1095, and 1055 cm^{-1}.

(22) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.10; H, 8.62.

3-(3-Cyclohexen-1-yl)propionic Acid (1). Method A.—This method constitutes a modification of the method of Finkbeiner and Cooper.[12] A solution of *n*-propylmagnesium bromide in 775 ml of tetrahydrofuran was prepared from 32.1 g (1.32 g-atoms) of magnesium and 147.8 g (1.20 mol) of *n*-propyl bromide under a nitrogen atmosphere. To this was added slowly 2.9 ml of titanium tetrachloride, and, after the vigorous reaction had subsided, 108 g (1.00 mol) of 4-vinylcyclohexene was added. The reaction mixture was heated under reflux for 15 hr. After 100 ml of diethyl ether had been added, the solution was cooled to −5° and carbon dioxide was passed over the stirred solution at a rate which permitted maintenance of the reaction mixture below 10°.

The solution was treated with a slurry of 550 ml of 10% sulfuric acid and ice chips. The aqueous layer was extracted with ether, and the combined organic layers were extracted with 20% sodium hydroxide. Careful neutralization of the cold, basic solution with concentrated hydrochloric acid gave an oil: bp 89–90° (0.05 mm); yield 76 g (49%); mp 33–35° (lit.[12] mp 31–32°).

Method B.—A mixture of 101 g (0.40 mol) of diethyl 2-(3-cyclohexen-1-yl)ethane-1,1-dicarboxylate and 750 ml of 10% aqueous potassium hydroxide was stirred at room temperature until the organic layer had dissolved. The mixture was washed with ethyl ether and acidified with dilute sulfuric acid. The acidic solution was extracted several times with ether. Evaporation of the ether gave 2-(3-cyclohexen-1-yl)ethane-1,1-dicarboxylic acid, mp 120–121° after recrystallization from benzene.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.86; H, 7.10.

The above acid (74.5 g, 0.376 mol) was heated in 800 ml of xylene at 132° for 16 hr. The xylene was removed by distillation and the residue was distilled, bp 87–88° (0.2 mm), to give 55.3 g (95%) of 3-(3-cyclohexen-1-yl)propionic acid, mp 34.5–36°.

Method C.—To 29.8 g (0.212 mol) of 3-(3-cyclohexen-1-yl)-propanol[9] in 1500 ml of acetone at 0° was added dropwise *ca.* 120 ml of a solution containing 32.0 g of chromium trioxide and 27.6 ml of sulfuric acid. As soon as the red color of the reagent persisted for a few minutes, the reaction mixture was allowed to stand overnight. About 500 ml of water was added and the acetone was removed under reduced pressure. The organic product was taken up in ether and was isolated by distillation: bp 81–82° (0.6 mm); mp 33–35°; yield 25.9 g (79%).

3-(3-Cyclohexen-1-yl)propionyl Chloride (2).—This acid chloride was prepared from the above acid by treatment with oxalyl chloride as described earlier.[5d] The crude product was used in the Friedel–Crafts step without further purification. The preparation of **2** was also carried out in larger scale, as described below.

A solution containing 120 g (0.78 mol) of 3-(3-cyclohexen-1-yl)-propionic acid and 69 g of pyridine in 1200 ml of dry benzene was cooled to 5°. Purified thionyl chloride (190 g, 1.6 mol) was added dropwise and the reaction mixture was stirred for 6 hr at 0–5° and 2 hr at 5–15°. Excess thionyl chloride and the benzene were removed under reduced pressure and the product was isolated by distillation, bp 58–60° (0.5 mm), yield 115 g (86%). This product was used without further purification.

7-Bicyclo[3.3.1]nonen-2-one (3).—The ketone **3** was prepared in 55% yield according to the procedure described earlier:[5d] nmr (CCl_4) δ *ca.* 6.0 and 5.8 (modified AB, $J_{AB} \cong 9$, $J_{AX} \cong 3$ Hz, 2 H), 2.82 (m, 1 H), and 2.6–1.7 (br m, 9 H).

8-Chlorobicyclo[3.3.1]nonan-2-one (4). Method A.—The still residues obtained after the isolation of **3** as described above contain by glpc analysis (190°, Ucon Polar column) mainly a mixture of **4** and **5**. These could be separated readily by chromatography on activity II alumina, **3** being eluted with 10–20% benzene–pentane and **4** by 80–100% benzene–pentane as a white, crystalline material: mp 40–46°; ir 1710, 750, and 684 cm^{-1}; nmr (CCl_4) δ 4.4 (br s, 1 H) and 2.6–1.5 (br m, 12 H).

Anal. Calcd for $C_9H_{13}OCl$: C, 62.61; H, 7.59. Found: C, 62.80; H, 7.55.

Method B.—To a solution containing 10 g (0.058 mol) of **1** in 500 ml of 1,2-dichloroethane was added dropwise 25 g (0.13 mol) of titanium tetrachloride. After the addition had been completed, the solution was stirred for 6 hr at 25°. A slurry of ice chips in 500 ml of 10% hydrochloric acid was added, and the layers were separated. The aqueous layer was extracted with methylene chloride, and the combined organic layers were dried (Na_2SO_4). After the solvent had been removed, the product was

distilled through a short column packed with glass helices, bp *ca.* 60–80° (0.8 mm), yield 4.2 g (38%). Glpc analysis (1/4 in. × 5 ft SF-96 on Chromosorb at 150°) showed that this fraction contained *ca.* 90% **4**. Further purification was achieved by fractional freezing. A product, mp 40–46°, was obtained (28%).

6-Chlorobicyclo[3.3.1]nonan-2-one (7).—A mixture containing 10.1 g (0.059 mol) of **2** and 17.2 g (0.129 mol) of aluminum chloride in 240 ml of 1,2-dichloroethane was stirred for 5 hr at 25°. The mixture was cooled in an ice bath and 120 ml of 10% hydrochloric acid was added. The aqueous layer was extracted with dichloroethane, and the combined organic layers were washed with sodium bicarbonate and water. The solution was dried ($MgSO_4$) and the solvent was removed *in vacuo*. After removal of a small amount of liquid material (2.0 g), the product was isolated from the tarry residue by vacuum sublimation, bp 165° (bath temperature, 0.05 mm). The product was purified by resublimation, giving 4.12 g (41%) of **7**: mp 78–81°; ir (CS_2) 1710, 986, 768, and 715 cm^{-1}; nmr (CCl_4) δ 4.28 (br s, 1 H) and 2.6–1.4 (m, 12 H).

Anal. Calcd for $C_9H_{13}OCl$: C, 62.61; H, 7.54; Cl, 20.57. Found: C, 62.54; H, 7.62; Cl, 20.42.

A semicarbazone derivative prepared according to the procedure of Cheronis and Entrikin[23] melted at 184–185°.

Anal. Calcd for $C_{10}H_{16}N_3OCl$: C, 52.29; H, 6.97. Found: C, 52.06; H, 6.98.

2-Bicyclo[3.3.1]nonanone (6).—A solution of 10.0 g (0.056 mol) of **2** in 150 ml of cyclohexane was added dropwise to a rapidly stirred suspension of 15.5 g (0.116 mol) of aluminum chloride in 1 l. of boiling cyclohexane. After addition was complete, the mixture was stirred for 15 min and cooled in an ice bath. *Ca.* 300 ml of dilute hydrochloric acid was added and the organic layer was separated, washed with saturated sodium sulfate, and dried ($MgSO_4$). The solvent was removed by distillation using a Vigreux column, and the product was isolated by distillation, bp 34–38° (0.02 mm). The solid which collected in the head was washed out with pentane and purified by sublimation, mp 127–130° (capillary) (lit.[14] mp 134–137°), yield 1.41 g.

The distillate was analyzed by glpc (15 ft × 0.125 in. 5% SE-30 on Chromosorb G column at 150°) and was found to contain two impurities which eluted before the ketone. Isolation of the impurities by preparative glpc (14 ft × 0.375 in. 20% SF-96 on firebrick column at 130°) and examination of their nmr spectra showed only aliphatic hydrogen.

For synthetic runs the distillate was chromatographed over activity II alumina. The impurities eluted in the first fractions with hexane as eluent and the desired ketone was eluted after these, mp 128–130° (capillary), yield 2.32 g. The overall yield was 3.73 g (46%).

2,3,4,5,6,7-Hexahydro-1-indenone (9).—A mixture of 4.07 g (0.026 mol) of 3-(3-cyclohexen-1-yl)propionic acid and 59 g of polyphosphoric acid was heated on a steam bath for 2.5 hr. The reaction mixture was shaken at regular intervals during this time. The cooled mixture was diluted to 200 ml with water, and this solution was extracted with ether. The ether extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. Distillation, bp *ca.* 70° (0.4 mm), gave 2.66 g (74%) of ketone, λ_{max} 238 nm (log ϵ 4.10) [lit.[24] λ_{max} 236 nm (log ϵ 4.09)]. The 2,4-dinitrophenylhydrazone derivative melted at 237–238° (lit.[24] mp 238–239°).

6-Bicyclo[3.3.1]nonen-2-one (8). Method A.—A mixture of 500 mg (2.9 mmol) of **7**, 16 ml of benzene, 5 ml of ethylene glycol, and 19 mg of *p*-toluenesulfonic acid was heated under reflux for 5.5 hr. Water was removed from the reaction mixture *via* a Dean–Stark separator. The reaction mixture was washed with 10 ml of 1% sodium hydroxide, and the aqueous layer was extracted with ether. The combined benzene and ether solutions were washed with water, and distilled until the head temperature reached 80°. The residue (5 ml) showed no carbonyl or enol ether bands in the infrared.

This residue was added to a solution containing 29 mmol of sodium glycolate in 20 ml of ethylene glycol, and the reaction mixture was heated at 155° for 4 hr. The cooled solution was acidified with 10% sulfuric acid and extracted with pentane. Most of the pentane was distilled from this solution and the residue was heated under reflux with 10 ml of acetone and 7 ml of 4% sulfuric acid for 1 hr. The solution was diluted with water and extracted with pentane. The main component of this solution was isolated by preparative glpc (5 ft × 0.25 in. 20% SF-96 column at 135°): mp 61.5–62.5°; yield 134 mg (34%); ir (CCl_4) 3050, 1710, and 1105 cm^{-1}; nmr (CCl_4) δ 5.84 (d, 2 H, J = 3 Hz) and 2.65–1.6 (m, 10 H); λ_{max} (CH_3OH) 293 nm (ϵ 41).

A semicarbazone derivative prepared according to the procedure of Cheronis and Entrikin[23] melted at 191–192°.

Anal. Calcd for $C_{10}H_{15}N_3O$: C, 62.12; H, 7.82. Found: C, 61.98; H, 7.69.

Method B.—Ketone **7** (200 mg, 1.16 mmol) was stirred for 36 hr with a solution of 506 mg (2.32 mmol) of silver trifluoroacetate in 10 ml of trifluoroacetic acid. The precipitate was removed by filtration, and the filtrate was diluted with water and extracted with pentane. The pentane solution was washed free of acid and concentrated *in vacuo*. Examination of the concentrate by glpc (SF-96 column at 160°) showed that the reaction had not proceeded to completion (60% from glpc). The product was isolated by preparative glpc as above, giving 42 mg (27% or 45% based on amount of **7** consumed) of material, mp 61–62°.

Hydrogenation of 3.—A sample of **3** was hydrogenated in methanol solution over palladium on charcoal. The catalyst was removed by filtration and the product was isolated by preparative glpc. The nmr and mass spectra of the compound were identical with those of an authentic sample of **6**.

2-Bicyclo[3.3.1]nonene from 7.—A sample of **7** (250 mg, 1.45 mmol) was mixed with 146 mg (3.01 mmol) of hydrazine hydrate and 240 mg of potassium hydroxide in 2.5 ml of diethylene glycol. The solution was placed in a 10-ml flask fitted with a cold-finger condenser, and was heated at 50° for 4 hr and then at 200° for 4 hr. The solid which collected on the condenser was purified by preparative glpc (5 ft × 0.25 in. 20% SF-96 column at 100°), mp 99–100° (lit.[16] mp 96.5–97°), yield 80 mg (32%).

Bicyclo[3.3.1]nonane from 7.—A solution of 500 mg (2.9 mmol) of **7** in a small amount of anhydrous ether was combined with 0.5 ml of ethanedithiol and 8 drops of boron trifluoride ethereate. The mixture was allowed to stand at room temperature for 2 hr, after which the excess ethanedithiol was removed by azeotropic distillation with absolute ethanol. The residue was diluted with 5 ml of absolute ethanol and heated at reflux for 10 hr over 5.5 g of W-2 Raney nickel.

The catalyst was removed by filtration, and the filtrate was diluted with water and then extracted with pentane. The product was isolated by glpc, mp 143–145° (lit.[16] mp 143–144°), yield 102 mg (28%).

2-Bicyclo[3.3.1]nonanol from 7.—A solution of 311 mg (1.81 mmol) of **7** in 5 ml of methanol was stirred at reflux with 3 g of W-2 Raney nickel for 10 hr. The catalyst was removed by filtration and extracted in a Soxhlet apparatus with methanol. The combined methanol solutions were diluted with water and extracted with pentane. Evaporation of the pentane gave 147 mg (47%) of 2-bicyclo[3.3.1]nonanol. Purification by preparaglpc (5 ft × 0.25 in. 20% SF-96 column at 145°) gave a sample, mp 178–182° (lit.[16] mp 177–178° for *endo*-2-ol and 176–177° for *exo*-2-ol). Glpc comparison with authentic samples showed this material to contain *ca.* 70% *endo*-2-ol and 30% *exo*-2-ol.

Reduction of 4.—Crude product from the stannic chloride catalyzed reaction of **2** containing *ca.* 40% **3**, 30% **4**, and 20% **5** (glpc analysis) was hydrogenated over palladium on charcoal in methanolic potassium hydroxide (10%) until no further hydrogen was absorbed. The catalyst was removed and the solution was neutralized with dilute hydrochloric acid. Water was added and the solution was extracted with pentane. After removal of the pentane, the residue was purified by sublimation. Analysis by glpc (SF-96 column at 150°) showed that **3** and **4** had disappeared and a new product with the same retention time as **6** (internal comparison) had appeared. However, **5** remained unaltered. The mass spectrum of the reduction product was identical with that of an authentic sample of **6**.

Dehydrohalogenation of 4. Method A.—A sample (400 mg, 2.35 mmol) of **4** was treated with 1.0 g of silver trifluoroacetate as described under the dehydrohalogenation of **7**. The product gave one peak on glpc analysis (5 ft × 0.25 in. SF-96 column): ir 3025, 1755, 1710, and 1645 cm^{-1}; λ_{max} 297 nm (ϵ *ca.* 100); nmr (CCl_4) δ 5.8 (m, 2 H) and unresolved multiplets at 3.1, 2.8, and 0.9–2.7.

Method B.—Ketone **4** (200 mg, 1.18 mmol) and 400 mg of silver nitrate were mixed in 30 ml of 95% ethanol. The mixture was boiled for 8 hr, and after the solution had been diluted with water, the product was taken up in pentane. The product was collected from glpc and had spectral properties in full agreement

(23) N. D. Cheronis and J. B. Entrikin, "Identification of Organic Compounds," Interscience Publishers, Inc., New York, N. Y., 1963, p 320.

(24) R. L. Frank and R. C. Pierle, *J. Amer. Chem. Soc.*, **73**, 724 (1951).

with those noted above. The intensities of the 1755- and 1710-cm^{-1} bands were approximately equal.

Registry No.—**2**, 22482-52-6; **3**, 16957-72-5; **4**, 22482-54-8; **6**, 2568-17-4; **7**, 22482-56-0; **7** semicarbazone, 22482-57-1; **8**, 22482-58-2; **8** semicarbazone, 22482-59-3; diethyl 2-(3-cyclohexen-1-yl)ethane-1,1-dicarboxylate, 22482-60-6; 2-(3-cyclohexen-1-yl)ethane-1,1-dicarboxylic acid, 22482-61-7; 3-(3-cyclohexen-1-yl)propionic acid, 22482-62-8.

Transannular Reactions during Solvolyses of *exo*-2,3-Epoxybicyclo[3.3.1]nonane[1]

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Received April 22, 1969

Solvolysis of *exo*-2,3-epoxybicyclo[3.3.1]nonane (**1**) at 0° in trifluoroacetic acid gave (50–60%) a mixture of 7-bicyclo[3.3.1]nonen-*exo*-2-ol (**3**) and 6-bicyclo[3.3.1]nonen-*exo*-2-ol (**4**). Acetolysis of **1** gave (95%) a mixture containing 53% diols and 47% enols. Glpc analysis of the total mixture showed 46% *exo*-2-*endo*-3-bicyclo[3.3.1]-nonadiol (**9**), 23% a mixture of **3** and **4**, 21% 3-bicyclo[3.3.1]nonen-*exo*-2-ol (**7**), 5% *exo*-2-*exo*-7-bicyclo-[3.3.1]nonadiol (**10**), 3% a compound tentatively identified as 7-bicyclo[3.3.1]nonen-*exo*-3-ol (**8**), and 2% a diol tentatively assigned the structure *endo*-2-*exo*-3-bicyclo[3.3.1]nonadiol (**11**). The results are compared with similar solvolyses of *cis*-cyclooctene oxide.

In 1944 the classic and elegant experiments of Bartlett, Condon, and Schneider[3] showed that hydride transfer from a nonactivated CH group to a carbonium ion can occur with great rapidity. With the exception of such special reactions as 1,2-hydride shifts and cases where the product of reaction with the solvent regenerates the carbonium ion,[4] this hydride shift was not found to compete successfully with reaction between the carbonium ion and a nucleophilic solvent. Thus the discovery that a transannular hydride shift will compete quite effectively with a nucleophilic solvent for the carbonium ions of medium rings[5] evoked considerable interest. Despite a great deal of effort by a number of investigators,[6] the relative importance of such factors as proximity of the CH group to the cation, strain in the ring, and hindrance to reaction with the solvent is not yet clear, and questions of whether sequential ion formation, rearrangement, and solvent reaction is required or whether partial or fully concerted processes are possible have not been unequivocally answered. The conformational mobility of the medium rings has served to complex the investigative problem and has prevented a better understanding of the role which conformation must play in the transannular hydride transfer.

Hoping to be able to answer some of these questions about transannular processes, we began a comprehensive study of the chemistry of medium rings conformationally restricted by bridging. Our first efforts were directed at the symmetrically bridged cyclooctane ring, *viz.*, bicyclo[3.3.1]nonane. For molecules having only hydrogen on the *endo* sides of carbons 3 and 7, this ring is known[7] to have a double-chair conformation. Thus it should provide an ideal substrate for study of the mechanistic details of transannular processes. The present paper reports a comparison of the behavior of *exo*-2,3-epoxybicyclo[3.3.1]nonane (**1**) with that of *cis*-cyclooctene oxide[8] under comparable conditions.[9]

Solvolyses and Product Identification.—Epoxidation of 2-bicyclo[3.3.1]nonene was carried out by the method of Payne.[10] The product was shown to be *exo*-2,3-epoxybicyclo[3.3.1]nonane (**1**) by reduction to the known *exo*-2-bicyclo[3.3.1]nonanol (**2**).[11] Solvolysis of **1** was performed first in trifluoroacetic acid, and a modest yield (50–60%) of monomeric product was recovered after hydrolysis with dilute base. The crude product was purified chromatographically and a crystalline enol was recovered. This enol was reduced to **2**, which shows that ring opening occurred without loss of configuration at C_2.

Based on the assumption that this enol must be derived from a C_7 carbonium ion, a mixture of 7-bicyclo[3.3.1]nonen-*exo*-2-ol (**3**) and 6-bicyclo[3.3.1]nonen-*exo*-2-ol (**4**) is expected. However, we were unable to separate the product either by glpc or thin layer chromatography. Therefore, the enol fraction was oxidized by Jones oxidant. It is assumed that under these conditions the position of the double bond is not altered, since this procedure is known to leave even sensitive β,γ double bonds unaltered.[12] The oxidation product, mp 55–68°, was again inseparable on thin layer chromatography or glpc. Both 7-bicyclo[3.3.1]-nonen-2-one (**5**)[13] and 6-bicyclo[3.3.1]nonen-2-one (**6**)[14] were synthesized, and known mixtures of the two

(1) The authors are pleased to make acknowledgment to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(2) Petroleum Research Fund Fellow, 1963–1964.

(3) P. D. Bartlett, F. E. Condon, and A. Schneider, *J. Amer. Chem. Soc.*, **66**, 1531 (1944).

(4) See, *e.g.*, P. D. Bartlett and J. D. McCollum, *ibid.*, **78**, 1441 (1956).

(5) V. Prelog and K. Schenker, *Helv. Chim. Acta*, **35**, 2044 (1952); A. C. Cope, S. W. Fenton, and C. F. Spencer *J. Amer. Chem. Soc.*, **74**, 5884 (1952).

(6) For a recent review, see V. Prelog and J. G. Traynham, "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 593–615.

(7) M. Dobler and J. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).

(8) (a) A. C. Cope, A. H. Keough, P. E. Peterson, H. E. Simmons, Jr., and G. W. Wood, *J. Amer. Chem. Soc.*, **79**, 3900 (1957); (b) A. C. Cope, J. M. Grisar, and P. E. Peterson, *ibid.*, **81**, 1640 (1959); (c) A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, *ibid.*, **82**, 6366 (1960).

(9) After this study was virtually complete, a report of a similar study was published: R. A. Appleton, J. R. Dixon, J. M. Evans, and S. H. Graham, *Tetrahedron*, **23**, 805 (1967). Fortunately, their work was confined to formolysis while ours was limited to trifluoroacetolysis and acetolysis.

(10) G. B. Payne, *ibid.*, **18**, 763 (1962).

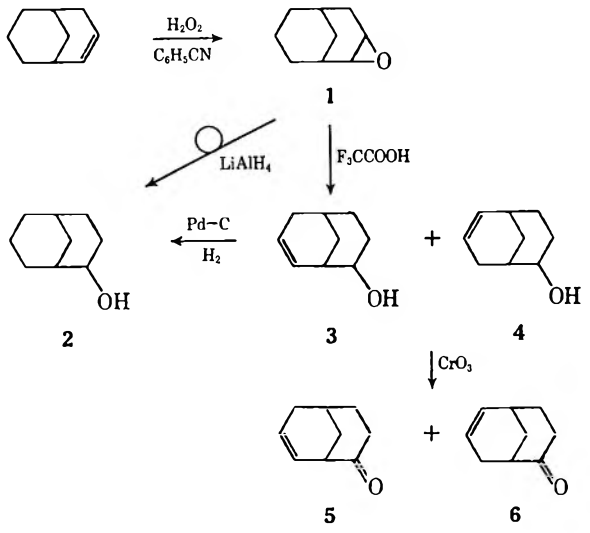
(11) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967).

(12) C. Djerassi, R. R. Engle, and A. Bowers *ibid.* **21**, 1547 (1956).

(13) E. N. Marvell, G. J. Gleicher, D. Sturmer, and K. Salisbury, *ibid.*, **33**, 3393 (1968).

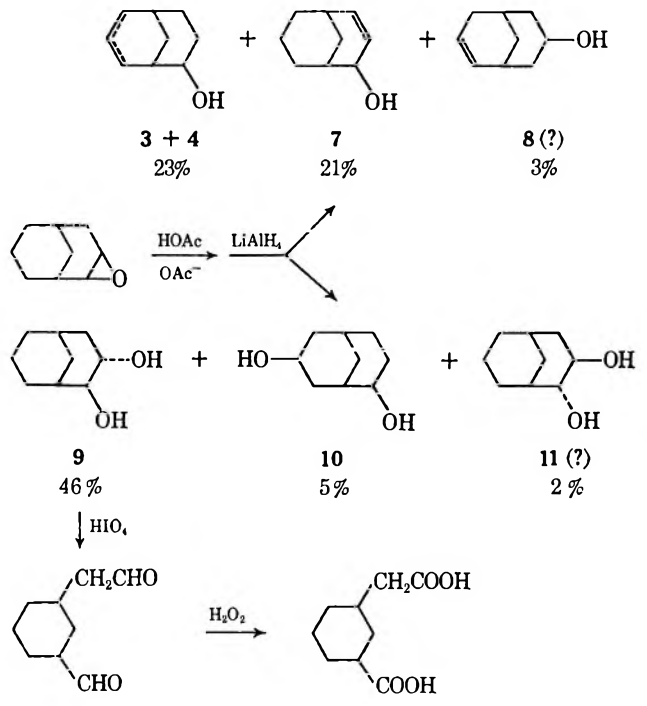
(14) E. N. Marvell, R. S. Knutson, T. McEwen, D. Sturmer, W. Federici, and K. Salisbury, *ibid.*, **35**, 391 (1970).

could not be separated under the same conditions. However, **5** shows λ_{max} 297 mμ (ε 184) and **6** has λ_{max} 297 mμ (ε 77). The oxidation product has λ_{max} 297 mμ (ε 100), which would correspond to a mixture of 79% **6** and 21% **5**. Similarly, **5** has a single-proton resonance (multiplet at 2.82 ppm) in its nmr spectrum in a region where **6** has no absorption. Integration of this region as compared with the two-proton olefinic region as a standard indicated that the oxidation product consisted of *ca.* 80% **6** and 20% **5**. Thus we consider that the enol from trifluoroacetolysis of **1** is a mixture containing 20 ± 5% **3** and 80 ± 5% **4**. Small amounts of a diol fraction were obtained (*ca.* 5–10%) from the trifluoroacetolysis but were not identified.



Acetolysis of **1** was carried out in the presence of sodium acetate at 100°. The reaction proceeded slowly and required *ca.* 72 hr. The crude reaction product was treated with lithium aluminum hydride and this product was analyzed by glpc. Enol and diol fractions were present in about equal amounts and each contained three components. The enol fraction contained 23% **3** + **4**, 21% 3-bicyclo[3.3.1]nonen-*exo*-2-ol (**7**), and 3% of a fourth enol. A crude sample of the 21% component of the enol fraction was isolated by preparative glpc. This was oxidized to the known 3-bicyclo[3.3.1]nonen-2-one.[11] Since reduction of the entire enol fraction gave **2** as the only important product, this second enol was assigned the structure **7**. Partial confirmation of this assignment was obtained by carrying out a formolysis of **1** under the published conditions[9] and showing by glpc comparison that the constituent that the previous workers had assigned structure **7** was identical with ours. Owing to the difficulty of the separation, we were not able to prepare a pure sample for comparison with the physical properties published for this substance.[11] Thus the structural assignment is based purely on the chemical data.

The minor constituent has not been fully identified, but it is not identical with either of the alcohols obtained from reduction of 6-bicyclo[3.3.1]nonen-2-one. Assuming that the configuration at C_2 or C_3 must be retained, this eliminates all possible enols except 6-bicyclo[3.3.1]nonen-*exo*-3-ol (**8**). Thus this structure is tentatively assigned to the minor enol.



The diol fraction was separated into three components by preparative thin layer chromatography. The main constituent (46%) in the diol fraction was shown to be a vicinal diol by oxidation with periodic acid. The ring-cleavage product was separated and oxidized to the known[15] *cis*-3-carboxymethylcyclohexanecarboxylic acid. This diol was not identical with *exo*-2-*exo*-3-bicyclo[3.3.1]nonadiol prepared by osmium tetroxide oxidation of 2-bicyclo[3.3.1]nonene. If the configuration is retained at either C_2 or C_3, then this must be either *exo*-2-*endo*-3-bicyclo[3.3.1]nonadiol (**9**) or *endo*-2-*exo*-3-bicyclo[3.3.1]nonadiol (**11**). Since **11** is expected to exist predominantly as a double-chair conformer, it should exhibit abnormally high frequency C–H stretching and bending modes in the infrared.[16] The major diol has no such abnormal bands and is therefore assigned the structure **9**, which should exist preferentially as a chair–boat conformer.

The diol of intermediate abundance was shown to be identical with the formolysis product which Appleton, *et al.*,[9] assigned the structure **10**. A complete proof of structure for the diol has not been carried out, but the structure is assigned on the mode of formation. A single attempt to prepare the diol **10** by hydroboration of **3** + **4** was not successful. Compound **10** is expected to adopt a double-chair conformation, and in accord with our assignment the diol product has abnormal bands in the infrared at 2985 and 1485 cm^{-1}.[16] The third component of the diol fraction was isolated only in impure form and a complete spectral examination was not possible. However, it was oxidized by periodic acid, and on that basis was tentatively assigned the structure **11**.

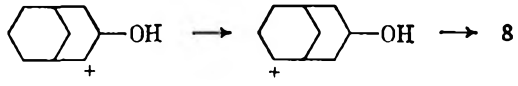
Discussion

The results of the present study are not particularly surprising, but they are revealing with respect to some aspects of the mechanism of transannular processes.

(15) V. N. Ipatieff, J. E. Germain, W. W. Thompson, and H. Pines, *J. Org. Chem.*, **17**, 272 (1952).

(16) G. Eglinton, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965).

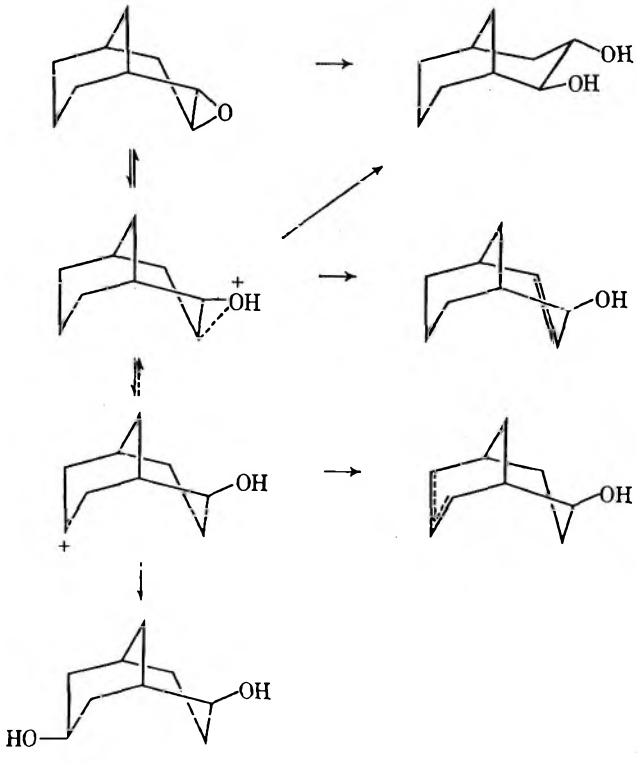
Consider first the probable routes to the products isolated from **1**. Clearly, ring opening of the epoxide occurs preferentially in the expected manner *via* cleavage of the equatoriallike C–O bond and retention of the axial. This is also favored by the formation of a carbonium ion at C_3 which eliminates the transannular C_3–C_7 hydrogen interactions. However, if our tentative structural assignments are correct, the presence of **8** and **11** indicates that cleavage in the reverse direction can occur, albeit much less readily. The formation of **8** would require a 1,3-hydrogen shift from C_8 to C_2. Schaefer and Honig[17] have found



evidence which points to this type of shift in a somewhat different case.

In view of the recent observation that solvolysis of *exo*-7-methyl-*exo*-3-bicyclo[3.3.1]nonyl tosylate shows no kinetic isotope effect when deuterium is substituted for the *endo* 7 hydrogen,[18] the route of Scheme I is suggested as the most likely for solvolysis

SCHEME I



of the bicyclic epoxide. Thus the initial protonated epoxide is converted into a carbonium ion which reacts either normally or transannularly. Complete absence of *cis*-1,2-diol in the product must mean that the hydroxyl at C_2 protects the carbonium ion from *exo* attack by the solvent, and that even in this relatively rigid molecule the protection is *complete*. Finally, the formation of the *exo*-2-*endo*-3-diol can be related to solvent attack from the *endo* side of the ion or to direct SN2 ring opening of the protonated epoxide by acetate ion. Either process requires an *endo* attack, which has no precedent in this ring system.

Comparison of these results with those of the solvolysis of *cis*-cycloocetene oxide (**12**) reveals several striking relations. As Table I shows, the bicyclic molecule shows an enhanced tendency to undergo elimination.

TABLE I

RESULTS OF SOLVOLYSIS OF *cis*-CYCLOOCTENE OXIDE (12) AND 1

Reactant	Solvent	Vicinal diol	Vicinal enol	Transannular diol	Transannular enol
12[a]	F_3COOH	...	...	56	43
1	F_3COOH	...	...	...	~100
12[a]	HCOOH	13	1	53	33
1[b]	HCOOH	24	2	36	36
12[a]	HOAc–OAc^-	77	...	9	11
1	HOAc–OAc^-	46	21	5	23

[a] Data from ref 8b. [b] Data from ref 9.

If, however, the ratio of vicinal to transannular product is considered, the two systems are very much alike, although the monocyclic reactant has a slightly greater tendency to undergo transannular reactions. This is quite different from the results with solvolysis of the tosylates, where the bicyclic molecule shows a dramatically reduced transannular reactivity.[19] Although this has been attributed[19] to the strain in the 3,7 hydrogen bridged transition state, the epoxide results suggest that the ratio of rates of transannular hydride shift *vs.* the collapse to normal products also plays an important role. Thus the strain relief in the transition state for elimination may increase this rate in the bicyclic system as compared with the cyclooctane case enough to reduce the competition by transannular shifts.

The results of acetolysis in the two systems shows that the rear side of the carbon atom at which displacement occurs is more available in the *cis*-cyclooctene oxide as compared with **1**. Also the absence of *cis*-1,2-diol in both systems indicates effective protection of the carbonium ion by the hydroxyl group in both cases. Finally, the analysis below indicates that the hydroxyl group may also play a further role in the transannular process.

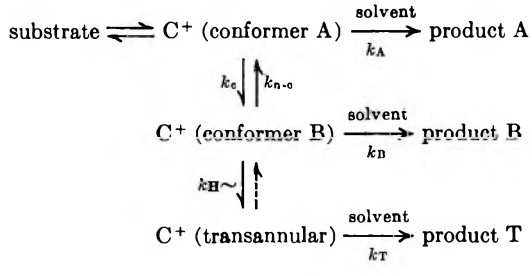
At present it is not possible to make an accurate conformational analysis of the *cis*-cycloocetene oxide solvolysis without making some assumptions. If we assume that **12** has a geometry only slightly distorted from one of the minima on the conformational surface described by Hendrickson,[20] it is possible to utilize his data for the analysis. Thus, if the geometry resembles the CC conformation, there would be four different positions for the epoxide. Ring opening of any one of these at an equatoriallike bond would lead to a carbonium ion which could pseudorotate in the TCC/CC system without loss of stereospecificity for transannular processes of 1,3 or 1,5 types. For all other pseudorotational systems, *i.e.*, BC/TBC, TC/C, and BB/S_4/B, a similar ring opening would give an ion whose pseudorotation would destroy the stereospecificity required (usually for the 1,3-hydride

(17) J. P. Schaefer and L. M. Honig, *J. Org. Chem.*, **33**, 2655 (1968).
(18) M. A. Eakin, J. Martin, W. Parker, C. Egan, and S. H. Graham, *Chem. Commun.*, 337 (1968).
(19) M. A. Eakin, J. Martin, and W. Parker, *ibid.*, 298 (1968).
(20) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7047 (1967).

shift).[21] It has been found[18] that *exo*-7-methyl-*endo*-3-bicyclo[3.3.1]nonyl tosylate undergoes transannular reactions to a moderate extent. This means that the initial carbonium ion, which is presumably a chair–boat conformer, must convert into the chair–chair conformer fast enough to permit the transannular hydride shift to compete with normal solvent reactions. If the transition state for this interconversion is assumed to lie at about the same energy level as that for the chair–boat interconversion in cyclohexane, then the finding[22] that the chair–boat form lies about 6.5 kcal/mol above the chair form of cyclohexane leads to a barrier of *ca.* 4–5 kcal for the bicyclic interconversion.

Among the general mechanistic schemes which must be considered for transannular reactions, one (Scheme II), which finds the substrate converted into a carbonium ion which can react with solvent directly but must undergo a conformational change before a transannular reaction can occur, is of considerable importance. For this mechanism the height of the energy barrier for conformational interconversion is of crucial importance. If it were too high, then $k_c < k_A$ and the transannular reaction would be excluded. The data above suggest that a barrier much in excess of 5 kcal/mol would exclude the transannular reaction. Thus in accounting for stereospecificity in a transannular reaction, conformational interconversions requiring energies above 5 kcal/mol might be ignored while those of lower activation energy would necessarily have to be taken into account. For cyclooctane chemistry Hendrickson's calculations[20] indicate that all pseudorotation processes would have to be considered but all symmetrical interconversion modes could safely be ignored. As a result the stereospecificity of the transannular reactions can be accounted for only if (a) the carbonium ion formed by ring opening falls into the TCC/CC conformational system, (b) the ion falls into another conformational system and the hydroxyl group restricts the pseudorotation, or (c) the conformations involved do not belong to any of the symmetrical ones studied by Hendrickson. Investigation of the alternative b is underway at present.

SCHEME II



Experimental Section

***exo*-2-*exo*-3-Epoxybicyclo[3.3.1]nonane (1).**—This compound was prepared by the method of Payne[10] using the directions of Marvell and Knutson.[22] The product, mp 182–183°, was purified by preparative layer chromatography and was obtained in *ca.* 30% yield.

***exo*-2-Bicyclo[3.3.1]nonanol (2).**—A mixture of 0.53 g (3.8 mmol) of **1** and 1.1 g (3 mmol) of lithium aluminum hydride in 45 ml of tetrahydrofuran was heated at 50° for 24 hr. A crude alcohol, mp 150–170°, was obtained from the mixture after hydrolysis of excess hydride and removal of the solvent. Glpc purification (silicone SF-96 at 148°) gave a single alcohol, mp 174–176° (lit.[11] mp 176–177°).

Trifluoroacetolysis of 1.—A cold solution of 3.6 g (26 mmol) of **1** in 25 ml of pentane was added to 36 ml of trifluoroacetic acid at 0°. The solution was stirred at 0° for 4 hr, after which a solution containing 28 g of sodium hydroxide in 125 ml of water was added. This mixture was stirred for 15 hr. The organic materials were extracted with ether, and the ether extracts were washed with saturated sodium sulfate solution. The ether layer was dried (K_2CO_3) and the ether was evaporated. The crude product was chromatographed over activity II/III alumina. Elution with benzene–ether gave an alcohol, mp 142–149°, which was further purified by sublimation: mp 150–151°; ir (CS_2) 3385 (br), 3040, 1096, 1060, 1040, 968, 955, and 715 cm^{-1}; nmr (CCl_4) δ 5.73 (m, 2 H), 3.77 (broad s, 1 H), 2.22 (s, 1 H), 2.20 (m, 2 H), 1.96 (m, 4 H), and 1.63 (br m, 6 H).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.99; H, 10.23.

Acetolysis of 1.—A solution of 93 mg (0.067 mmol) of **1** and 145 mg (1.7 mmol) of sodium acetate in 2.9 ml of glacial acetic acid was heated in a sealed tube for 73 hr at 100°. Water was added to the cooled reaction mixture, and the solution was extracted with ether. The dried ($MgSO_4$) extracts were treated with an excess of lithium aluminum hydride at 25° for 24 hr. Excess hydride was destroyed and the solution was treated with 0.1 *N* hydrochloric acid. The organic products were taken up in ether. The solution was concentrated *in vacuo* and analysis *via* glpc (12 ft × 0.125 in. 5% FFAP column at 193°) showed 47% enol and 53% diol. The diols separate in three peaks, **11** (2%), **9** (46%), and **10** (5%). Analysis of the enols on the same column showed three peaks, **7** (21%), **3** + **4** (23%), and **8** (3%).

Identification of Trifluoroacetolysis Product.—The enol mixture was obtained as a solid, mp 150–151°, as was described above. A sample of the enol (53 mg, 0.38 mmol) was hydrogenated over palladium on charcoal. The product was purified by sublimation, mp 176–179°, and was identical by both glpc analysis and spectral examination with an authentic sample of **2**.[23]

A further sample of enol, mp 134–141°, isolated from chromatography on alumina and sublimed once (79 mg), was dissolved in 20 ml of acetone. An aqueous solution containing 2.67 g of chromic anhydride and 2.3 ml of sulfuric acid in 10 ml of solution was added dropwise to the acetone solution cooled to −8° in an ice–salt bath. When the orange color persisted (*ca.* 0.25 ml of oxidant), the solution was stirred for 20 min and a few drops of methanol were added. The solution was diluted with water and neutralized with sodium bicarbonate. Organic products were taken up in ether and the solution was dried ($MgSO_4$). Evaporation of the ether gave 80 mg of solid which showed a single peak on glpc (5% SE-30 on Chromosorb W). After sublimation, 49 mg of white solid, mp 55–68°, was obtained: λ_{max} 297 nm (ε *ca.* 100); nmr (CCl_4) δ 5.8 (d, 2 H), 2.8 (m, 0.2 H), and 2.6–1.0 (m, *ca.* 10 H).

Stability of 7 in Trifluoroacetic Acid.—An impure sample of **7**, mp 127–131°, isolated from the acetolysis product by preparative gas chromatography, was stirred with trifluoroacetic acid at 0° for 4 hr. The reaction mixture was worked up as described under the solvolysis and the product was purified by sublimation. The infrared and nmr spectra were identical with those of the starting material.

Identification of Acetolysis Products.—The acetolysis product was separated into diol and enol fractions either by column chromatography (alumina activity II/III, benzene–ether followed by methanol) or preparative layer chromatography [alumina Merck PF_{254}, methylene chloride–methanol (95:5)].

Diol Fraction.—The diol fraction was separated into three components by preparative layer chromatography. One component (5%) separated on the alumina plate with methylene chloride–methanol (95:5). The other two (2% and 46%) were separated using alumina with methanol as eluent.

The 5% component (10) was a white crystalline solid: mp 215–216° after sublimation and recrystallization from ethanol (lit.[9] mp 204°); ir (CCl_4) 2985, 2920, 2885, 2875, 2854, 1485, 1466, and 1446 cm^{-1}; ir (KBr) 3350, 1355, 1280, 1265, 1090 (s),

(21) It should be noted that **12** gives only *cis*-1,4-cyclooctanediol, and that this is formed by both 1,5- (61%) and 1,3-hydride shifts (39%)[8c]

(22) E. N. Marvell and R. S. Knutson, *J. Org. Chem.*, **35**, 388 (1970).

(23) We are indebted to Dr. Jack Martin, The University, Glascow, for furnishing us with spectral data on this compound for comparison purposes.

1062 (s), 998, 973 (s), 956 (s), and 902 (s) cm^{-1}; nmr ($CHCl_3$) δ 3.9 (br s, 2 H), 3.5 (br unresolved m, 2 H), 2.0 (m, 5 H), and 1.61 (br s, 7 H). A sample of **10** was prepared according to the directions of Appleton, *et al.*,[9] and spectral comparison showed it to be identical with the 5% diol above.

The 2% component (**11**) was not isolated in pure form, being contaminated with stopcock grease and traces of alumina. This crude material (84 mg) was stirred at 25° with 75 ml of 0.0125 *M* potassium periodate solution and 7.5 ml of 2.0 *N* sulfuric acid for 24 hr. Titration according to the directions given by Jackson[24] showed that periodate equivalent to 17.4 mg of diol was consumed.

The 46% component (**9**) was isolated as a crystalline solid and was purified by sublimation: mp 118–121°; ir (KBr) 3320, 1150 (w), 1074, 1052 (s), 1034, 1008 (s), 996, 906, and 720 cm^{-1}; ir (CCl_4) 2930, 2872, 2856, 1468, and 1456 cm^{-1}; nmr ($CHCl_3$) δ 4.05 (br s, 2 H), 3.49 (m, 2 H), 2.16 (m), 1.93 (br s), 1.58 (br s), and 1.0–2.4 (12 H).

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.48; H, 10.38.

A sample (118 mg, 0.76 mmol) of this diol was oxidized with periodate as described above. In 24 hr at 25°, 113% of the theoretical amount of periodate was consumed. The reaction mixture was concentrated *in vacuo*, saturated with sodium chloride, and extracted with chloroform. The extracts were dried ($MgSO_4$) and the solvent was evaporated to give 130 mg of solid, mp 154–156°, which reacted with dinitrophenylhydrazine and showed bands in the infrared at 2710 and 2810 cm^{-1}. Treatment of the crude material with 30% hydrogen peroxide gave a crystalline acid, mp 153–155° (lit.[15] mp 150–152°).

Enol Fraction.—Glpc examination of the enol fraction showed three components. The major component (23% of the solvolysis product or 50% of the enol fraction) was shown by glpc comparison (12 ft × 0.125 in. 5% FFAP column at 145°) to be identical with the main component of the trifluoroacetolysis, *i.e.*, **3** + **4**. The minor component (3% of the solvolysis product or 6% of the enol fraction) was not isolated, but was shown by glpc comparison to be different from the hydride reduction products of either **5** or **6**.

A sample of the enol fraction (110 mg) was hydrogenated over palladium on charcoal in methanol solution. The main product was collected from a preparative gas chromatographic run: mp 176–178°; ir 3400, 2980, 1480, 1040, 982, 963, and 910 cm^{-1}. The spectral data and melting point identify this as **2**.

Partial separation of the two main enol components was achieved in a preparative scale gas chromatography run on 5 ft × 0.25 in. 20% SE-30 on Chromosorb W column at 90°. A crude sample enriched in component **7** (21% of the solvolysis mixture) was obtained: mp 127–131°; ir (CCl_4) 3620, 3360 (br), 3020, 2920, 1458, 1446, 1250, 1220, 1067 (w), 1045 (m), and 985 cm^{-1} (s); nmr (CCl_4) δ 5.5–6.0 (m, 2 H), 3.82 (unresolved, 1 H), 2.23 (m), 2.08 (s, 1 H), 2.0 (m), 1.5 (br s), and 1.2–2.4 (11 H). Compound **7** is reported[11] to melt at 103–103.5°, but the overlap between the peaks for enols **3** + **4** and **7**, even on an analytical level, prevented isolation of pure **7** on a preparative scale.

A portion of this enol (125 mg) was treated with 200 mg of chromium trioxide in 5 ml of pyridine at 25° for 14 hr. The solution was diluted with ether and an excess of water was added. The ether layer was separated and passed through an activity IV alumina column. The ether eluate was concentrated and the ketonic products were separated by preparative gas chromatography (10% SF-96 on silanized Chromosorb at 114°). The main product was isolated as a white solid: mp 98–100° (lit.[11] mp 97.5–98.5°); ir (CCl_4) 1675 cm^{-1}; uv λ_{max} 235 nm; nmr (CCl_4) δ 6.89, 6.12 (modified AB, 2 H, J_{AB} = 9.8 Hz), and 1.5–2.8 (m, 10 H).

Registry No.—**1**, 13366-99-9; **9**, 22485-96-7.

(24) E. L. Jackson, *Org. Reactions*, **2**, 341 (1944).

The Lactonization of Camphene-8-carboxylic Acid

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Received March 11, 1969

Whereas lactonization of camphene-8-carboxylic acid with formic acid has been reported to give β lactone **2**, the initial product has been identified as the γ lactone **3**. The structure and configuration of bornane-1-carbo-2-*exo*-lactone (**3**) have been established by conversion with excess phenyllithium into the same glycol **10** as obtained from 10-benzoyl-2-*exo*-bornanol (**9**) with excess phenylmagnesium bromide. The configuration of **8**, previously reported as the *endo* alcohol, was proven by degradation to isoborneol (2-*exo*-bornanol). A second lactone, *exo*-2,3-dimethyl-*endo*-3-hydroxynorbornane-*endo*-2-acetic acid lactone (**4**), is produced from **1** and **3** on longer heating with formic acid or prolonged standing with trifluoroacetic acid. A third lactone, *endo*-2,3-dimethyl-*exo*-3-hydroxynorbornanane-*exo*-2-acetic acid lactone (**5**), is also formed in small quantity. Lactone **5** is the major or exclusive product when **1**, **3**, or **4** are treated with 10% sulfuric acid–formic acid for 6.5 hr, 50% sulfuric acid, or concentrated sulfuric acid, respectively. The structure and configuration of lactone **5** have been unequivocally established by degradation to 9-methylcamphene, which has been synthesized by a stereospecific reaction sequence. Convenient syntheses of optically active **1** from nopol (10-hydroxymethyl-α-pinene) and camphene *via* camphene-8-methanol are described, and it is noted that lactonization of optically active **1** is accompanied by complete racemization. Deuterium exchange reactions involving **1** and the lactones **3**, **4**, and **5** are described and a probable mechanistic pathway from **1** to the lactones is suggested. Finally, hydrochlorination of **1**, previously described by Langlois, is shown to produce *exo*-2-chlorocamphane-10-carboxylic acid rather than the reported 2-chloro-3,3-dimethylbornane-2-acetic acid.

For a number of years, studies in one of these laboratories have been concerned with the various types of rearrangements encountered in the camphane–isocamphane systems[3–5] with particular attention to camphene racemization,[4,5] while studies in the other laboratory have been concerned with devising simple synthetic routes to certain terpene intermediates.[6] In the course of these studies the attention of both groups of investigators was attracted independently to a paper

(1) Work supported in part by Public Health Service Grants CA 05406 and 10202 from the National Cancer Institute and a Faculty Research Grant from the Horace H. Rackham School of Graduate Studies, The University of Michigan. Inquiries should be addressed to W. R. Vaughan, The University of Connecticut or J. Wolinsky, Purdue University.

(2) Abstracted in part from Ph.D. dissertations The University of Michigan, by F. S. Seichter, 1959, and R. R. Dueltgen, 1967, and by S. Grey, 1968, Purdue University.

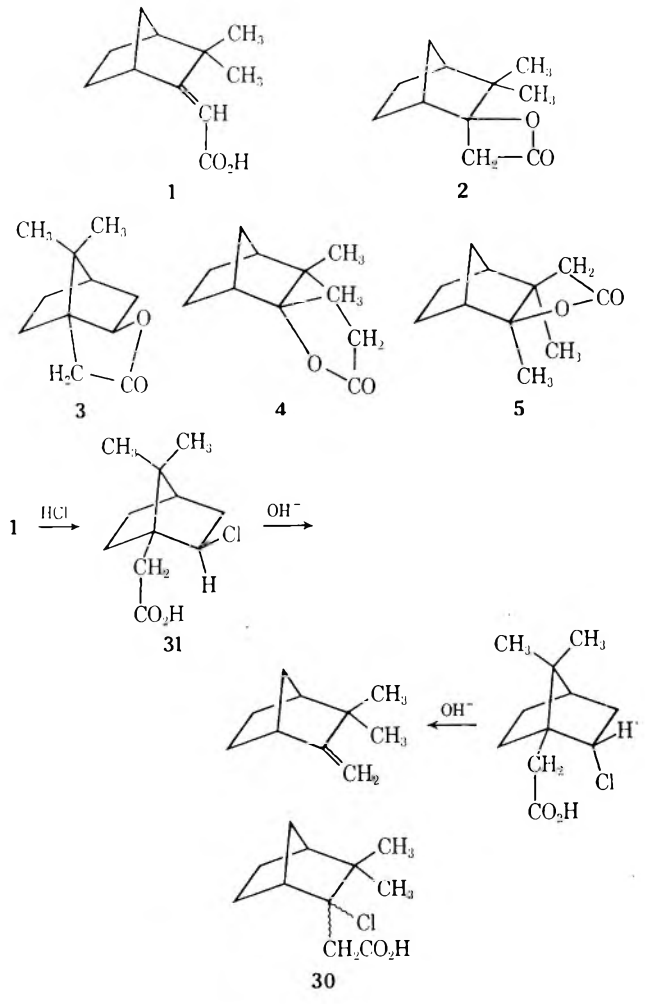
(3) W. R. Vaughan and R. Perry, Jr., *J. Amer. Chem. Soc.*, **74**, 5355 (1952).

(4) W. R. Vaughan and R. Perry, Jr., *ibid.*, **75**, 3168 (1953).

(5) W. R. Vaughan, C. T. Goetschel, M. H. Goodrow, and C. L. Warren, *ibid.*, **85**, 2282 (1963).

(6) J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).

by Langlois[7] in which camphene-8-carboxylic acid (**1**) was converted by treatment with formic acid or formic–sulfuric acids into a substance with unspecified optical properties alleged to be β lactone **2**. In view of the unusual stability of this lactone, both groups were prompted to reexamine the lactonization of camphene-8-carboxylic acid, and it may now be jointly reported that, depending upon conditions, one or more of three different lactones, **3**–**5**, are produced. In this paper the structures of these lactones will be delineated and probable pathways for their formation will be considered.



The conditions described by Langlois[7] for the lactonization of acid **1** were followed explicitly and solids were obtained whose melting points corresponded exactly with those reported. When acid **1** was heated for 1–2 hr in 90% formic acid[7] or allowed to stand at ambient temperature in trifluoroacetic acid for 3 days, a lactone mixture was produced from which pure lactone **3**, mp 198.5–199.5°, could be obtained by recrystallization. Examination of the nmr spectrum of the mother liquors from the formic acid lactonization demonstrated the presence of lactone **4**. As shown in Table I, optimum conditions for the production of lactone **3** involve heating acid **1** for 1–2 hr in formic acid or allowing it to stand in trifluoroacetic acid for 2–3 days. Optically active acid **1** gave optically inactive **3** using these methods.

(7) G. Langlois, *Bull. Soc. Chim. Fr.*, **41**, 384 (1927).

Conditions which favor the production of lactone **4** as the major lactonic product (see Table I) include allowing acid **1** to stand in trifluoroacetic acid for any length of time in excess of 9 days, heating it with formic acid or trifluoroacetic acid for longer than 3–4 days, or heating it with 10% sulfuric acid in 90% formic acid[7] for 30–90 min. Lactone **4** is readily isolated in pure form by recrystallization from pentane.

TABLE I

LACTONIZATION OF CAMPHENE-8-CARBOXYLIC ACID (**1**)

Conditions	Time	Lactone 3, %	Lactone 4, %	Lactone 5, %
90% formic acid	1 hr	28.2	18.8	
at 100°	2 hr	31.1	25.2	
	6 hr[a]	20.5	41.9	?
	4 days	9.9	73.1	?
	10 days	6.5	81.0	?
	14 days		84.5	15.5
CF_3CO_2H at 25°	2 hr	9.0		
	6 hr	12.3	1.7	
	16 hr	23.8	3.2	
	2 days	50	9.4	
	6 days	46.4	42.8	
	9 days	41.7	54	
	15 days	26.4	73.6	
	25 days		100	Trace
CF_3CO_2H at 72°	3.5 days		79.4	21.6
10% H_2SO_4 in	0.5 hr		92	9
formic acid	1.0 hr		82.5	17.5
	3.0 hr		57	43
	6.5 hr		37	63
50% H_2SO_4	0.5 hr		47	53
	1.0 hr		45	55
	2.0 hr		25.6	74.4
95% H_2SO_4 at 0°	6 hr		11	89

[a] An unknown product with a methyl resonance at δ 0.8 ppm builds up to a maximum of 25% at 6 hr and disappears slowly thereafter.

Prolonged heating of acid **1** with 10% sulfuric acid–90% formic acid, heating it at 150° with 50% sulfuric acid, or allowing it to stand at 0° with 95% sulfuric acid for 6 hr gives lactone **5** as the major product.

Finally, it was observed that treatment of α-pinene-10-carboxylic acid with trifluoroacetic acid for 4 months gave a poor yield of a lactone mixture which appeared to be predominantly lactone **4**.

The three lactones, whose properties are listed in Table II, are isomeric and presumably arise as a consequence of rearrangements common to the extremely labile bicyclic systems from which they are necessarily derived. We turn next to explicit proofs of structure for each of the lactones.

TABLE II

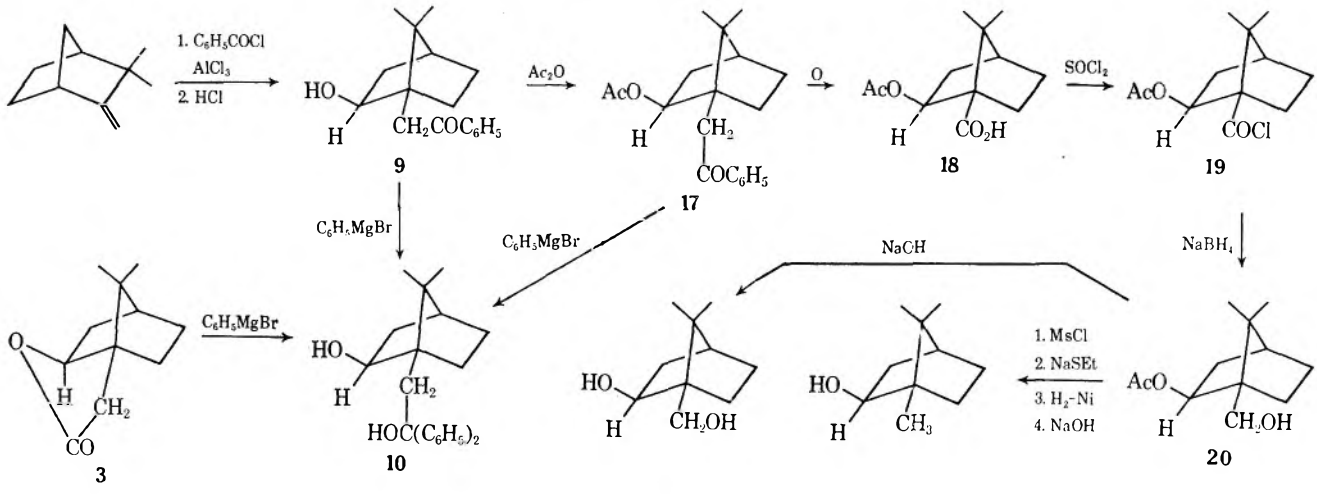
PROPERTIES OF LACTONES **3**–**5**

Lactone	Mp, °C	Ir carbonyl stretch, μ	Glpc[a] retention time, min	Nmr[b] CH_3CCH_3	Nmr[b] HCO
3	198.5–199.5	5.65	19.8	0.94	4.19
				0.98	
4	170–171	5.65	20.6	1.16	
				1.32	
5	157–161	5.65	27.6	1.12	
				1.32	

[a] DEGS at 175°, 12 psi, 10-ft column. [b] δ in parts per million (60 Mc, internal TMS).

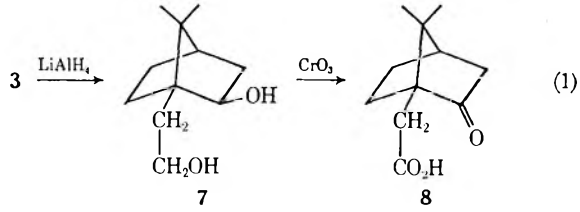
SCHEME I

CONFIGURATION PROOF FOR 3 AND 9



Examination of the infrared spectrum of **3** immediately disposed of Langlois' β-lactone hypothesis, since the carbonyl absorption corresponds to that characteristic of a typical γ lactone. If **1** experiences a rearrangement typical of the camphene system, it seemed likely that **3** should be identical, except for its lack of optical activity, with a lactone obtained by Bain[8] as a minor product of treatment of *endo*-2-chlorocamphane-10-carboxylic acid (**6**) with base. Comparison of infrared spectra of optically inactive **3** and optically active lactone kindly furnished by Dr. Bain established the identity of the two lactones, and consequently provided a strong inference as to the structure of **3**.

Further inferences regarding the structure of **3** are possible. The skeletal arrangement is confirmed by lithium aluminum hydride reduction to 10-hydroxymethylisoborneol (**7**), which was oxidized according to the Jones procedure[9] to the known camphor-10-carboxylic acid (**8**) (eq 1), and the *exo* configuration



(1)

of the oxygen at C-2 in 3 is suggested by the nmr spectrum of diol **7**, in which the multiplicity of the C-2 proton is characteristic of an *endo* 2 proton and the substantial nonequivalence of the geminal methyl groups is typical of bornane derivatives with an *exo* hydroxyl group.[10]

The configuration of **3** was definitively established *via* the following correlation. The reaction product of camphene with benzoyl chloride in the presence of aluminum chloride upon hydrolysis, had been reported as 10-benzoylborneol,[11] whereas its degradation to isoborneol (Scheme I) requires that it be 10-benzoylisoborneol (**9**). Originally, it was planned to degrade **3** *via* the Barbier–Wieland procedure, and to this end it was converted by treatment with excess phenylmagnesium bromide into 10-(diphenylhydroxymethyl)isoborneol (**10**), which could also be obtained by treatment of **9** or its acetate with excess phenyllithium, thereby establishing both structural and configurational relationships between **3** and **9**. Unfortunately the attractive prospect of such a degradation could not be realized directly. Thus simple dehydration of **10** afforded a cyclic ether **11**, and acetylation of the secondary hydroxyl yielded the glycol monoacetate **12**, which upon dehydration afforded 10-benzhydrylideneisobornyl acetate (**13**), which failed to react with ozone, as did its hydrolysis product, 10-benzhydrilideneisoborneol (**14**). Nor was it possible to oxidize the double bond in **13** or **14** with any other reagent. On the other hand, **14** could be oxidized to 10-benzhydrilidenecamphor (**15**) by Jones reagent,[9] and sodium borohydride reduction of **15** regenerated **14**. The only reaction affecting the double bond in this system was catalytic hydrogenation of **13** to give 10-benzhydrylisobornyl acetate (**16**).

However, **9** was readily acetylated to a 10-benzoylisobornyl acetate (**17**), and **17** could be oxidized, albeit in poor yield, to *exo*-2-acetoxyapocamphane-1-carboxylic acid (**18**).[12] Conversion of the carboxyl group into methyl involved acid chloride (**19**) formation, reduction by sodium borohydride to the carbinol **20** (which upon hydrolysis of the acetate afforded the known 10-hydroxyisoborneol[13,14]), and an adaptation of Stork's conversion of hydroxymethyl groups in the cantharidine synthesis[15] into the present system. Identification of the final product as isoborneol was accomplished by comparison of infrared spectra, melting points, and mixture melting points and preparation and comparison of *p*-nitrobenzoates. This degradation (see Scheme I) explicitly defines the configuration of the lactone **3** as well as that of 10-benzoylisoborneol (**9**).

We turn next to the gross structures of lactones **4** and **5**. Both lactones displayed the characteristic

(8) J. P. Bain, A. H. Best, B. L. Hampton, G. A. Hawkins, and J. L. Kitchen, *J. Amer. Chem. Soc.*, **72**, 3124 (1950).

(9) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

(10) J. Musher, *Mol. Phys.*, **6**, 93 (1963).

(11) P. Lipp, P. Küppers, and H. Holl, *Chem. Ber.*, **60**, 1575 (1927).

(12) P. Lipp, H. Bräucker, and H. Sauer, *ibid.*, **73**, 1146 (1940).

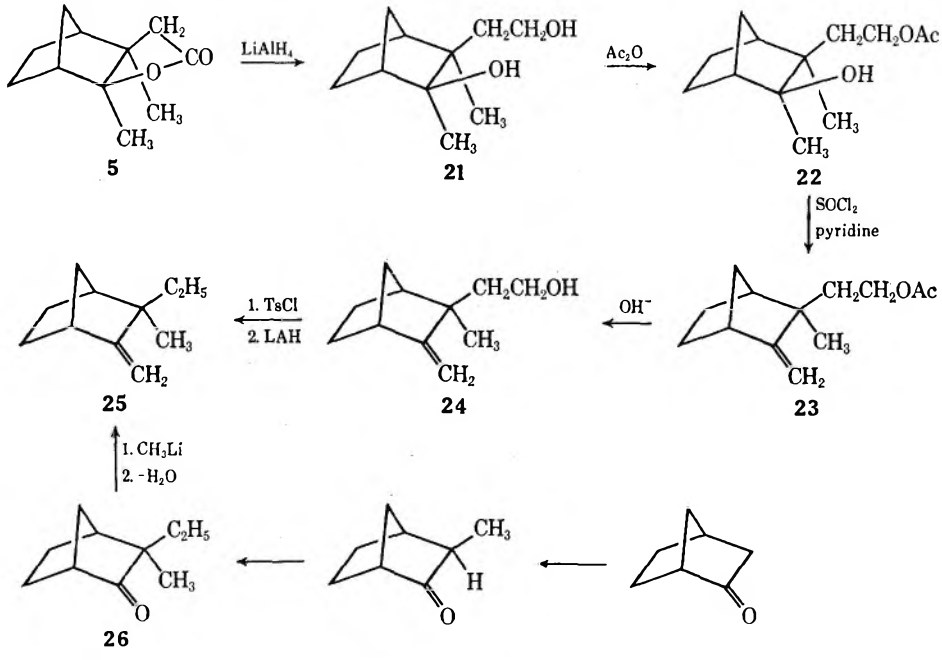
(13) B. A. Arbuzov and Z. G. Iseva, *Zh. Obshch. Khim.*, **21**, 1250 (1954).

(14) T. Kuusinen, *Suomen Kemistilehti, B*, **31**, 179 (1958).

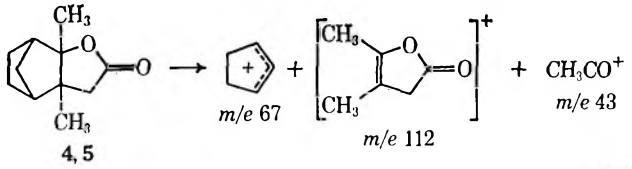
(15) G. Stork, E. E. Van Tamelen, L. J. Friedman, and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **75**, 384 (1953).

SCHEME II

STRUCTURE PROOF FOR 5



γ-lactone absorption of 5.65 μ, which eliminates possible formulations involving a δ-lactone ring. The nmr spectra of lactones **4** and **5** exhibit two distinctive singlet methyl resonances (see Table II) and wholly lack a signal for a proton on an oxygen-bearing carbon atom. The mass spectra of **4** and **5** are almost identical and show abundant ions at *m/e* 43, 67, and 112 which correlate[16] with the breakdown pattern shown in eq 2. Taken together, these observations establish



(2)

the gross structures for both compounds, and, since a *trans* ring junction is extremely unlikely, it is reasonable to infer that one isomer is the *endo,cis* lactone **4** while the other is the *exo,cis* lactone **5**.

The structure and configuration of lactone **5** are definitively established by the following transformations (Scheme II). Lithium aluminum hydride reduction of **5** afforded the crystalline diol **21**, which was converted into the monoacetate **22** by reaction with acetic anhydride and a catalytic amount of pyridine. Dehydration of **22** with thionyl chloride in pyridine gave 9-acetoxymethylcamphene (**23**). This was converted *via* 9-hydroxymethylcamphene (**24**) into the tosylate, which was then reduced with lithium aluminum hydride to 9-methylcamphene (**25**), identical with an authentic sample obtained from *exo*-3-ethyl-*endo*-3-methylnorbornan-2-one (**26**).[6,17] This series of reactions unambiguously establishes the *exo* ring fusion of lactone **5** and by inference establishes an *endo* ring fusion for lactone **4**.

Prior to the availability of nmr and mass spectrometric data, it was thought that **4** might possibly be the *endo* isomer of **3**. Samples of **4** prepared from α-pinene[18-20] or from nopol (10-hydroxymethyl-α-pinene) resisted crystallization. However, it was possible to treat the impure **4** with excess phenylmagnesium bromide and obtain the same glycol (**27**) as could be similarly prepared from pure samples of **4**, thus confirming the product identity of isomerizations of **1** and α-pinene-10-carboxylic acid. Attempts to monoacetylate this glycol (**27**) were for the most part unproductive, cyclization to an ether **28** occurring readily. However, in one attempt a very small amount of glycol monoacetate **12** was isolated. It is possible that this arose from slight contamination of the original lactone **4** with lactone **3**, but it is just conceivable that a retro rearrangement occurred. Experimentally most significant is the fact that 10-benzhydrilidenecamphor (**15**) can be reduced under equilibrating conditions with aluminum isopropoxide to 10-benzhydrilideneborneol (**29**), whose nmr spectrum, as expected, exhibits a signal for a proton on oxygen-bearing carbon, whereas no such signal is present in the nmr spectrum of either **4** or **27**. Thus the original hypothesis had to be abandoned, and structural and configurational proofs for **4** depend upon its relationship to **5** as suggested by the nmr and mass spectrometric data cited above.

Langlois[7] claimed that the addition of hydrogen chloride to camphene-8-carboxylic acid (**1**) gave chloro acid **30**. The nmr spectrum of this compound (see Experimental Section) demonstrates that it should be reformulated as the *exo*-chloro acid **31**. Like the *endo*-chloro acid **6**,[8] the *exo* isomer **31** is largely transformed

(16) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 2735 (1967).

(17) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *J. Amer. Chem. Soc.*, **84**, 2611 (1962).

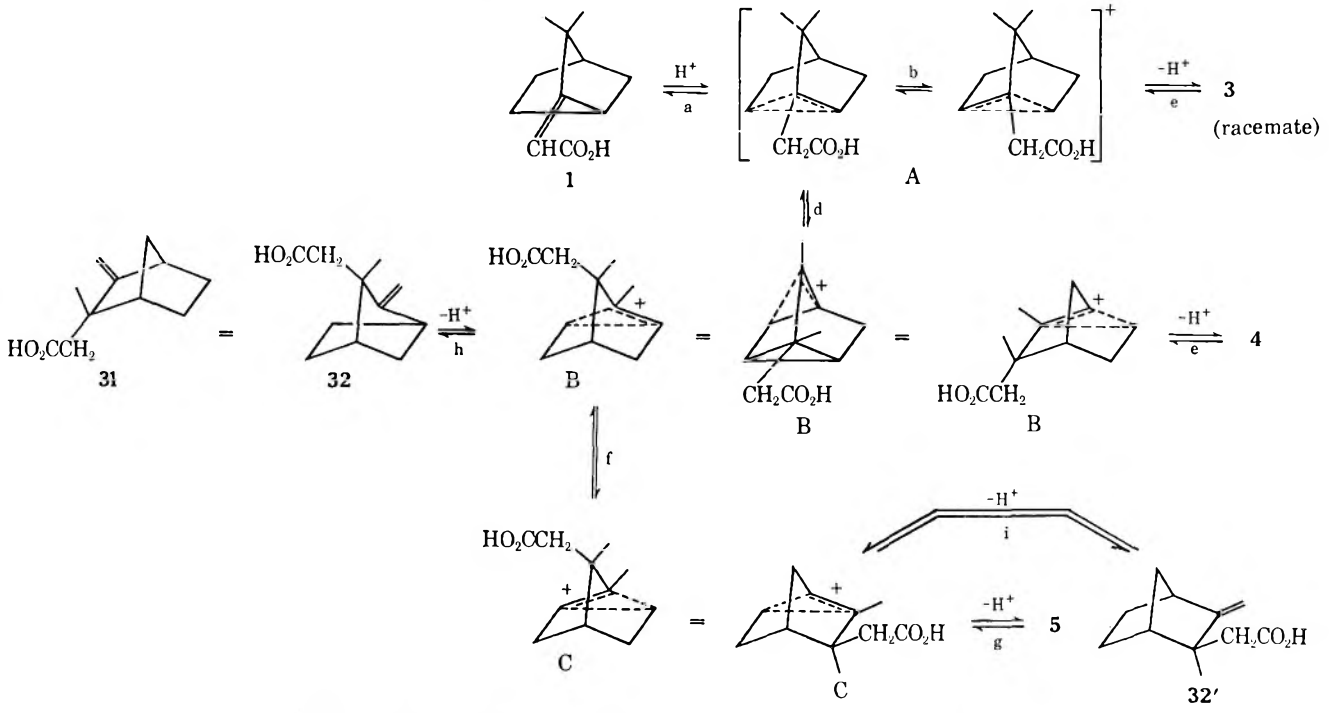
(18) V. N. Ipatieff, C. J. Czajkowski, and H. Pines, *ibid.*, **73**, 4098 (1951).

(19) H. Rupe and H. Hertier, *Justus Liebigs Ann. Chem.*, **459**, 171 (1927).

(20) D. Tishchenko, N. Persiantseva, and V. Foliadov, *J. Gen. Chem. USSR*, **22**, 1829 (1952).

SCHEME III[a,b]

LACTONIZATION–REARRANGEMENTS



[a] Steps are as follows: a, protonization and bridging; b, 2,6-hydride shift (+A → − A); c, ring closure and deprotonizaton (A → **3**); d, *exo*-methyl shift (A → B); e, ring closure and deprotonization (B → **4**); f, 2,6-hydride shift (B → C); g, ring closure and deprotonization (C → **5**); h and i, deprotonization. [b] Note that the lower case letters apply to the forward reactions (*e.g.*, A → B). The lettered ions are pictured as nonclassical ions for convenience only.

TABLE III

THE ACTION OF ACIDS ON LACTONES **3–5**

Lactone	Conditions	Time	Lactone 3, %	Lactone 4, %	Lactone 5, %
3	10% H_2SO_4 in HCO_2H at 100°	0.5 hr	...	90.8	9.2
		1.0 hr	...	82.5	17.5
		2.0 hr	...	71.8	28.2
		3.0 hr	...	56.9	41.8
		6.5 hr	...	37.4	62.6
	50% H_2SO_4 at 150°	2.5 hr	...	21.0	79.0
4	50% H_2SO_4 at 150°	2.5 hr	...	23.8	76.2
5	90% HCO_2H at 100°	3.0 days	...	...	100.0
5	Refluxing CF_3CO_2H	3.0 days	...	...	100.0
5	10% H_2SO_4 in HCO_2H at 100°	3.0 hr	...	...	100.0
5	50% H_2SO_4 at 150°	2.0 hr	...	...	100.0

into camphene when treated with sodium carbonate in water.

Possible Reaction Paths.—Examination of Table I demonstrates that camphene-8-carboxylic acid (**1**) is first converted into lactone **3**, which is then transformed into lactone **4** with passage of time. Lactone **5** only appears much later in the reaction sequence and is only an important product when sulfuric acid is present or the mixture in trifluoroacetic acid is heated for some time. Control experiments (Table III) confirm the reaction sequence **1** → **3** → **4** → **5**. Thus, bearing in mind that starting with optically active **1** only racemic products are obtained, it becomes possible to delineate the sequence of mechanistic steps (Scheme III).

The lactonization of acid **1** in deuteriotrifluoroacetic acid was followed by nmr spectroscopy and the resulting lactone **4** was isolated and analyzed by mass spectroscopy. Little, if any, deuterium exchange of the olefinic proton in acid **1** was noted, suggesting that protonation of acid **1** is a rate-determining step which triggers the Wagner–Meerwein rearrangement and accompanying 6,2-hydride shift which culminate in the formation of lactone **3**. The slower rate of lactonization in the deuterated acid ($k_H/k_D \cong 2$) is in accord with this assumption. Mass spectrometric analysis of lactone **4**, which eventually is produced, demonstrated it to be a mixture of d_1–d_5 isomers with the d_2 and d_3 compounds accounting for *ca.* 60% of the mixture. At least two deuterium atoms were located at the carbon atom α to the carbonyl group, and the presence of ions in the region of m/e 43–46 placed the remaining deuterium atoms in the CH_3CO group. This is supported by the integrated values for the methyl groups in the nmr spectra (see Experimental Section). This conclusion was confirmed by the examination of the mass spectrum of lactone **4**-d_2, prepared by the exchange of the hydrogens α to the carbonyl group using sodium methoxide in CH_3OD. Incorporation of deuterium into the methyl group most likely proceeds by way of unsaturated acid **32**.

Extensive exchange of CH_3CO and CH_2CO_2 hydro-

gens occurred when lactone **3** was heated for 3 days in deuteriotrifluoroacetic acid. This observation suggests the existence of an equilbrium between lactone **4**, ion B, and unsaturated acid **32** in this solvent. Deuterium exchange also took place with lactone **5** under the same conditions, but to a much lesser extent in the CH_3CO group. This is in accord with the greater thermodynamic stability of lactone **5** and its lesser tendency to revert to ion C.

Since only racemic products (lactones) are obtained, and since rate control appears to be vested in protonation of **1**, it can be assumed that reaction b is a relatively rapid one, reaction c being slower than b but faster than a; *i.e.*, that lactone **3** is the primary kinetically controlled product.

Lactone **4** appears later in the course of reaction and, given the proper conditions, can be isolated essentially free of **3** or **5**; it can be formed (without isolation of **3**) from **1** or from **3**. Therefore, one may postulate that, under the reaction conditions used, **4** is thermodynamically more stable than **3**, while the energy barrier in reactions d and e is higher than that in reactions a–c. Otherwise, **4** would be formed more readily than **3**.

Finally, since **5** does not revert into other members of the series, it must be assumed that, under conditions leading to its formation, **5** is the most stable lactone and that the energy barrier in reactions f and g is still higher than that in reactions d and e. In other words, the thermodynamic stabilities of the acid **1** and lactones **3–5** are in the order $1 < 3 < 4 < 5$ and the energy barriers for the conversions are in the order $1 \rightarrow 3 < 3 \rightarrow 4 < 4 \rightarrow 5$. Racemization of A (reaction b) is probably the fastest reaction, and the principal energy barriers are probably to be associated with reactions a, d, and f, since there is no *a priori* reason why the ring-closure deprotonation reactions (c, e, and g) should have markedly different energy requirements or even be involved until actual work-up. Thus bridging (*i.e.*, Wagner–Meerwein rearrangement) appears to be easier than an *exo*-methyl shift (Nametkin rearrangement), which in turn is easier than a 2,6-hydride shift. If these inferences are valid, then the most notable situation is the implied large difference in ease of accomplishment between the two 2,6-hydride shifts (b and f), one being the fastest reaction (interconversion of enantiomers) and the other the slowest reaction (interconversion of epimers) in the sequence.

There are, of course, four additional lactones which could form in these transformations; one, a δ lactone, could be produced from ion C (Scheme III), and three, bornane-8-carbo-3-*exo*-lactone, 1,2-dimethylnorbornane-2-*exo*-acetic acid 3-*exo*-lactone, and 1,2-dimethylnorbornane-2-*endo*-acetic acid 3-*endo*-lactone, could be produced from an ion, not shown, formed from ion C by a 3,2-hydride shift. However, lack of signals for a proton on a carbon atom bearing an oxygen atom (except those exhibited by lactone **3**) in all nmr spectra rules out these lactones, as it does the C-2 epimer of lactone **3**.

Failure to obtain a δ lactone is consistent with the greater thermodynamic stability of γ lactones relative to δ lactones and is paralleled by the formation of γ lactones in the lactonization of teresantalic acid,[21] 2,3-dimethyl-3-hydroxynorbornane-2-carboxylic acid,[22] tricycloekasantalic acid,[23,24] and the isomeric bicycloekasantalic acids.[24]

In summary, the lactonization of camphene-8-carboxylic acid (**1**) involves a rapid, reversible Wagner–Meerwein rearrangement accompanied or followed by a 6,2-hydride shift, followed by a slower exclusive *exo*-methyl Nametkin migration. The *exo* lactone **5** would appear to be most readily accessible by an *endo*-methyl shift in ion A or related classical counterparts. However, there is to date no compelling evidence in support of an *endo*-methyl migration in the norbornane series, whereas *exo*-methyl migration is well documented.[25] Lactone **5** is most likely produced from ion B *via* ion C or classical counterparts.

Experimental Section

Camphene-8-carboxylic Acid (1).—The racemic acid was prepared most conveniently by the oxidation of camphene-8-methanol obtained by the reaction of camphene with formaldehyde. Compound (−)-**1**, of high optical purity, was obtained from nopol utilizing a modification of Bain's procedure.[8]

A.[26]—A solution of 200 g (1.47 mol) of camphene, 47 g (1.56 mol) of paraformaldehyde, 20 ml of acetic anhydride, and 300 ml of glacial acetic acid was heated at reflux for 48 hr. Most of the acetic acid was distilled at atmospheric pressure and the residue was distilled under diminished pressure to give 170.0 g of β-acetoxymethylcamphene, bp 90–104° (1.5 mm), and 30.0 g of a mixture of 10-acetoxymethylisobornyl acetate and another unidentified acetate, bp 135–141° (1.5 mm).

From 8.0 g of (+)-camphene, $[\alpha]^{29}D$ +35.8°, there was obtained 5.5 g of 8-acetoxymethylcamphene, $[\alpha]^{29}D$ +29.4° {lit.[27] $[\alpha]^{25}D$ +18.9° from (+)-camphene, $[\alpha]^{25}D$ + 25.5°}.

Alkaline hydrolysis of (±)-8-acetoxymethylcamphene gave 39.4 g (82%) of (±)-camphene-8-methanol: bp 85–93° (1.8 mm); $n^{23}D$ 1.5028; ir 3.0 and 6.01 μ; nmr δ 1.02 and 1.04 (s, 6, CH_3CCH_3), 0.85–1.97 (complex m), 2.87 (s, 1, C-1 H), 3.45 (s, 1, OH), 4.0 (d, 2, J = 7 Hz, CH_2OAc), and 5.1 ppm (t, 1, J = 7 Hz, HC=C).

To an ice-cooled solution of 20.0 g of camphene-8-methanol in 50.0 ml of pure acetone was added 60 ml of 8 *N* chromium trioxide in sulfuric acid–water. After the solution was stirred for 30 min, the excess oxidant was destroyed with isopropyl alcohol. After the usual work-up, distillation gave 16.5 g of (±)-8-formylcamphene: bp 128–130° (12 mm) [lit.[28] bp 130° (12 mm)]; ir 5.95 and 6.01 μ; λ_{max} 235 mμ (ϵ 11,200).

The 2,4-dinitrophenylhydrazone of this aldehyde was crystallized from ethanol–ethyl acetate, mp 201–203°.

8-Formylcamphene, 16.5 g, was placed in a large beaker and kept in contact with air for 5 days. The partially solidified mixture was taken up in ether and extracted with 5% sodium carbonate solution. The basic solution was acidified and extracted with ether. The ether was removed and the residue was recrystallized from hexane to give 11.0 g of (±)-camphene-8-carboxylic acid: mp 122–124°; nmr 1.10 (s, 2-CH_3), 4.04 (s, C-1 H), 5.44 (s, HC=C), and 11.86 ppm (s, CO_2H). The acid **1** obtained from partially active (±)-8-acetoxymethylcamphene exhibited $[\alpha]^{29}D$ −49.8°.

B.[29]—The direct addition of hydrogen chloride to nopol (instead of to the acetate of nopol[8]) and molecular distillation proved the most convenient route to 2-*endo*-chlorocamphane-10-methanol.[8] A 20.3-g (0.100 mol) sample of this material was refluxed in 100 ml of glacial acetic acid for 2 hr with 16.7 g (0.100 mol) of silver

(21) T. Hasselstrom, *J. Amer. Chem. Soc.*, **53**, 1097 (1931).

(22) A. M. T. Finch, Jr., and W. R. Vaughan, *ibid.*, **87**, 5520 (1965).

(23) G. E. Cream and D. Wese, *Tetrahedron*, **22**, 2583 (1966).

(24) P. R. Bai, S. Y. Kamat, B. B. Ghatege, K. K. Chakravarti, and S. C. Bhattacharyya, *ibid.*, **21**, 629 (1965).

(25) J. Berson in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 155.

(26) Work was done at Purdue University.

(27) J. J. Ritter and G. Vlases, *J. Amer. Chem. Soc.*, **64**, 583 (1942).

(28) G. Langlois, *Ann. Chim.* (Paris), **12** (ix), 193 (1919).

(29) Work was done at The University of Michigan and The University of Connecticut. Microanalyses were done by Spang Microanalytical Laboratory, Ann Arbor, Mich.

acetate. The mixture was then filtered and the filtrate was made slightly basic with 5% sodium bicarbonate solution, after which the aqueous mixture was continuously extracted with ether for several hours and dried over magnesium sulfate. The ether was removed and the residue was distilled and then twice redistilled to give 18.7 g (90%) of (+)-8-acetoxymethylcamphene: bp 75° (0.03 mm); sp gr 0.996 (27°); $n^{27}D$ 1.4843; $[\alpha]^{27}D$ +93.72°. The infrared spectrum is identical with that of a racemic sample.[28]

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.68. Found: C, 74.83; H, 9.47.

Hydrolysis of the ester using 50% aqueous ethanol and potassium hydroxide afforded 24 g (85%) of (+)-camphene-8-methanol, whose infrared spectrum is identical with that of a racemic sample:[28] bp 76° (0.40 mm); sp gr 0.9705 (30°); $n^{28}D$ 1.5015; $[\alpha]^{30}D$ +92.42° {lit. bp 125–126° (8 mm); sp gr 0.987 (15°); $[\alpha]D$ +45° [8]}.

Oxidation to (−)-camphene-8-carboxylic acid was carried out according to the directions of LoCicero.[30] The product was recrystallized from low-boiling petroleum ether, mp 119.5–121° $[\alpha]^{26}D$ −260° (chloroform). The infrared spectrum is indistinguishable from those of the racemic samples.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.22; H, 8.90.

(+)-α-Pinene-10-carboxylic Acid.[29] **A.**—(+)-α-Pinene was converted into (+)-myrtenol: bp 100–101° (10 mm); d^{27} 0.9809; $n^{26}D$ 1.4966; $[\alpha]^{27}D$ +25.4° {lit.[31] bp 105° (9 mm); n_D 1.4966; $[\alpha]D$ +49.7°}. Oxidation with selenium dioxide followed by reduction with lithium aluminohydride was used.

(+)-α-Pinene-10-carboxylic acid was prepared from (+)-myrtenol *via* the bromide (phosphorus tribromide)[19] and nitrile,[20] $[\alpha]^{27}D$ +10 ± 2°. A 4.0-g sample of the nitrile was converted into the amide by mixing it with 8.4 g of 30% hydrogen peroxide, and enough absolute ethanol was added to provide homogeneity. The pH was adjusted to 9.0 by addition of dilute sodium hydroxide and the solution was refluxed for 4 hr. The pH was adjusted to 5.0 and the solution was extracted with chloroform. Removal of the solvent and recrystallization from ethanol–water afforded white crystals, mp 98.5–101°, yield 95%.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.51; H, 9.52.

The nitrile was hydrolyzed in aqueous alcoholic potassium hydroxide to the free acid as described by Arnold and Danzig,[32] with similar results.

B.—A hot solution of 5.10 g of nopyl tosylate[32] in dry dimethyl sulfoxide was added as fast as possible, with due regard for the possibility of the reaction getting out of hand, to a solution of 445 g of sodium bicarbonate in 2 l. of dimethyl sulfoxide held at 150°. After complete addition, the reaction was held at 145–150° for 15 min and the stirred solution was cooled to room temperature and filtered. The filtrate was diluted with an equal volume of water, and the combined extracts were dried over anhydrous magnesium sulfate and distilled, yield 319 g of colorless distillate, bp 72–79° (0.25 mm). Analysis by glpc showed this material to be a 1:1 mixture of the desired aldehyde and nopol.

This mixture was dissolved in 1750 ml of absolute ethanol containing a solution of 204 g (1.2 mol) of silver nitrate in 300 ml of water, and, with rapid stirring, there was added a solution of 144 g (3.6 mol) of sodium hydroxide in 2 l. of water at a rate sufficient to maintain ambient temperature. After complete addition, stirring was continued for 24 hr and the mixture was filtered the residue being thoroughly washed with water and ethanol. The filtrate was extracted with *ca.* 3 l. of ether, and the aqueous alcoholic basic phase was acidified to pH 2 and extracted with 2 l. of ether in 250-ml portions. The ethereal extracts were combined, dried over magnesium sulfate, and distilled to yield 18.85 g of light yellow oil, bp 122–129° (0.45 mm) [lit.[32] bp 95° (0.05 mm)], which solidified on cooling, mp 50–60°. Recrystallization from aqueous ethanol afforded white crystals, mp 73.0–74.5°.

The infrared spectrum of this acid shows a strong olefinic absorption at 6.14 μ and a carbonyl absorption at 5.92 μ, comparable with that of the amide reported above (6.14 μ, carbonyl 5.99 μ). These data strongly suggest conjugation; but, as reported,[32] the acid can be reduced to nopol by treatment with lithium aluminum hydride.

10-Carboxyisoborneol Lactone (3).[26]—A solution of 3.0 g of (±)-camphene-8-carboxylic acid (1) in 10 g of 90% formic acid was heated at reflux for 1 hr. The dark solution was poured into water and extracted with ether. The ether was washed repeatedly with 5% sodium carbonate solution, and water and dried. Evaporation of the solvent left a reddish solid which displayed a carbonyl peak at 5.65 μ. One half of this solid was sublimed *in vacuo* and the other half was recrystallized from hexane. The sublimed material showed a melting point of 149–165°, and its infrared spectrum indicated that it was contaminated with a trace of acid 1. Vpc analysis showed only one major peak; however, the nmr of this solid displayed, in addition to the methyl resonances at 0.9 ppm characteristic of lactone 3, singlets at 1.12 and 1.32 ppm which are characteristic of lactone 4. It was estimated that the solid contained 64% 3 and 36% 4.

The recrystallized portion exhibited a melting point of 190–195° and displayed an infrared spectrum identical with that of Bain's lactone 3: nmr δ 0.94 and 0.98 (s, 6, CH_3CCH_3), 2.32 (CH_2CO), 4.19 (m, 1, CHO), and 1.02–1.90 ppm (complex m); mass spectrum *m/e* 180 (parent peak) and abundant ions at *m/e* 152, 137, 122, 108, 93, 80, 67, 55, and 43.

When[29] a solution of 3.3 g of (−)-1 in 15 ml of trifluoracetic acid was kept at room temperature for *ca.* 3 days, there was obtained 3.2 g of crude lactone. The crude lactone was first recrystallized from ethanol–water and then repeatedly from petroleum ether (bp 60–75°) to give a solid, mp 198.5–199.5° (lit.[7] mp 198–199°). The lactone 3 is optically inactive, and its infrared spectrum is superimposable upon that of the lactone 3 kindly supplied by Dr. J. P. Bain.[8]

***exo*-2,3-Dimethylbicyclo[2.2.1]heptane-*endo*-3-hydroxy-*endo*-2-acetic Acid Lactone (4). A. Formic–Sulfuric Acid Lactonization of Camphene-8-carboxylic Acid (1).**[26]—A solution of 8.0 g of camphene-8-carboxylic acid (1), 6.95 g of concentrated sulfuric acid, and 46.5 g of 88% formic acid was allowed to stand for 6.25 days at 25°. The solution was diluted to *ca.* 350 ml with water and extracted with ether. The ether solution was washed with 10% bicarbonate and water and dried over anhydrous magnesium sulfate. The solvent was removed to leave 7.0 g of crude product, mp 155°. Recrystallization from petroleum ether (bp 30–60°) and chromatography on a short Florisil column (chloroform eluent) gave pure lactone 4: mp 170–171°; ir 5.55 μ; nmr, two methyl singlets at δ 1.32 and 1.16 ppm and no signals below δ 2.45 ppm; mass spectrum *m/e* 180 (parent ion) and abundant ions at *m/e* 112, 97, 67, and 43.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.31; H, 8.95. Found: C, 73.11; H, 8.79.

B. Trifluoroacetic Acid Lactonization of 1.[26,29]—A solution of 2.0 g of acid 1 in 15 ml of trifluoroacetic acid was allowed to stand for 7 days at room temperature. Work-up gave 1.94 g of crude lactone, which was recrystallized from petroleum ether (bp 30–60°) to yield 4, mp 170°.

C.[29]—A solution of 40 g of α-pinene-10-carboxylic acid in 100 ml of trifluoroacetic acid was kept for 4 months. Work-up in the usual manner gave 2.0 g (10%) of an optically inactive oil whose infrared spectrum was nearly identical with that of lactone 4. Reaction with phenylmagnesium bromide gave diol 27, mp 167–168°, which was dehydrated to ether 28, mp 118–119°. Identity of these samples was established by comparison of nmr spectra of authentic materials (see below).

***endo*-2,3-Dimethyl-*exo*-3-hydroxybicyclo[2.2.1]heptane-*exo*-2-acetic Acid Lactone (5).**[26]—A mixture of 8.0 g of camphene-8-carboxylic acid (1) and 50 ml of 50% sulfuric acid was heated at 160–165° for 2 hr. The resulting dark brown solution was washed thoroughly with 5% sodium carbonate and dried, and the ether was removed to give a dark brown oil which on recrystallization from hexane afforded 5.5 g of lactone 5: mp 155–159° (sublimation *in vacuo* raised the melting point to 157–161°); ir 5.65 μ; nmr, prominent methyl signals at δ 1.32 and 1.12 ppm and no signals below δ 2.45 ppm; mass spectrum *m/e* 180 (parent ion) and abundant ions at *m/e* 112, 92, 67, and 43.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.24; H, 8.95. Found: C, 73.30; H, 9.02.

Vpc analysis of the crude lactone mixture using a DEGS column at 170° indicated the presence of lactones 5 and 4 in a 4:1 ratio. The minor component with a shorter retention time was collected, mp 155–164°, and shown to be identical with lactone 4 by infrared and nmr comparison.

Alternatively, a solution of 4.0 g of acid 1 and 5.0 g of concentrated sulfuric acid in 30 ml of 90% formic acid was heated at

(30) J. C. LoCicero and R. T. Johnson, *J. Amer. Chem. Soc.*, **74**, 2094 (1952).

(31) A. R. Penfold, G. R. Ramage, and J. L. Simonsen, *J. Proc. Roy. Soc. N. S. Wales*, **68**, 36 (1934).

(32) R. T. Arnold and M. J. Danzig, *J. Amer. Chem. Soc.*, **79**, 892 (1957).

reflux for 3.5 hr. Work-up gave 3.2 of crude lactone. Recrystallization from hexane afforded 3.0 g of white solid, mp 163 167°. Vpc analysis indicated the presence of lactones **5** and **4** in a ratio of 5:1.

10-Hydroxymethylisoborneol (7).[26]—To a stirred slurry of 0.5 g of lithium aluminum hydride in 20 ml of ether was added slowly a solution of 2.0 g of lactone **3** in ether. The mixture was stirred overnight and then decomposed with saturated sodium sulfate solution. The ether layer was separated, dried, and concentrated to give 1.7 g of solid. Recrystallization from hexane afforded 1.5 g of white crystals, mp 84–87°, which displayed two singlet methyl resonances at δ 0.82 and 1.03 ppm, complex multiplets at δ 1.10–1.92 ppm owing to nine protons, a three-proton multiplet at δ 3.72 ppm, and a broad two-proton multiplet at δ 4.52 ppm.

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.77; H, 10.89.

The diacetate derivative of 10-hydroxymethylisoborneol showed carbonyl absorption at 5.77 μ and nmr signals at δ 0.85 and 1.0 (s, 2-CH_3), 2.1 [s, 2 $CH_3(C{=}O)O$], 4.0 (m, CH_2O), and 4.72 ppm (m, CHO).

Camphor-10-carboxylic Acid (8).[26]—To a stirred and ice-cooled solution of 1.0 g of 10-hydroxymethylisoborneol (**7**) in 20 ml of acetone was added 5.5 ml of 8 *N* chromium trioxide solution. After 5 min the excess oxidant was destroyed with isopropyl alcohol and the mixture was worked up in the usual manner to give, after two recrystallizations from hexane, 0.77 g of camphor-10-carboxylic acid: mp 95–97° (lit.[9] mp 92–93°); nmr singlets at δ 0.90 and 1.02 ppm for two methyl groups, two-proton multiplets at δ 2.11 and 2.2–2.33 ppm, and a carboxyl proton at 11.14 ppm.

The semicarbazone derivative of the keto acid was recrystallized from aqueous ethanol, mp 196–199° (lit.[8] mp 199–200°).

10-(Dimethylhydroxymethyl)isoborneol.[29]—Treatment of **3** with 2 equiv of methylmagnesium iodide afforded an 80% yield of product, white needles from ethyl acetate–petroleum ether (bp 60–75°), mp 143–145°.

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.79; H, 11.36.

10-(Diphenylhydroxymethyl)isoborneol (10).[29]—Treatment of **3** with 2 equiv of phenylmagnesium bromide (ammonium chloride work-up) afforded a 98% yield of **10**, recrystallized from ethyl acetate–petroleum ether (bp 60–75°) and benzene–petroleum ether (bp 60–75°), mp 158–159°.

Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.26; H, 8.45.

This substance was also prepared from 10-benzoylisoborneol (**9**)[11] and 10-benzoylisobornyl acetate (**17**)[11] (both originally assigned the bornyl configuration[11]) using phenyllithium in appropriate amounts. The infrared spectra are superimposable and mixture melting points show no depression.

10a,10a-Diphenyl-2-*exo*-10a-epoxy-10-homobornane (11).[29]—This ether was most readily prepared from **9** by refluxing in benzene with a catalytic amount of iodine, using 0.33 g of **10**, 0.03 g of iodine, and 25 ml of benzene, for 24 hr. The iodine was removed with 5% sodium thiosulfate and the product was obtained as an oil on evaporation. Recrystallization from petroleum ether (bp 60–75°) affords a 90% yield of product, mp 141.0–142.5°. The infrared spectrum lacks absorption in the hydroxyl region.

Anal. Calcd for $C_{23}H_{26}O$: C, 86.74; H, 8.23. Found: C, 86.54; H, 8.19.

10-(Diphenylhydroxymethyl)isobornyl Acetate (12).[29]—This acetate may be prepared from **10** in acetic anhydride alone by gently refluxing for 18 hr, or in benzene solution containing acetic anhydride and a catalytic amount of sodium acetate by refluxing, using 0.45 g of **10**, 13 g of acetic anhydride, and 0.10 g of sodium acetate in 12 ml of dry benzene, for 2.5 days. In either case an essentially quantitative yield may be obtained. Recrystallization from benzene–petroleum ether (bp 60–75°) affords analytically pure material, but there appear to be several different crystal forms, as indicated by different melting points on different batches of product with superimposable infrared spectra, mp 134.0–134.5°, remelted at 144–145° and 150–153°.

Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.53; H, 8.16.

10-Benzhydrylideneisobornyl Acetate (13).[29]—A 5.0-g sample of **12** and 50 mg of iodine in 50 ml of dry benzene were refluxed for 15 hr, after which the iodine was removed by washing with 5% sodium thiosulfate. Evaporation after drying afforded an oil, which was recrystallized from petroleum ether (bp 60–75°) or ethanol–water (98%), mp 108–109°.

Anal. Calcd for $C_{25}H_{28}O_2$: C, 83.29; H, 7.83. Found: C, 83.21; H, 7.57.

The product gave a negative test with bromine in carbon tetrachloride but produced a color with tetranitromethane

10-Benzhydrylideneisoborneol (14).[29]—Hydrolysis of **13** was achieved with sodium hydroxide in 50% aqueous ethanol by refluxing, using 1.1 g of **13** and 2.5 g of sodium hydroxide in 50 ml, for 3 hr. The ethanol was removed by distillation and the product was extracted into 1:1 ether–benzene and dried. After removal of solvent there remained 0.96 g (93%) of an oil which was recrystallized from petroleum ether (bp 60–75°), mp 108–109°.

Anal. Calcd for $C_{23}H_{26}O$: C, 86.74; H, 8.23. Found: C, 87.53; H, 8.39.

10-Benzhydrylidenecamphor (15).[29]—A 1.0-g sample of **14** in 30 ml of acetone was titrated at room temperature with Jones reagent[9] and then the reaction mixture was diluted with ice–water and extracted several times with ether. The ether extracts were combined and washed free of acid, dried over magnesium sulfate, and evaporated to dryness, leaving 1 g of solid product which was twice recrystallized from petroleum ether (bp 60–75°), mp 110–111°.

Anal. Calcd for $C_{23}H_{24}O$: C, 87.30; H, 7.65. Found: C, 87.27; H, 7.80.

10-Benzhydrylisobornyl Acetate (16).[29]—A 1.0-g sample of **13** in 50 ml of glacial acetic acid was hydrogenated for 1.5 hr at 1-atm pressure over 0.021 g of Adams catalyst. Removal of the solvent and recrystallization from petroleum ether (bp 30–40°), ethanol–water, and finally ethanol afforded the product, mp 78–84°.

Anal. Calcd for $C_{25}H_{30}O_2$: C, 82.83; H, 8.34. Found: C, 83.00; H, 8.11.

***exo*-2-Acetoxyapocamphane-1-carboxylic Acid (18).**[29]—A mixture of 12 g (0.040 mol) of 10-benzoylisobornyl acetate (**17**)[11] and 8.0 g (0.80 mol) of chromic anhydride in 200 ml of glacial acetic acid and 40 ml of water was refluxed for 12 hr with stirring, and then the greater portion of the acetic acid was removed by evaporation in an air stream. The residual oil was dissolved by shaking with equal volumes of 10% sodium carbonate and ether. From the ether layer there was recovered 8 g of **17** (infrared spectrum). Acidification of the aqueous layer with concentrated hydrochloric acid, extraction with ether–benzene, washing of the extract with water, drying (magnesium sulfate), and evaporation afforded a mixture of benzoic acid and **18**. These were finally separated on a Florosil column by eluting the benzoic acid with carbon tetrachloride, yield 2.0 g of **18**, mp 117–119° (lit.[12] 121–122°), neut equiv 228 ± 2.

The acid chloride **19** was prepared by means of thionyl chloride, bp 94–96° (0.75 mm). [The previous report, bp 111–113° (0.30 mm),[2] is probably in error, 3.0 mm being more likely for the pressure used.] A Rosenmund reduction on this material failed. On a larger scale, chromatography of the oxidation products is better omitted and separation achieved by fractional distillation of the acid chlorides.

10-Hydroxyisobornyl Acetate (20).[29]—To a well-stirred suspension of 10 g (0.26 mol) of sodium borohydride in 150 ml of dioxane (dried over calcium hydride and distilled from lithium aluminum hydride) was added 31 g (0.13 mol) of **19** in 50 ml of dioxane (similarly dried) at room temperature. The heterogeneous mixture was heated on the steam bath for 1 hr with stirring, cooled, hydrolyzed with a small amount of ice–water, and evaporated in an air stream to *ca.* one-fourth its volume. The gelatinous residue was stirred with equal volumes of water and ether, which were then separated, the ether layer being washed well with water, dried, and evaporated to give a dense oil, yield (24 g). Distillation afforded a single liquid fraction, bp 130–135° (0.10 mm), yield 15 g (54%), and a solid residue, yield 9.0 g (40%). A portion of the distillate was hydrolyzed with sodium hydroxide, and the hydrolysate and solid residue were each recrystallized from petroleum ether (bp 60–75°), mp 246–248°, no depression of mixture melting point, identical infrared spectra. The reported melting point for 10-hydroxyisoborneol is 241–243°.[13] *Ca.* 4% of the original **18** was recovered from the initial alkaline solution.

Conversion of 10-Hydroxyisobornyl Acetate (20) into Isoborneol.[29]—A solution of 2.4 g of **20** in a mixture of 10 ml of pyridine and 10 ml of benzene was cooled to 5°, and a solution of 1.8 g of methanesulfonyl chloride in 4 ml of pyridine was added

with stirring. After standing for 14 hr at 5°, the mixture (containing a precipitate) was poured into ice–water and the new mixture was acidified with concentrated hydrochloric acid. The resultant solution was extracted with ether, and the ethereal extract was washed well with 5% sodium hydroxide and then with water, dried over magnesium sulfate, and evaporated to give a light yellow oil (10-methanesulfonoxyisobornyl acetate) which could not be distilled owing to extensive decomposition above 80°.

A solution of 1.40 g (0.0048 mol) of the preceding mesylate in 20 ml of dry benzene was added to a solution of 0.022 mol (0.85 g potassium metal) of potassium *t*-butoxide in 18 ml of *t*-butyl alcohol at room temperature to which had been added 1.78 g (2.0 ml) of ethyl mercaptan. The mixture was refluxed with mechanical stirring for 15 hr, during which time it became a thick, viscous gel. Next it was carefully diluted with a large volume of water, extracted with ether, and dried. After removal of the solvent, the residual oil, 10-ethylthioisobornyl acetate, was obtained, yield 1.1 g (90%), bp 102–104° (0.25 mm).

This distillate was added to *ca.* 20 g of freshly prepared Raney nickel[33] in 80 ml of reagent grade methanol. The mixture was refluxed for 3 hr, cooled, and filtered, and on evaporation the semisolid residue was dissolved in 200 ml of 50% aqueous ethanol containing 10 g of sodium hydroxide. After this solution was stirred for 8 hr at 40°, the ethanol was distilled and the residual alkaline solution was cooled, extracted with ether, and dried. The ether was evaporated, leaving 0.5 g (80%) of isoborneol, mp 211–212°, with no depression on mixture with an authentic sample. The infrared spectrum was identical with that of an authentic sample, and the *p*-nitrobenzoate, mp 127–128° (with no depression on mixture with an authentic sample), has an infrared spectrum identical with that of an authentic sample

Diol 21.[26]—A solution of 2.5 g of lactone **5** in ether was added to a suspension of 1.5 g of lithium aluminum hydride in ether. The mixture was stirred at room temperature overnight and then decomposed with sodium sulfate solution. The salts and solvent were removed, leaving 2.2 g of a waxy solid. Recrystallization from hexane afforded 2.0 g of diol **21**: mp 97–100°; nmr δ 0.87 and 1.14 (ss, 6, CH_3CCH_3), 3.54 (m, 2, CH_2O), 5.52 (m, 2, OH), and 1.19–2.2 ppm (complex m, 10).

Unsaturated Acetate 23.[26]—A solution of 2.0 g of diol **21** in 30 ml of acetic anhydride containing a trace of pyridine was heated at reflux for 2 hr. Work-up gave an oil which showed infrared absorption at 2.9 and 5.76 μ (OH and $OCOCH_3$).

The crude hydroxy acetate **22** was dissolved in 15 ml of methylene chloride, and to the cooled solution was added 10 ml of thionyl chloride and 10 ml of pyridine. The stirred mixture was poured into cold water after 30 min and extracted with ether. The ether solution was washed with 5% hydrochloric acid and water, dried, and the ether removed to leave 1.6 g of an oil which on vpc analysis showed only one major peak. A vpc purified sample showed infrared peaks at 5.76, 6.01, and 11.25 μ and prominent nmr signals at δ 2.1 (CH_3CO) and 4.52 and 4.82 ($C{=}CH_2$) ppm.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.67. Found: C, 74.90; H, 9.63.

9-Hydroxymethylcamphene (24).[26]—Unsaturated ester **23** (1.5 g) was saponified with 10% potassium hydroxide in ethanol to give 1.1 g of a colorless liquid, bp 93–96° (1.5 mm), which showed infrared absorption at 3.0, 6.01, and 11.25 μ and prominent nmr signals at δ 1.01 (s, CH), 3.74 (OH), and 4.48 and 4.71 (s, CH_2) ppm.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.41; H, 10.85. Found: C, 79.66; H, 11.15.

9-Methylcamphene (25).[26]—A mixture of 0.57 g of *p*-toluene sulfonic acid, 0.5 g of 9-hydroxymethylcamphene (**24**), and 5 g of pyridine was stirred overnight and then poured into ice. The mixture was extracted with ether and the ether solution was washed with dilute hydrochloric acid, 5% sodium carbonate, and water and dried. The ether was evaporated, leaving an oil which could not be induced to crystallize.

A hexane solution of the crude tosylate derivative was added to a stirred solution of 0.8 g of lithium aluminum hydride in ether. The excess hydride was decomposed after 16 hr. The salts and solvent were carefully removed and the residue was purified by vpc to give a liquid whose infrared spectrum showed peaks at 6.02 and 11.30 μ, characteristic of a terminal methylene group. The mass spectrum had a parent ion at *m/e* 150 and abundant ions at *m/e* 122, 121, 94, 93, 79, 67, and 41. The nmr spectrum displayed signals at 1.00 (s, CH_3), 2.62 (m, C-1 H), and 4.42 and 4.72 (s, $C{=}CH_2$) ppm

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.05. Found: C, 87.75; H, 11.97.

3-*endo*-Methyl-3-*exo*-ethyl-2-norbornanone (26).[26]—To a stirred solution of 5.0 g (0.042 mol) of 3-methyl-2-norbornanone in 15 ml of anhydrous ether was added an ethereal solution of tritylsodium until the red color persisted. Ethyl iodide, 70.0 g (0.57 mol), was added and the solution was stirred at room temperature for 24 hr. Water was added, and the ether solution was separated, washed with water, and dried, and the ether was evaporated. Distillation of the residue gave 3.82 g of **26**, bp 50–55° (1.5 mm), which was shown to be about 95% pure by vpc. The infrared spectrum of **26** showed a strong carbonyl band at 5.73 μ. The nmr spectrum showed prominent signals at δ 2.42 ppm for a two-proton multiplet, a singlet methyl group at δ 0.92 ppm, and a triplet methyl at δ 1.0 ppm. The mass spectrum showed a parent ion at *m/e* 152 and abundant ions at *m/e* 124, 83, 67, 55, and 41.

9-Methylcamphene from Ketone 26.[26]—To an ether solution containing 0.092 mol of methyllithium was added an ether solution of 3.5 g (0.023 mol) of 3-*endo*-methyl-3-*exo*-ethyl-2-norbornanone (**26**). The resulting solution was heated and stirred for 2 days. The reaction mixture was poured into–ice water and the ether solution was separated. Distillation gave 2.8 g (80%) of tertiary alcohol, bp 65–73° (1.5 mm), which showed strong hydroxyl absorption but no carbonyl absorption.

The alcohol was dissolved in 30 ml of methylene chloride and treated at −5° with 15 ml of thionyl chloride and 15 ml of pyridine, and the mixture was stirred for 40 min. Pentane was added and the reaction mixture was poured into ice–water. The organic layer was separated, washed with dilute hydrochloric acid and water, and dried over anhydrous magnesium sulfate. Distillation gave 1.2 g of liquid, bp 58–62° (1.7 mm), whose infrared spectrum showed the presence of terminal methylene at 11.31 μ. Vpc analysis using a SF-96 column at 140° indicated the presence of a minor component (*ca.* 5–10%) with lower retention. The major component was collected and displayed terminal olefin absorption at 6.02 and 11.30 μ and two olefin protons as singlets at δ 4.71 and 4.42 ppm. The infrared, nmr, and mass spectrum of this sample of 9-methylcamphene were identical with those of the methylcamphene obtained by degradation of lactone **5**.

***cis*-2,3-Dimethyl-*endo*-3-hydroxy-2-(2,2-diphenyl-2-hydroxyethyl)bicyclo[2.2.1]heptane (17).**[29]—The Grignard reagent from 2.24 g (14.0 mmol) of bromobenzene and 0.292 g (12.5 mg-atoms) of magnesium turnings was prepared in a total of 35 ml of dry ether. To this was added 0.75 g (4.16 mmol) of lactone **4** in a solution of 10 ml of dry ether and 10 ml of dry benzene. After addition, the mixture was stirred and refluxed for 30 min and poured into 50 ml of saturated ammonium chloride solution containing 10 drops of concentrated hydrochloric acid. The organic layer was separated, dried over magnesium sulfate, and evaporated. The resulting crude solid was triturated with cold petroleum ether (bp 30–60°) to give a white solid, mp 148–149°, yield 0.73 g (52.5%). Recrystallization from petroleum ether (bp 30–60°) gave an analytical sample, mp 163.0–163.5°.

Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.17; H, 8.39. Found: C, 82.09; H, 8.23.

Dehydration of Diphenyl Glycol 27. Formation of Ether 28.[29]—Several attempts were made to obtain a monoacetate from the glycol **27**. These met with uniform failure, the products being either unchanged diol or the derived ether **28**. In all cases an excellent material balance was realized.

The ether, *endo,cis*-3a,7a-dimethyl-2,2-diphenyl-4,7-methanooctahydrobenzofuran, was obtained as white crystals, mp 115–116°, from aqueous ethanol.

Anal. Calcd for $C_{23}H_{26}O$: C, 86.74; H, 8.23. Found: C, 86.89; H, 8.31.

Possible Retrorearrangement.[29]—In one attempted acetylation, 6 mmol of **27**, 6 mmol of previously reacted acetyl chloride, and 7 mmol of pyridine in 10 ml of dry benzene were refluxed for 5 days. Extensive chromatography on Florisil finally yielded 50 mg of monoacetylated glycol, which was recrystallized from petroleum ether (bp 60–70°) to give 43 mg of **12**, mp 142.5–143.5°.

Anal. Calcd for $C_{25}H_{30}O_3$: C, 79.33; H, 7.99. Found: C, 79.42; H, 8.06.

The nmr and infrared spectra correspond with those for **12**. Further confirmation is provided by iodine dehydration to **13**,

(33) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, **65**, 1013 (1943).

TABLE IV

Time, days	Lactone 3, %	Lactone 4, %
1	21.1	...
2	27.6	4.6
8	33.5	9.1
14	68.0	12.4
21	70.2	14.3

phene-8-carboxylic acid (1) in 0.9 ml of deuterated trifluoroacetic acid was placed in an nmr tube and the progress of the reaction at ambient temperature (Table IV) was followed by periodically examining the nmr spectrum of the solution.

endo **Lactone 4-d_2.**[26]—To a stirred solution prepared by adding 600 mg of sodium to 5 ml of CH_3OD was added 600 mg of *endo* lactone **4**. The solution was kept at room temperature for 3 days, concentrated, and diluted with deuterium oxide. The solution was extracted with ether. The ether solution was dried over anhydrous magnesium sulfate, the ether was removed, and the resulting solid was recrystallized from hexane and sublimed to give 106 mg of lactone **4**-d_2. The mass spectrum showed a parent ion at *m/e* 182 and abundant ions at *m/e* 139, 114, 113, 93, 67, and 43.

TABLE V

DEUTERIUM EXCHANGE AT ROOM TEMPERATURE IN DEUTERIOTRIFLUOROACETIC ACID

Starting compd	Lactone 4						$OCCH_3$			
	d_0, %	d_1,[a] %	d_2, %	d_3, %	d_4, %	d_5	*m/e* 43; d_0, %	*m/e* 44;[a] d_1, %	*m/e* 45; d_2, %	*m/e* 46; d_3, %
1	9.7	27.7	33.2	19.1	7.3	2.9	61.7	28.9	8.5	0.9
4	7.5	15.6	35.1	18.5	12.0	7.4	32.1	36.8	24.5	6.6
5	54.8	34	11.2	...	...	...	88	7.5	3.9	...

[a] Corrected for natural contribution of M + 1.

mp 106–108°, no depression on mixture with authentic **13**. The ultraviolet, infrared, and nmr spectra correspond with those of **13**. In view of the very small amount of **12** isolated from 2.0 g of **27**, it is possible that **27** was contaminated with a trace of **10**, arising from **4** having been contaminated with a trace of **3**.

10-Benzhydrilideneborneol (29).[29]—A 4.95-g (0.015 mol) sample of **15** was sealed in a glass tube with 12.24 g (0.060 mol) of aluminum isopropoxide (excess to permit complete equilibration to the more stable epimer[34]) and 40 ml of isopropyl alcohol (a preliminary experiment using the toluene solvent recommended afforded very little product). The tube was heated at 135° for 10.5 days, cooled, and opened, and the contents were poured into 100 ml of cold 10% hydrochloric acid. After four 50-ml ether extractions were performed, the extracts were combined, washed with saturated sodium chloride solution until neutral, and dried over anhydrous magnesium sulfate. Evaporation of the solvent (oil pump at end) left a gum whose infrared spectrum showed some residual **15**. The gum was chromatographed on Florisil, and, after elution with pure petroleum ether (bp 60–70°) and benzene–petroleum ether (bp 60–70°) mixtures up to 50%, pure benzene afforded a crystalline eluate, mp 103–113°. Several recrystallizations from aqueous ethanol gave **29**, mp 118–119° no carbonyl in the infrared. The nmr spectrum showed a singlet for one vinyl proton at δ 5.98 ppm and a multiplet (two closely spaced quartets) at δ 5.04 ppm, characteristic for the borneol system in these compounds.

Anal. Calcd for $C_{23}H_{26}O$: C, 86.74; H, 8.23. Found: C, 86.67; H, 8.25.

The melting point of the acetate, 74–76°, clearly differs from that of the epimer **13**.

Anal. Calcd for $C_{25}H_{28}O_2$: C, 83.29; H, 7.83. Found: C, 83.18; H, 7.72.

Addition of Hydrogen Chloride to Camphene-8-carboxylic Acid to Give 31.[26]—A solution of 5.0 g of **1** in 35 ml of acetic acid was saturated with hydrogen chloride gas and stirred for 2 days. The solvent was removed under diminished pressure, leaving 3.6 g of a dark brown solid. Recrystallization from hexane followed by sublimation *in vacuo* gave a white solid: mp 150–156° (lit.[7] mp 150–156°); nmr 0.90 and 1.14 (s, 6, CH_3CCH_3), 2.41 and 2.70 (CH_2CO_2), 4.42 (m, 1, HCCl), and 11.42 ppm (s, 1, CO_2H).

The recrystallized chloro acid **31** was washed several times with 5% sodium carbonate solution. The aqueous solution was extracted with ether. The ether solution was dried and the ether was removed to leave a semisolid. Vpc analysis of this material showed one component, which was collected and spectrally identified as camphene.

Lactonization of Camphene-8-carboxylic Acid (1) with Deuterated Trifluoroacetic Acid.[26]—A solution of 250 mg of camphene-8-carboxylic acid (**1**) in 0.9 ml of deuterated trifluoroacetic acid was placed in an nmr tube and the progress of the reaction at ambient temperature (Table IV) was followed by periodically examining the nmr spectrum of the solution.

Treatment of Acid 1 and Lactones 3–5 with Deuterated Trifluoroacetic Acid.[26]—Samples of *ca.* 500 mg of camphene-8-carboxylic acid (**1**), lactone **3**, and lactone **4** in *ca.* 0.5 ml of deuterated trifluoroacetic acid were heated at reflux for 3 days. The solution was worked up in the usual manner and the resulting deuterated lactone **4** was analyzed by mass spectroscopy. Lactone **5** was treated in a similar manner and the recovered lactone **5** was analyzed by mass spectroscopy.

The integrated areas of the methyl resonances at δ 1.34 and 1.16 ppm in lactone **4** are in a ratio of 23:29, supporting the mass spectrometric assignment of deuterium incorporation into the CCH_3 group (*cf.* Table V above).

Registry No.—(±)-**1**, 22485-76-3; (−)-**1**, 22485-80-9; **3**, 22485-77-4; **4**, 22485-78-5; **5**, 22485-79-6; **7**, 22528-22-9; **10**, 22479-79-4; **11**, 22479-80-7; **12**, 22479-81-8; **13**, 22479-82-9; **14**, 22482-99-1; **15**, 22483-00-7; **16**, 22528-23-0; **21**, 22483-01-8; **23**, 22528-24-1; **24**, 22483-02-9; **25**, 22483-03-0; **26**, 22485-68-3; **27**, 22485-69-4; **28**, 22485-70-7; **29**, 22528-25-2; **29** acetate, 22485-71-8; (±)-camphene-8-methanol, 22485-72-9; (+)-8-acetoxymethylcamphene, 22485-73-0; (+)-α-pinene-10-carboxamide, 22485-74-1; 10-(dimethylhydroxymethyl)isoborneol, 22485-75-2.

Acknowledgment.—The Michigan authors wish to acknowledge the contributions to this research by Dr. C. T. Goetschel and Dr. A. M. T. Finch, whose efforts improved several of the reported procedures; to Hi Laboratories, Whitmore Lake, Mich., for preparation of a large sample of 10-benzhydrylidenecamphor; to Dr. William Cartwright and Dr. Jack K. Reed, whose senior honors theses led to improvements in the preparations of various compounds in the series; and to Mr. R. B. Clark, Mr. R. A. Dunn, Mr. P. E. Krieger, Mr. A. H. Parkman, Mr. R. E. Servis, and Mrs. Heather Simonson, all of whom assisted at various stages of the investigation. Thanks are also due to Mr. Frank Parker and Mr. Gunther Schütze for preparation of infrared and nmr spectra (60 Mc).

(34) C. F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

Conjugate Addition Reactions of Ethyl Atropate with Certain Alkali Nucleophiles. Alkylations[1a]

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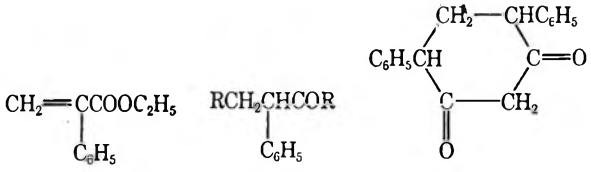
Received June 23, 1969

Ethyl atropate, $CH_2{=}C(C_6H_5)COOC_2H_5$, underwent conjugate addition with phenylmagnesium bromide and with alkali di- and triphenylmethides to form corresponding β-substituted products. Ethyl atropate also underwent conjugate additions with the 1,2-dialkali salts of benzophenone and benzophenone anil to afford a lactone and a γ-amino ester, respectively. Several new β-amino esters were prepared by similarly condensing ethyl atropate with certain alkali amides or with appropriate free amines. Various alkylations of intermediate carbanions were effected to afford α-substituted derivatives. Some related reactions were also realized.

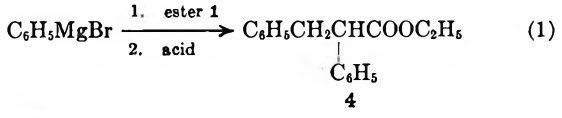
Methyl atropate and ethyl atropate (**1**) have previously been shown to undergo polymerization with catalytic amounts of various nucleophiles, including sodium amide,[2] alkali triphenylmethide,[2] *n*-butyllithium,[3,4] and *n*-butylmagnesium bromide.[4] Most of these reactions presumably involved a series of conjugate 1,4 additions of the ester, first with the nucleophile and then with intermediate carbanions. However, only two types of reactions of these esters with 1 molar equiv or more of nucleophiles appear to have been reported previously. One type involved methyl atropate with methyl- or phenylmagnesium halide to form ketone **2a** or **b**;[5] the other involved ethyl atropate (**1**) with phenylacetone in the presence of sodium ethoxide to give cyclic β diketone **3**.[6] Apparently, the first type of reaction involved both 1,2 and 1,4 additions, and the second both Michael and Dieckmann condensations.



1 **2a**, R = CH_3; **b**, R = C_6H_5 **3**

In the present investigation, ethyl atropate (**1**) was found to undergo single conjugate addition reactions with several types of nucleophiles to furnish useful methods of synthesis of a number of monomeric products.

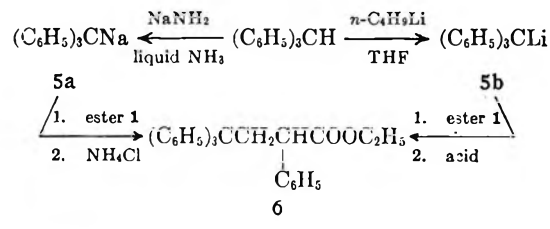
Results with Carbanions.—In contrast to methyl atropate,[5] **1** underwent 1,4 addition with phenylmagnesium bromide at room temperature to form **4** in 32–58% yield (eq 1).



4 (1)

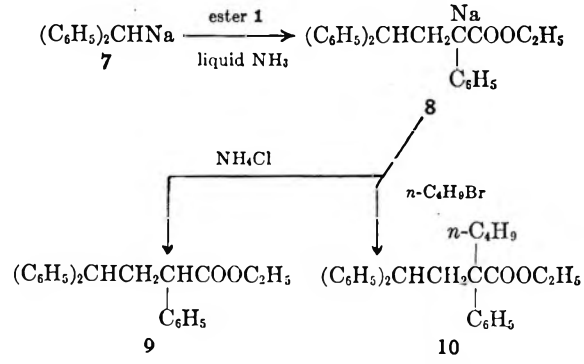
Although ester **1** has been reported to produce polymers with catalytic amounts of alkali triphenylmethides **5a** or **b**,[2] **1** afforded the monomeric β-trityl derivative **6** with 1 molar equiv of these reagents in liquid ammonia or tetrahydrofuran (THF); the yields of **6** were 40 and 66%, respectively (Scheme I).

SCHEME I



Similarly, ester **1** was condensed with sodium diphenylmethide (**7**) in liquid ammonia to form the β-diphenylmethyl derivative **9** in 61% yield. That sodium adduct **8** was present in the reaction mixture before neutralization was shown by *in situ* alkylation with *n*-butyl bromide to give the α-*n*-butyl derivative **10** in 38% yield (Scheme II).

SCHEME II



Ester **1** underwent conjugate addition, accompanied by cyclization, with disodium salt **11** to form lactone **13** in 37% yield; presumably, disodium adduct **12** was an intermediate (Scheme III). However, it was not established whether the cyclization occurred before or after neutralization.

Similarly, ester **1** was condensed with dialkali salts **14a** or **b** in liquid ammonia to give γ-amino ester **15** in 20–30% yield. None of the corresponding cyclic lactam was isolated.

(1) (a) Supported at the University of Missouri by the Petroleum Research Fund, administered by the American Chemical Society, and at Duke University by the Office of Army Research (Durham); (b) University of Missouri; (c) Duke University; (d) Union Carbide Corp., South Charleston, W. V.

(2) C. de Saint-Gobain, French Patent 1,357,679 (1964); *Chem. Abstr.*, **61**, 12167*d* (1964).

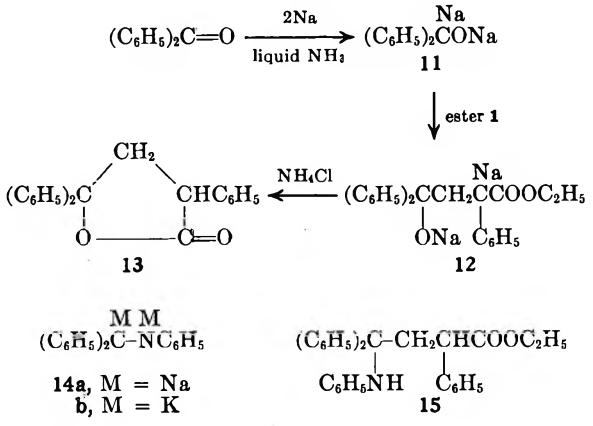
(3) H. Hopff, H. Luessi, and L. Borla, *Makromol. Chem.*, **82**, 268 (1965); *Chem. Abstr.*, **62**, 13250*a* (1965).

(4) K. Chikanishi and T. Tsuruta, *Makromol. Chem.*, **73** 231 (1964); *Chem. Abstr.*, **61**, 728*g* (1964).

(5) A. McKenzie and E. R. Winton, *J. Chem. Soc.*, 840 (1940).

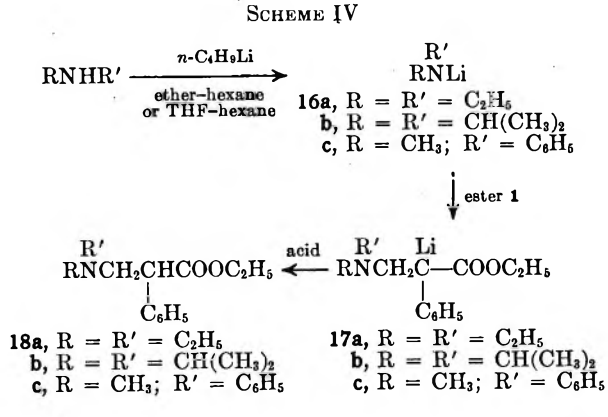
(6) G. R. Ames and W. Davey, *ibid.*, 1794 (1958).

SCHEME III

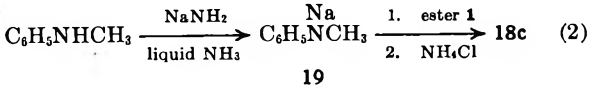


Results with Anions of Amines.—Similar to the previously reported polymerization of ester **1** with a catalytic amount of sodium amide in THF, anisole, and dimethyl sulfoxide,[2] we observed some polymerization of **1** even with 1 molar equiv of alkali amides in liquid ammonia and with lithioethylamide in ether–hexane or THF–hexane. More significantly, however, single conjugate addition reactions were realized with ester **1** and 1 molar equiv of the lithio derivatives of secondary amines, **16a–c**, in ether–hexane or THF–hexane to form β-dialkylamino esters **18a–c** in yields of 62, 33, and 48–54%, respectively (Scheme IV). That lithio adduct **17** was present in the reaction mixture before neutralization was shown by *in situ* alkylation with benzyl chloride to form the α-benzyl derivative **21a**.

SCHEME IV



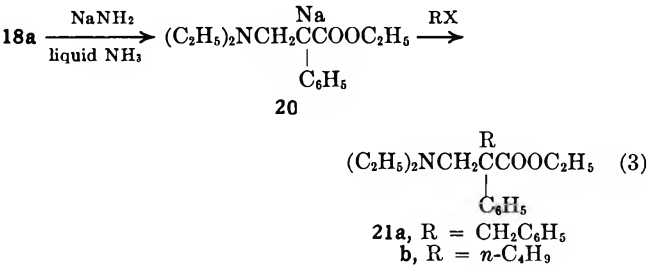
β-Amino ester **18c** was also prepared through sodium methylaniline (**19**) in liquid ammonia, the yield being 66% (eq 2). This method, however, does not appear



(2)

suitable for the two purely aliphatic amines, with which the equilibrium of the acid–base reaction would presumably be on the side of the free amine and sodium amide.

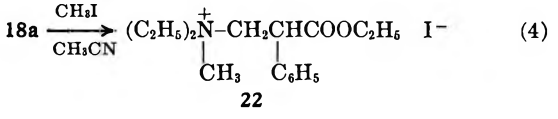
β-Amino ester **18a** was alkylated at its α carbon with certain halides by means of sodium amide in liquid ammonia. Thus, the intermediate sodium salt **20** underwent alkylation with benzyl chloride and *n*-butyl bromide to form the α-alkyl derivatives **21a** and **b** in yields of 71 and 75%, respectively (eq 3).



(3)

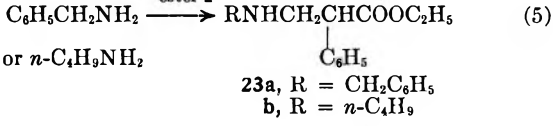
At least for the preparation of **21a**, this sodium amide method seems preferable to the above-mentioned *in situ* benzylation of the lithium adduct **17a**, which required a relatively longer reaction period for a satisfactory yield (see Scheme IV and Experimental Section).

Also, β-amino ester **18a** was methylated at its nitrogen atom with methyl iodide in acetonitrile to form the quaternary ammonium iodide **22** in 80% yield (eq 4).



(4)

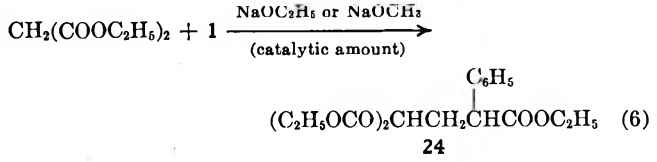
Results with Free Amines and Basic Catalysis.—Ester **1** underwent an uncatalyzed conjugate addition reaction with benzylamine and *n*-butylamine in ethanol to form the β-amino derivatives **23a** and **b** in yields of 71 and 50%, respectively (eq 5).



(5)

Although this method would presumably be suitable with certain other primary amines, it failed with free diethylamine. Even in the presence of catalytic amounts of sodium ethoxide, sodium methoxide, or *n*-butyllithium, ester **1** underwent only a little conjugate addition with diethylamine and methylaniline to form β-amino esters **18a** and **c**, respectively.

Results with Malonic Ester.—Ester **1** underwent a typical Michael condensation with ethyl malonate in the presence of a catalytic amount of sodium ethoxide or sodium methoxide neat or in ethanol to form the β derivative **24** in 55–60% yield (eq 6).



(6)

When malonic ester was converted into its sodium salt with 1 molar equiv of sodium ethoxide in ethanol or sodium amide in liquid ammonia and ester **1** was added, the yields of **24** were only 5 and 24%, respectively.

Discussion

Interestingly, in spite of the tendency of ester **1** to be polymerized by strong nucleophiles, the reactions described herein stopped at the initial stage to form mono-

mers with most of the nucleophiles studied. Since even 1 molar equiv of alkali amides and lithium derivatives of primary amines afforded polymeric material, success in arresting the present reactions at the monomeric stage with the alkali derivatives of secondary amines may be ascribed to a steric factor. Possibly a steric factor was instrumental also in the success of the preparation of monomers with the alkali derivatives of the polyphenyl compounds.

With the exceptions of the Grignard and malonic ester derivatives, **4** and **24**, respectively, all of the products described in this paper appear to be new. Their structures were supported by elemental analyses and absorption spectra (see Experimental Section).

Although **4** can be prepared more conveniently by alkylation of sodium ethyl phenylacetate,[7] **24** seems better prepared by the present method than by an earlier one involving alkylation of sodium malonic ester with 2-phenyl-3-chloropropionate, for which no yield was reported.[8] The latter reaction may have been accompanied by dehydrohalogenation, a type of reaction that occurred exclusively in an attempt to alkylate potassium diphenylmethide with ethyl 3-bromopropionate.[9]

While there appear to be no earlier examples for conjugate additions of an α,β-unsaturated ester with an alkali derivative of a secondary amine, such reactions with the other types of nucleophiles have been described previously. Thus, besides the well-known Grignard and Michael types of reactions, conjugate additions of ethyl cinnamate with potassium diphenylmethide,[10] of chalcone with disodium salt **11**,[11] and of methyl or ethyl acrylate with primary or secondary amines[12] have been reported. Similar to our observation with ester **1** and free diethylamine (see above), ethyl cinnamate has been reported not to react with this amine.[13]

The present results, as well as earlier ones, fit into two categories with regard to affecting satisfactorily conjugate addition reactions of α,β-unsaturated esters (or other such systems) with nucleophiles: (a) those that form a sufficiently more stable (more weakly basic) adduct carbanion; and (b) those that produce a more thermodynamically stable nuetral adduct compared to the two starting neutral components. Category a includes the reactions of Grignard reagents, the polyphenyl carbanions, and the anions of amines, though the magnesium of the Grignard reagent may also play an important role.[14] Category b includes the reactions of the neutral free amines and the base-catalyzed Michael condensations.

Apparently, the equilibrium of the conjugate addition reaction of ester **1** with a free secondary amine, *e.g.*, diethylamine, is on the side of the secondary amine, since **1** failed to react satisfactory with diethylamine even in the presence of catalytic amounts of sodium ethoxide or other basic reagents. Also, β-amino ester **18c** was found to undergo cleavage with a catalytic quantity of sodium ethoxide in ethanol to form methylaniline and ethyl atropate (**1**), though the equilibrium may have been shifted in favor of these components by polymerization of most of **1** (see Experimental Section). Therefore, the satisfactory conjugate additions of **1** with the alkali derivatives of the secondary amines appear attributable to formation of the more weakly basic adduct anion such as **17**, although the metallic cation may also be influential, especially when it is lithium.[14]

On the other hand, the equilibrium of the conjugate addition reaction of ester **1** with malonic ester is evidently on the side of the neutral adduct **24**, since **24** was obtained in good yield with a catalytic amount of sodium ethoxide but not with **1** equiv of this base. Thus, conjugate addition reactions of ester **1** with malonic ester occur better with a catalytic amount than with **1** equiv of sodium ethoxide, since the resulting adduct carbanion, which is a stronger base than the malonic ester carbanion, needs to acquire a proton to afford the more thermodynamically stable netural adduct.

Experimental Section[15]

Preparation of Ethyl Atropate (1).—This ester was prepared by a modification of the procedure of Ames and Davey.[6] Sodium ethoxide (2.27 mol), prepared in 1200 ml of anhydrous xylene from 105.8 g (2.3 mol) of ethanol and 52.2 g (2.27 g-atoms) of sodium, was treated with 328.5 g (2.25 mol) of diethyl oxalate, followed by 489.0 g (2.98 mol) of ethyl phenylacetate. Each addition required 30 min, and the temperature was maintained below 35° with a water bath. The solution was allowed to stand overnight, and the yellow solid which precipitated was collected under suction and washed with ether until the ether washings were colorless. The solid was then slurried with 1 l. of ether and made acidic by the addition of 1 *N* hydrochloric acid. The resulting phases were separated, the aqueous phase was extracted with two 300-ml portions of ether, and the ether extracts were combined and concentrated under reduced pressure. The remaining oil was treated with 300 ml of 38% aqueous formaldehyde and 1 l. of water. The resulting rapidly stirred mixture was then treated at 12–18° during 3 hr with a solution of 243.0 g (1.76 mol) of potassium carbonate in 450 ml of water, and stirred for an additional 4 hr. The organic phase was extracted with 1 l. of ether and the aqueous phase was extracted with two 300-ml portions of ether. Work-up followed by distillation of the crude product on a 40 theoretical plate spinning-band distillation column afforded 230 g (58%) of ethyl atropate (**1**), bp 88–91° (2.5 mm) [lit.[6] bp 76–77° (1.2 mm)]. The nmr of the product showed the presence of 97.5% ethyl atropate and 2.5% ethyl phenylacetate. Ethyl atropate could be preserved without the presence of polymerization inhibitors by refrigerator storage under a nitrogen atmosphere.

Purer ethyl atropate (**1**) was realized in 65% yield when the preparation was repeated employing 2.25 mol each of ethyl phenylacetate and diethyl oxalate along with 2.5 mol of sodium ethoxide.

Addition of Phenylmagnesium Bromide to Ethyl Atropate.—Phenylmagnesium bromide, prepared from 0.60 g (0.025 g-atom) of magnesium and 3.93 g (0.025 mol) of bromobenzene in 50 ml of ether, was treated during 12 min with a solution of 4.4 g

(7) W. G. Kenyon, R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **28**, 3108 (1963).

(8) V. Breznak, *Biochem. Z.*, **205**, 417; Beilsteins Handbuch der organischen chemie, Vol. 9, II, Springer-Verlag, 1944, p 715.

(9) See W. G. Kofron and N. I. Gottfried, *J. Org. Chem.*, **31**, 3426 (1966).

(10) M. T. Tetenbaum and C. R. Hauser, *ibid.*, **23**, 229 (1958).

(11) See P. J. Hamrick, Jr., and C. R. Hauser, *J. Amer. Chem. Soc.*, **81**, 493 (1959).

(12) R. Mozingo and J. H. McCracken, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 258.

(13) K. Morsch, *Monatsh. Chem.*, **61**, 229 (1932).

(14) For the metallic cation effect in carbonyl addition reactions, see W. I. O'Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, *J. Org. Chem.*, **26**, 2306 (1961).

(15) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin–Elmer Infracord Model 137 either neat, as Nujol mulls, or in KBr disks. Nmr spectra were obtained with a Varian Associates A-60 spectrometer using tetramethylsilane as internal standard. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Triangle Chemical Laboratories, Chapel Hill, N. C. Unless indicated, the reactions were worked up by extracting the aqueous phase with three or four 50-ml portions of ether, drying ($CaSO_4$ or $MgSO_4$), and concentrating the combined extracts on the rotary evaporator.

(0.025 mol) of ethyl atropate (1) in 50 ml of ether. After 5 hr, the white suspension was cooled to 0° and hydrolyzed by 100 ml of 3 *N* hydrochloric acid. Work-up[15] and distillation of the resulting residue afforded 2.0 g (32%) of ethyl 2,3-diphenylpropanoate (4), bp 168–170° (4 mm) [lit.[7] bp 115–116.5° (0.13 mm)].

Similarly, addition of a twofold excess of phenylmagnesium bromide to 0.025 mol of ethyl atropate for 16 hr gave ester 4 in 58% yield. Saponification of a portion of ester 4 according to published procedures[7] afforded the expected 2,3-diphenylpropanoic acid, mp 83–84° (lit.[7] mp 84–85°).

Addition of Triphenylmethane to Ethyl Atropate. A. By Means of Sodium Amide in Liquid Ammonia.—To 0.027 mol of sodium amide in 300 ml of anhydrous liquid ammonia,[16] prepared from 0.64 g (0.027 g-atom) of sodium, was added 6.7 g (0.027 mol) of solid triphenylmethane, followed after 30 min by a solution of 4.4 g (0.025 mol) of ethyl atropate in 50 ml of ether added during 10 min. The reaction mixture was treated immediately with 20 g of solid ammonium chloride and the ammonia was allowed to evaporate. The resulting residue was hydrolyzed by 100 ml of 3 *N* hydrochloric acid. Work-up[15] afforded a gumlike material which was crystallized from 95% ethanol to afford 4.2 g (40%) of ethyl 2,4,4,4-tetraphenylbutanoate (6): mp 125–128°; ir (KBr) 1730 (C=O), 770, 747, and 695 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.25 (d, 20 ArH), 3.5 (m, 5, CH, CH_2), and 0.9 (t, 3, CH_3).

Anal. Calcd for $C_{30}H_{28}O_2$: C, 85.80; H, 6.77. Found: C, 85.45; H, 6.82.

B. By Means of *n*-Butyllithium.—To a solution of 4.88 g (0.02 mol) of triphenylmethane in 50 ml of THF and 25 ml of ether was added, during 5 min, 20 ml (0.03 mol) of 1.6 *M n*-butyllithium in hexane.[17] After the solution was stirred for 4 hr at 0° (ice bath), the bright red suspension was treated with a solution of 3.6 g (0.02 mol) of ethyl atropate in 20 ml of THF. After 30 min, the resulting clear red solution was poured into 300 ml of ice–water. Work-up[15] gave 5.8 g of ester 6, mp 125–128°; recrystallization from 95% ethanol afforded 5.5 g (66%) of this compound, mp 126–128°.

Addition of Sodium Diphenylmethane to Ethyl Atropate.—This reaction was effected essentially as described above for sodium triphenylmethane employing 0.025 mol of sodium amide,[16] 4.2 g (0.025 mol) of diphenylmethane, and 4.4 g (0.025 mol) of ethyl atropate. Distillation of the crude product gave 5.21 g (61%) of ethyl 2,4,4-triphenylbutanoate (9): bp 203–204° (2 mm); ir (neat) 1720 (C=O), 752, and 708 cm^{-1} (ArH); nmr (CCl_4) δ 7.08 (d, 15, ArH), 3.9 (q, 2, OCH_2), 2.93 (m, 4, CH, CH_2), and 1.04 (t, 3, CH_3).

Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.88; H, 6.99. Found: C, 84.00; H, 7.09.

***In situ* Butylation of the Diphenylmethyl Adduct of Ethyl Atropate.**—This reaction was accomplished essentially as described in the preceding experiment, except that as soon as the addition of the ethyl atropate was completed, the reaction mixture was treated during 2 min with a solution of 3.45 g (0.025 mol) of *n*-butyl bromide in 50 ml of ether. After 1 hr, the mixture was neutralized by the addition of 10 g of solid ammonium chloride. Work-up[15] afforded 3.75 g (38%) of 1,1,3-triphenyl-3-carbethoxyheptane (10): bp 239–240° (1 mm); ir (neat) 1720 (C=O), 752, and 708 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.2 (m, 15 ArH), 3.8 (m, 3, OCH_2, Ar_2CH), 3.0 (m, 2, CH_2), 1.9 (m, 2, CH_2), and 0.89 (m, 10, CH_2, CH_3).

Anal. Calcd for $C_{28}H_{32}O_2$: C, 84.00; H, 8.00. Found: C, 84.01; H, 8.24.

Addition of Disodium Benzophenone (11) to Ethyl Atropate.—To 250 ml of liquid ammonia was added 1.15 g (0.05 g-atom) of sodium metal followed by a solution of 4.55 g (0.025 mol) of benzophenone in 30 ml of ether. The resulting purple solution was stirred for 10 min and then treated during 2 min with a solution of 4.4 g (0.025 mol) of ethyl atropate in 25 ml of ether. The resulting ink-blue solution was stirred for 2 min and poured into 200 ml of ammonia containing 10 g of ammonium chloride. The ammonia was allowed to evaporate from the yellow solution and the residue was hydrolyzed by 100 ml of 3 *N* hydrochloric acid. Solid which did not dissolve was combined with that obtained by evaporating the ether from three extractions of the aqueous phase. Recrystallization of the solid from ethyl acetate gave 2.85 g (37%) of 2,4,4-triphenylbutyrolactone (13): mp 159–162°; ir (Nujol) 1760 (C=O) and 700 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.0 (m, 15, ArH) and 3.3 (m, 3, CH, CH_2).

Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.07; H, 5.73. Found: C, 84.16; H, 5.77.

Benzophenone (1.85 g, 21%) was recovered from the reaction mixture and isolated as its 2,4-dinitrophenylhydrazone derivative, mp and mmp 238–240°.

Addition of Dialkalibenzophenone Anil to Ethyl Atropate.—This reaction was effected essentially as described above for disodium benzophenone by adding 6.43 g (0.025 mol) of solid benzophenone anil in small portions to an ammonia solution of 1.15 g (0.05 g-atom) of sodium followed by a solution of 4.4 g (0.025 mol) of ester 1 in 50 ml of ether. Work-up[15] afforded an insoluble solid that was collected and treated with aqueous sodium hydroxide. Further work-up[15] afforded, upon recrystallization from absolute ethanol, 3.3 g (30%) of ethyl 2,4,4-triphenyl-4-phenylaminobutanoate (15): mp 140.5–142.5°; ir (Nujol) 3150 (NH), 1700 (C=O), 710, and 690 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.37 (m, 20, ArH), 6.4 (s, 1, NH), 3.25 (m, 5, CH, CH_2), and 1.05 (t, 3, CH_3).

Anal. Calcd for $C_{30}H_{29}NO_2$: C, 82.75; H, 6.66; N, 3.21. Found: C, 82.63; H, 6.65; N, 3.16.

When the reaction was repeated employing 1.95 g (0.05 g-atom) of potassium metal, γ-amino ester 15 was obtained in 20% yield.

Addition of N-Lithioamides to Ethyl Atropate. A. General Procedure.—To a solution of 0.025 or 0.05 mol of the appropriate amine in 100 ml of anhydrous ether was added 17.3 or 34.5 ml (0.027 or 0.055 mol) of 1.6 *M n*-butyllithium in hexane.[17] After 15–60 min, the reaction mixture was treated during 30 min with a solution of 4.4 or 8.8 g (0.025 or 0.05 mol) of ethyl atropate in 50 ml of ether. The resulting yellow solution was stirred for 5 hr at 25°, and then treated with 100 ml of 3 *N* hydrochloric acid The aqueous phase was extracted with three 50-ml portions of ether, which were discarded. The aqueous phase was neutralized by solid Na_2CO_3 and worked up,[15] and the crude product was distilled.

B. Diethylamine.—This reaction was effected on a 0.05-mol scale to afford 7.63 g (62%) of ethyl 2-phenyl-3-diethylaminopropanoate (13a): bp 115–116° (2.5 mm); ir (neat) 1740 (C=O), 733, and 700 cm^{-1} (ArH); nmr (neat) δ 7.2 (m, 5, ArH), 3.25 (m, 9, all CH_2, CH), 1.05 (t, 6, CH_3), and 0.93 (t, 3, CH_3).

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.38; H, 9.20; N, 5.96.

When the reaction was repeated essentially as described above employing THF as the solvent rather than ether, amino ester 18a was obtained in 48% yield.

C. Diisopropylamine.—Similarly, 0.05 mol of the appropriate reagents afforded 4.6 g (33%) of ethyl 2-phenyl-3-diisopropylaminopropanoate (18b): bp 142–144° (2 mm); ir (neat) 1740 (C=O), 732, and 699 cm^{-1} (ArH); nmr (neat) δ 7.1 (m, 5, ArH), 3.3 (m, 7, CH_2, CH), and 0.9 (m, 15, CH_3).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.63; H, 9.75; N, 5.05. Found: C, 73.59; H, 9.84; N, 5.24.

D. N-Methylaniline.—Likewise, 0.025 mol of the appropriate reagents gave 3.23 g (48%) of ethyl 2-phenyl-3-N-methylanilinopropanoate (18c): bp 160–161° (2 mm); ir (neat) 1730 (C=O), 758, and 695 cm^{-1} (ArH); nmr ($CDCl_3$) δ 6.9 (m, 10, ArH), 3.9 (m, 5, OCH_2, CH_2CH), 2.8 (s, 3, NCH_3), and 1.3 (t, 3, CH_3).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.13; H, 7.55; N, 4.92.

Addition of N-Methylaniline to Ethyl Atropate By Means of Sodium Amide in Liquid Ammonia.—To 0.025 mol of sodium amide in 300 ml of liquid ammonia[16] was added a solution of 2.675 g (0.025 mol) of N-methylaniline in 25 ml of ether. After 15 min, the resulting green suspension was treated during 20 min with a solution of 4.4 g (0.025 mol) of ethyl atropate in 100 ml of ether. After the mixture was stirred for 4 hr, the now gray suspension was neutralized by 15 g of solid ammonium chloride and the ammonia was allowed to evaporate. Work-up[15] gave 4.65 g (66%) of β-amino ester 18c, bp 160–161° (2 mm).

***In situ* Benzylation of Lithium Ethyl 2-Phenyl-3-diethylaminopropanoate (17a).**—Lithium salt 17a, prepared as above, was treated during 10 min with a solution of 6.33 g (0.05 mol) of benzyl chloride in 50 ml of ether. Heat was applied and the yellow mixture was refluxed for 17 hr. Upon cooling, the mixture was hydrolyzed and worked up[15] to afford 3.59 g (29%) of recovered ethyl atropate, bp 115–118° (3 mm), and 4.85 g (28%) of ethyl 2-benzyl-2-phenyl-3-diethylaminopropanoate (21a):

(16) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(17) Supplied by the Foote Mineral Co., Exton, Pa.

bp 179–180° (3.5 mm); ir (neat) 1725 (C=O), 740, and 705 cm^{-1} (ArH); nmr (neat) δ 7.15 (s, 5, ArH), 7.0 (s, 5, ArH), 4.0 (q, 2, OCH_2), 3.51 (s, 2, $ArCH_2$), 3.1 (s, 2, $ArCCH_2N$), 2.4 (q, 4, NCH_2), and 0.9 (m, 9, CH_3).

Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.56; H, 8.52; N, 4.28.

When the reaction was repeated by refluxing the reaction mixture for 50 hr instead of 17 hr, amino ester **21a** was obtained in 50% yield.

Alkylations of Ethyl 2-Phenyl-3-diethylaminopropanoate (18a) by Means of Sodium Amide in Liquid Ammonia. A. Benzyl Chloride.—To a suspension of 0.0275 mol of sodium amide in 300 ml of liquid ammonia[16] was added during 5 min a solution of 6.125 g (0.025 mol) of amino ester **18a** in 50 ml of ether. After 30 min, the resulting pale green solution was treated during 5 min with a solution of 3.16 g (0.025 mol) of benzyl chloride in 50 ml of ether. After 4 hr, the mixture was treated with 15 g of solid ammonium chloride and the ammonia was allowed to evaporate. The resulting residue was worked up[15] to afford 6.0 g (71%) of benzyl derivative **21a**, bp 162–163° (2 mm).

B. *n*-Butyl Bromide.—This reaction was accomplished essentially as described in part A above by employing 3.43 g (0.025 mol) of *n*-butyl bromide to afford 5.69 g (75%) of ethyl 2-*n*-butyl-2-phenyl-3-diethylaminopropanoate (**21b**): bp 126–128° (1 mm); ir (neat) 1725 (C=O), 755, and 705 cm^{-1} (ArH); nmr ($CDCl_3$) δ 7.2 (s, 5, ArH), 4.1 (q, 2, OCH_3), 3.04 (d, 2, NCH_2-CAr), 2.34 (q, 4, NCH_2), and 1.0 (m, 18, CH_2, CH_3).

N-Methylation of Amino Ester 18a.—To a solution of 10.0 g (0.041 mol) of amino ester **18a** in 100 ml of acetonitrile was added 20 g of methyl iodide. Sufficient heat was applied to the reaction mixture to cause gentle reflux. After 24 hr, the solution was allowed to cool before it was poured into 750 ml of ether. The resulting precipitate was collected and recrystallized from acetonitrile–ether to afford 12.85 g (80%) of (2-carbethoxy-2-phenyl)-ethyl diethyl methyl ammonium iodide (**22**): mp 122–124°; ir (Nujol) 1725 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.43 (m, 5, ArH), 4.0 (m, 9, CH_2, CH), 3.26 (s, 3, NCH_3), 1.38 (t, 6, CH_3), and 1.2 (t, 3, CH_3).

Anal. Calcd for $C_{16}H_{26}NO_2I$: N, 3.57. Found: N, 3.45.

That **22** was the actual structure of this quaternary salt was fruther demonstrated by effecting a β elimination on it by lithium diethylamine to give ethyl atropate (**1**).

Reactions of Ethyl Atropate with Primary Amines. A. With Benzylamine.—A solution of 1.4 g (0.008 mol) of ethyl atropate and 0.86 g (0.008 mol) of benzylamine in 5 ml of absolute ethanol was allowed to stand at 25° for 24 hr. Subsequent removal of solvent under reduced pressure gave a thick oil which, upon distillation, afforded 1.6 g (71%) of ethyl 2-phenyl-3-N-benzylamino propanoate (**23a**): bp 172–174° (1 mm); ir (neat) 3350 (NH) and 1725 cm^{-1} (C=O); nmr (CCl_4) δ 7.2 (m, 10, ArH), 4.05 (q, 2, OCH_2), 3.71 (s, 2, $ArCH_2N$), 3.1 (m, 3, CH, CH_2N), 1.45 (s, 1, NH), and 1.10 (t, 3, CH_3).

Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.19; H, 7.29; N, 4.88.

B. With *n*-Butylamine.—As in part A, 4.4 g (0.025 mol) of ethyl atropate and 1.85 g (0.025 mol) of *n*-butylamine were condensed in 10 ml of absolute ethanol. Work-up gave 3.12 g (50%) of ethyl 2-phenyl-3-*n*-butylaminopropanoate (**23b**): bp 107–108° (0.2 mm); nmr (CCl_4) δ 7.26 (m, 5 ArH), 4.10 (q, 2, OCH_2), 3.15 (m, 5, CH_2, CH), and 1.10 (m, 10, CH_2, CH_3).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.29; N, 5.62. Found: C, 72.45; H, 9.38; N, 5.81.

Miscellaneous Condensations of Diethylamine with Ethyl Atropate. A. In the Absence of Bases.—To 0.9 g (0.012 mol) of diethylamine in 25 ml of absolute ethanol containing a few crystals of hydroquinone was added, in 1-ml portions, a solution of 4.4 g (0.025 mol) of ethyl atropate in 5 ml of absolute ethanol.[18] After 6 days, the ethanol was stripped and the mixture was distilled to only give 3.22 g (73%) of ethyl atropate, bp 104–106° (3 mm). The nmr of the recovered ester was identical with that of an authentic sample.

B. By Means of Catalytic Quantities of Sodium Alkoxides.—Sodium ethoxide (0.0017 mol) was prepared from 0.04 g (0.0017 g-atom) of sodium in 10 ml of absolute ethanol. The ethanol was removed under high vacuum, and the resulting white solid was treated with a mixture of 1.3 g (0.017 mol) of diethylamine and 2.2 g (0.012 mol) of ethyl atropate. After 30 min, the resulting yellow solution was hydrolyzed by 150 ml of water. The usual work-up and distillation afforded small amounts of volatile products, the nmr of which indicated the presence of only trace amounts of amino ester **18a**. Similar results were obtained when catalytic amounts of commercial sodium methoxide or *n*-butyllithium were employed to affect the condensation.

Likewise, condensation of N-methylaniline with ethyl atropate effected by means of a catalytic amount of sodium ethoxide afforded only trace amounts of the desired amino ester **10c**.

Additions of Diethyl Malonate to Ethyl Atropate.—Solid sodium ethoxide (0.0017 mol), prepared as described above, was treated with a mixture of 2.2 g (0.012 mol) of ethyl atropate and 2.0 g (0.012 mol) of diethyl malonate. The resulting yellow solution was stirred for 30 min and poured into 150 ml of water. After work-up,[15] the resulting crude product was distilled to give 2.3 g (55%) of 1-phenyl-1,3,3-tricarbethoxypropane (**24**): bp 185–187° (1.5 mm) [lit.[8] bp 215° (15 mm)]; nmr ($CDCl_3$) δ 7.1 (s, 5, ArH), 4.0 (m, 6, OCH_2), 3.3 (m, 2, CH), 2.4 (q, 2, CH_2), and 1.1 (m, 9, CH_3).

Anal. Calcd for $C_{18}H_{24}O_6$: C, 24.28; H, 7.14. Found: C, 64.48; H, 7.17.

When the reaction was repeated using 4.4 g (0.025 mol) of ethyl atropate, 4.0 g (0.025 mol) of diethyl malonate, and 0.19 g (0.0035 mol) of commercial sodium methoxide, ester **24** was obtained in 60% yield.

When the reaction was repeated using 1 equiv of sodium ethoxide in 100 ml of absolute ethanol for 5 hr, 0.4 g (5%) of ester **24** was obtained, bp 185–187° (1.5 mm). Much polymeric material remained in the pot.

Likewise, when the reaction was effected by 1 equiv of sodium amide in ammonia for 5 min, 1.98 g (24%) of ester **24** was obtained; ethyl atropate and diethyl malonate were recovered in yields of 21 and 50%, respectively.

β Elimination of Ethyl 2-Phenyl-3-N-methylanilinopropanoate (18c).—To a solution of 50 ml of absolute ethanol containing a catalytic amount of sodium ethoxide was added 2.33 g (0.01 mol) of ester **18c** and the yellow solution was refluxed for 24 hr. The solution was cooled to room temperature and treated with several drops of acetic acid, and the solvent was removed to afford an oily residue. Subsequent distillation gave 0.3 g (29%) of methylaniline (identified by comparison of its ir spectrum and boiling point with those of an authentic sample), 0.1 g of recovered amino ester **18c**, bp 174–178° (1.2 mm), a small amount of ethyl atropate, bp 70–75° (1 mm), and about 1.5 g of polymeric material.

Registry No.—**1**, 22286-82-4; **6**, 22286-83-5; **9**, 22286-84-6; **10**, 22286-85-7; **13**, 2286-86-8; **15**, 22319-44-4; **18a**, 22286-87-9; **18b**, 22319-45-5; **18c**, 22286-88-0; **21a**, 22319-46-6; **21b**, 22286-89-1; **22**, 22319-47-7; **23a**, 22319-48-8; **23b**, 22286-90-4; **24**, 22319-49-9.

(18) This procedure is similar to that described for the condensation of methylamine with ethyl acrylate (ref 12).

Base-Catalyzed Reactions. XXXVI.[1] Sodium- and Potassium-Catalyzed Reactions of Selected 4-Alkylpyridines with Isoprene

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Received June 11, 1969

The addition of various 4-alkylpyridines to isoprene in a sodium- or potassium-catalyzed reaction has been observed. The pyridines selected for this study were 4-methyl-, 4-ethyl-, 4-*n*-propyl-, 4-isopropyl-, and 4-*sec*-butylpyridine. The reaction proceeds readily at 0–25° *via* a Michael-type addition mechanism to yield mono-, di-, and triaddition products. The addition of isoprene occurs exclusively on the alkyl carbon atom α to the pyridine ring, and no double-bond isomerization was noted in the product formed. In all cases, tail addition predominates over head addition, and the ratios of the products seem to be determined by both the relative stabilities of the resultant carbanions and the steric hindrance to addition. The alkenylation reaction is discussed, as is the determination of structure of the produced alkenylated pyridines by various physical and chemical means. The nmr spectra of most head addition products show a diamagnetic upfield shift for the interior methyl group. These same addition products also fail to undergo hydrogenation under conditions employed to hydrogenate the tail-addition isomers.

The reaction of olefins with alkylaromatics changes markedly with the type of catalyst and/or experimental conditions used. A good example of this is the reaction of toluene with propylene. With an acid catalyst, the main product is *p*-cymene, the result of ring alkylation;[3] however, under free-radical conditions, side-chain alkylation is found and *n*-butylbenzene is produced,[4] while a base catalyst produces isobutylbenzene, also a product of side-chain alkylation.[5] The side-chain alkylations of alkylaromatics catalyzed by alkali metals, in which the actual catalyst is an organoalkali metal complex, have been under intensive study in our laboratories. The initial study concerned the alkylation of alkylbenzenes having a benzylic hydrogen.[6,7] It was necessary to initiate these reactions with a promoter and to perform the reactions in an autoclave at temperatures varying from 150–200°, depending upon the reactants. When toluene was added to isoprene, only the mono-addition products were examined as further alkenylation occurred to give chain-lengthening isomers, presumably because addition to isoprene is faster than protonation.[8] Even though the possibility of 1,2 addition to isoprene exists, as has been found in polymerization studies of isoprene,[9] only 1,4-addition products were found in this case, which may be attributed to steric hindrance to protonation.

The first alkylations of 2- and 4-alkylpyridines were performed using ethylene at temperatures of 130–160°.[10] Recently, the alkenylation and aralkylations of various 2- and 4-alkylpyridines with butadiene and styrenes have been reported.[11,12] The alkenylation of 4-picoline with butadiene proceeded to give mono-, di-, and triaddition products, all from substitution on the picolyl carbon.

The present work was initiated to give further insight into the alkenylation mechanism. Since isoprene has an unsymmetrical structure, and can thus add in two different ways, it should be more instructive in following the reaction pathway. It was also desirable to compare the results of this study with the analogous additions of alkylbenzenes to isoprene.[8] Complete conversion of alkylpyridines to products was found when care was taken to purify the reactants. In the present work, 4-picoline, 4-ethylpyridine, 4-*n*-propylpyridine, 4-isopropylpyridine, and 4-*sec*-butylpyridine were used as the aromatics, and product structure determinations were made by both physical and chemical means.

Results and Discussion

The addition of various 4-alkylpyridines to isoprene was carried out in a pseudohomogeneous solution of dispersed catalytic amounts of metallic sodium or potassium. The reactions were observed to proceed at 0° for 4-picoline, 4-ethylpyridine, and 4-*n*-propylpyridine, but no addition product was produced with 4-isopropylpyridine or 4-*sec*-butylpyridine until the reaction mixture was warmed to room temperature. To obtain complete conversion of the pyridines to products, it was essential that all of the materials be distilled, dried over molecular sieves, and then redistilled immediately before use. If the dispersion of the alkali metal was aided by applying heat, varying amounts of side products, probably dipyridyls, were produced, and complete conversion of the pyridines to products was no longer found. The dispersion of potassium was always more difficult than that of sodium metal.

When sodium is dissolved in substituted pyridines, a radical anion is formed,[13] and thus it is proposed that the mechanism of metalation goes through the radical anion as discussed previously.[14] The radical anion could then abstract a proton, leading directly to the picolyl anion,[15] or could go through a ring-metalated anion in a kinetically controlled sequence followed by conversion to the more thermodynamically stable α

(1) (a) For paper XXXV, see N. E. Sartoris and H. Pines, *J. Org. Chem.*, **34**, 2119 (1969). (b) Paper VII of the series Alkylation of Heteroaromatics. For paper VI, see ref 1a.

(2) Monsanto Predoctoral Fellow, 1965–1966; Ethyl Corp. Predoctoral Fellow, 1967–1968.

(3) S. H. Patinkin and B. S. Friedman in "Friedel-Crafts and Related Reactions," Vol. II, part I, G. A. Olah, Ed., John Wiley & Sons, Inc., New York, N. Y., 1964, pp 9–16 and 149–151.

(4) H. Pines and J. T. Arrigo, *J. Amer. Chem. Soc.*, **79**, 4958 (1957).

(5) H. Pines and V. Mark, *ibid.*, **78**, 4316 (1956).

(6) H. Pines and L. Schaap, *Advan. Catal.*, **12**, 117 (1960).

(7) J. Shabtai and H. Pines, *J. Org. Chem.*, **30**, 3854 (1965), and references cited therein.

(8) H. Pines and N. C. Sih, *ibid.*, **30**, 280 (1965).

(9) See C. E. H. Bawn and A. Ledwith, *Quart. Rev.* (London), **16**, 361 (1962).

(10) H. Pines and B. Notari, *J. Amer. Chem. Soc.*, **82**, 2209 (1960).

(11) H. Pines and J. Oszczapowicz, *J. Org. Chem.*, **32**, 3183 (1967).

(12) H. Pines and N. E. Sartoris, *ibid.*, **34**, 2113 (1969).

(13) M. Itoh and S. Nagakura, *Tetrhedron Lett.*, 417 (1965).

(14) B. Stipanović and H. Pines, *J. Org. Chem.*, **34**, 2107 (1969).

(15) Picolyl anion throughout the paper is defined as an anion on the α-carbon atom of the alkyl group on pyridine.

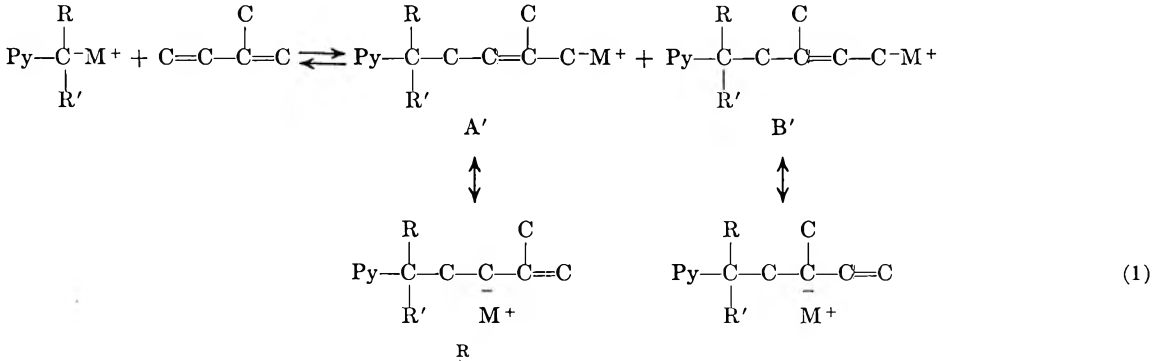
TABLE I

PENTENYLATION OF 4-PICOLINE[a]

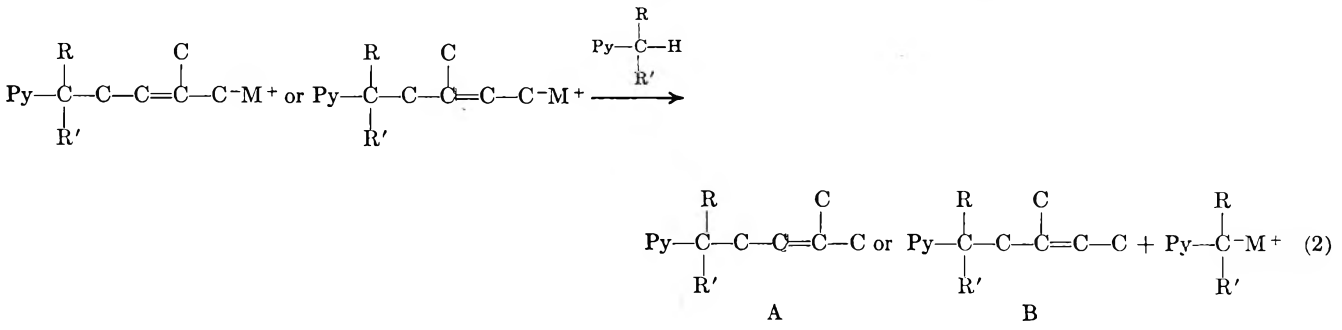
Catalyst	Sample no.	Time, hr	Conversion of alkylpyridine, %	Yield, % Monoaddition 1	Monoaddition 2	Diaddition[b] 3 + 4 + 5	Triaddition 6	Triaddition 7	Triaddition 8	Triaddition 9
Sodium	1	0.5	12	56	34	10	..	..	...	...
	4	2.0	56	35	22	43	..	..	...	...
	7	4.0	100	Trace	Trace	96	3	1	Trace	...
	11	15.0	100	...	...	82	12	5	1	...
Potassium	1	1.0	35	29	21	50	..	..	...	...
	2	1.5	51	13	9	78	..	..	...	...
	4	2.5	69	3	3	94	..	..	...	...
	6	3.8	81	4	2	85	5	4	Trace	...
	12	10.0	99+	Trace	Trace	69	16	13	2	...
	13	18.5	99+	...	...	32	36	27	5	Trace

[a] Reaction carried out at 20–25°. [b] From nmr it was estimated that about 40% of diadduct was **3**, 45% was **4**, and 15% was **5**.

isomer of the alkylaromatic, as described by Benkeser, *et al.*, for the metalation of cumene and ethylbenzene.[16] After the picolyl anion is formed, the reaction proceeds *via* a carbanion mechanism to give the alkenylation products. Equations 1 and 2 illustrate how the reaction is assumed to proceed, where R and R′ = H, alkyl, or alkenyl, PyC⁻M⁺ = the catalyst complex, and M = sodium or potassium. It is apparent that, if R and/or R′ = H, further alkenylation can and does occur to produce di- and triaddition products. The exact products obtained from the reaction of the various 4-alkylpyridines with isoprene are given in Schemes I–III.



(1)

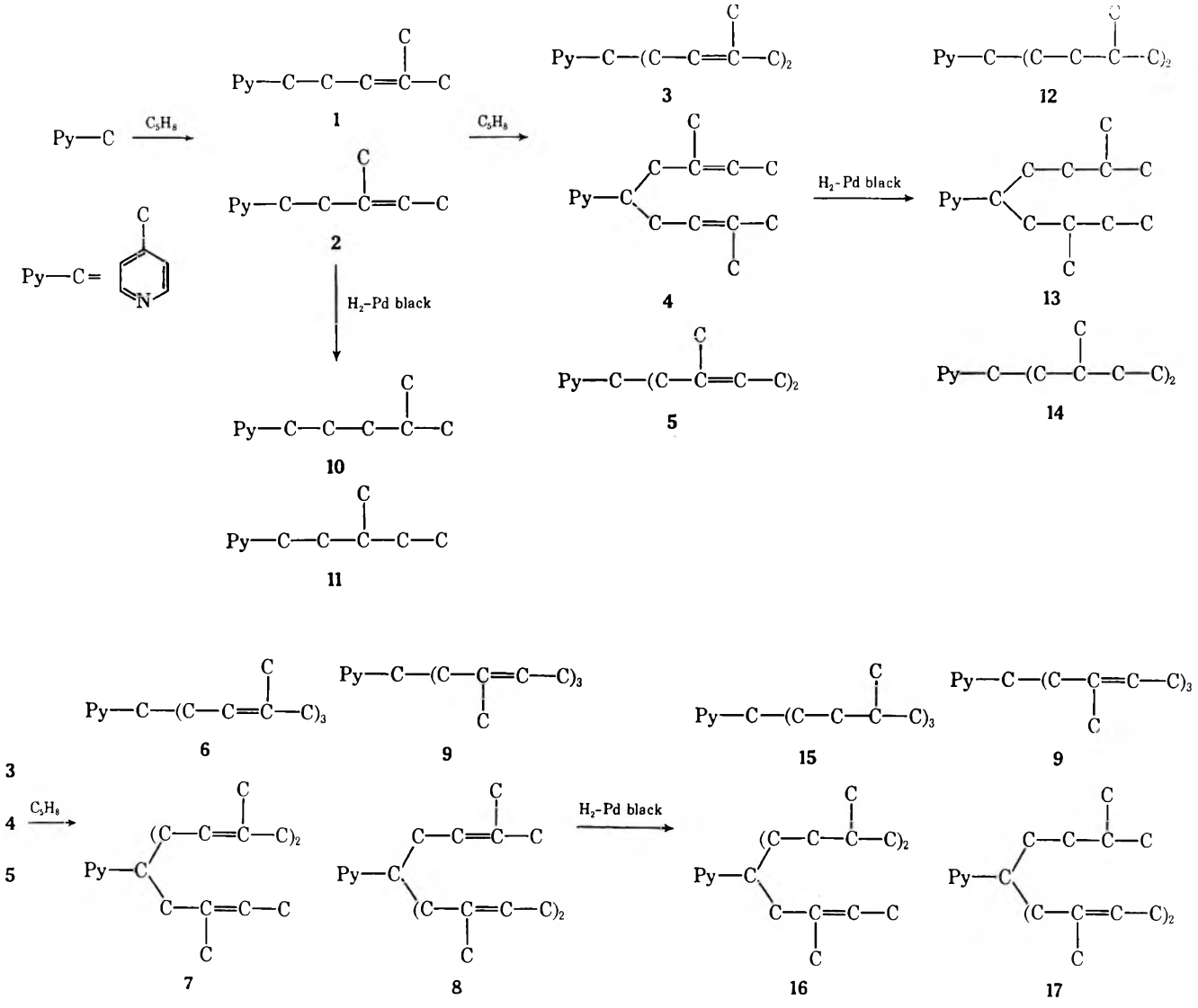


(2)

As can be seen in Schemes I–III, all of the possible products are formed, but the ratio of products changes depending on whether sodium or potassium is used as the catalyst. Tables I–III summarize the products produced throughout these reactions. The amount of catalyst used was 5 g-atom %, based on the moles of 4-alkylpyridine used for the reaction. The mole per cent yields as determined by vapor phase chromatography are corrected for variations in thermal conductivity, and compound numbers correspond to those given in Schemes I–III. Examination of Tables I–III shows that in all cases the tail-addition (A in eq 2) compound predominates, but that potassium yields a higher percentage of the head-addition (B in eq 2) isomer than does sodium. The preferential formation of type A compounds over type B for the same anion is likely to be due to the difference in the stabilities of the carbanion A′ and B′ (primary ↔ secondary *vs.* primary ↔ tertiary) given in eq 1. Steric factors begin to determine product distributions with the alkenylation of *n*-propylpyridine and are the major controlling factors when the trisubstituted products are produced. The product distributions given in Tables I–III for the moncadduct yield the following ratios for A/B when potassium is used as a catalyst: 1.4:1 for 4-picoline, 1.2:1 for 4-ethylpyridine, *ca.* 2:1 for 4-*n*-propylpyridine, 1.3:1 for 4-isopropylpyridine, and 6.5:1 for 4-*sec*-butylpyridine. It is possible to explain the above results by considering the anion stability and steric hindrance to attack by isoprene. The anion of picoline would be expected to be the most stable anion of the series if extrapolation can be made from the hydrocar-

(16) (a) R. A. Benkeser, A. E. Trevillyan, and J. Hooz, *J. Amer. Chem. Soc.*, **84**, 4971 (1962); (b) R. A. Benkeser, J. Hooz, T. V. Liston, and A. E. Trevillyan, *ibid.*, **85**, 3984 (1963).

SCHEME I



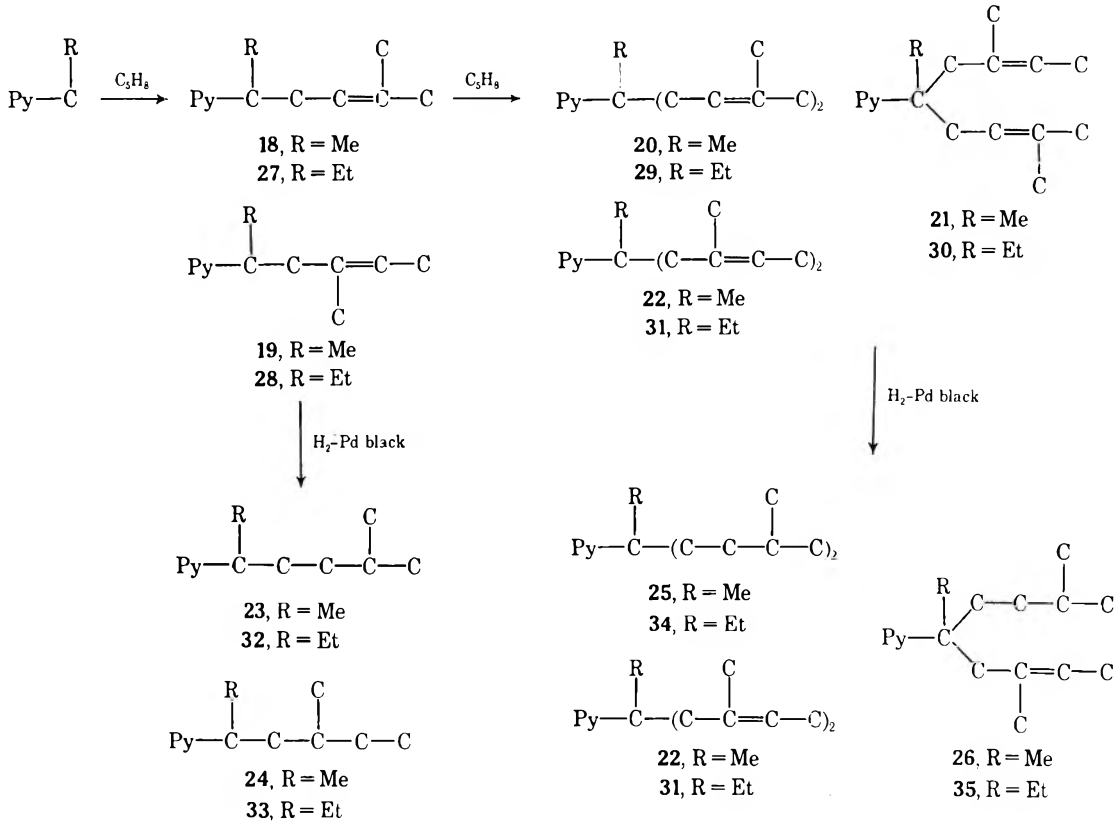
bon analogs.[17] The product ratio then agrees with the concept that the less reactive reagent shows the greater selectivity. In the case of 4-ethylpyridine, examination of molecular models indicates that the terminal methyl group can situate itself so that it does not sterically hinder the addition of isoprene and, being a more reactive anion than picoline, it thus gives a slightly lower A/B ratio. The selectivity for 4-*n*-propylpyridine is greater, since the extra ethyl group is situated so that head addition to give B is sterically hindered, whereas tail addition to give A is not affected; this point is further discussed in the following paper.[18] The most reactive anions would be those of 4-isopropylpyridine and 4-*sec*-butylpyridine. Using a potassium ion catalyst, 4-isopropylpyridine reacts about as fast and selectively as 4-ethylpyridine, but 4-*sec*-butylpyridine reacts much slower and again shows steric hindrance to head addition as did 4-*n*-propylpyridine.

In general, with sodium as a catalyst the anion seems to be less reactive and the selectivity greater, thus giving larger proportions of tail-addition products (A) than when potassium is used as a catalyst. The product ratios of A/B found when sodium was used were 1.6:1 for 4-picoline, 2.1:1 for 4-ethylpyridine, *ca.* 2:1 for 4-*n*-propylpyridine, 3:1 for 4-isopropylpyridine, and 9:1 for 4-*sec*-butylpyridine. Tables I–III also show that the reaction rates proceed in the following order, starting with the most reactive alkylpyridine: 4-ethylpyridine > 4-*n*-propylpyridine > 4-isopropylpyridine > 4-methylpyridine > 4-*sec*-butylpyridine. These results compare favorably with those found when competitive reactions are run.[18]

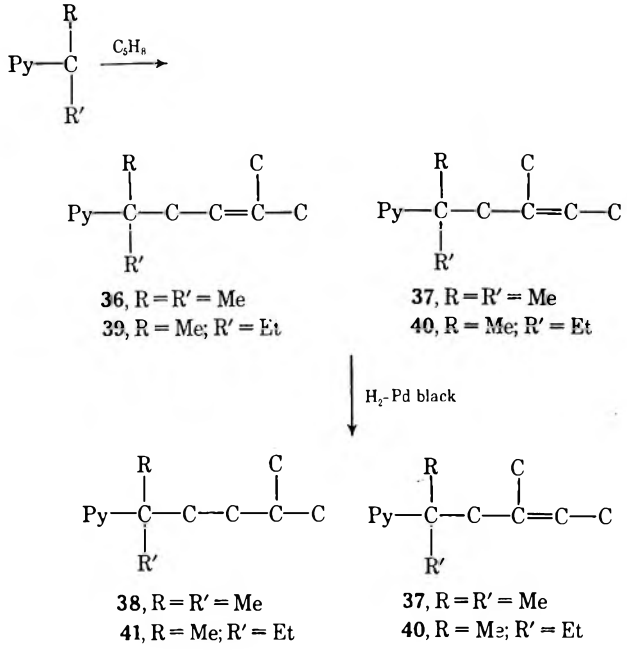
It should be noted that in all cases the product distribution percentages are applicable only for the particular molar ratios of reactants used. Also, the reaction times given in the tables are those derived from one experiment and are generally reproducible for the reactions in which all reactants are purified. The reactions were run using *ca.* 5 g-atom % of dispersed alkali metal and a 25–50% excess of isoprene based on complete reaction of the 4-alkylpyridine to give the fully substituted product; *i.e.*, 1 mol of 4-ethylpyridine was treated with 2.5–3.0 mol of isoprene. The reactions were followed in all cases to 100% conversion of the alkylpyridine to products, and in many cases the reaction was followed longer to see if the product distribution changed.

(17) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 1–27 and references cited therein.
(18) W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 422 (1970).

SCHEME II



SCHEME III



As in the previous work,[11] no double-bond isomerization was noticed in the products found. In addition, unlike the reactions of isoprene with alkylbenzenes,[8] no chain lengthing was observed when two isoprenoid units were added. While the present study was in progress, a report of the sodium-catalyzed addition of isoprene to 3-picoline at 140° was made; however, the authors only reported finding the tail-addition isomers.[19]

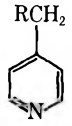
(19) Yu. I. Chumakov and V. M. Ledovskikh, *Ukr. Khim. Zh.*, **31**, 506 (1965); *Chem. Abstr.*, **63** 5594*a* (1965).

The mono-, di-, and triaddition products were roughly separated by distillation. To ease the separation of similarly boiling hydrogenated isomers, selective hydrogenation was performed in the presence of a palladium oxide catalyst. This method selectively hydrogenated only the tail-addition isomers while leaving the head-addition units unsaturated. This hydrogenation procedure was effective on all compounds having a fully substituted picolyl carbon (see Schemes I–III). It was not possible to separate the products formed when a secondary anion was added to isoprene; *i.e.*, **3**, **4**, and **5** were inseparable, as was **20** from **22** and **29** from **31**. In these cases the product ratios were determined by nmr (see below). The structural determinations of the products were made on the pure compounds separated by means of preparative gas chromatography. The physical constants of the reaction products and their corresponding hydrogenated species are given in Table IV. A few of the hydrogenated isomers were compared with products synthesized by independent means.[18] As the infrared spectra were all consistent with the compounds formed and also similar to one another, they will not be discussed. The main tool used for structural determinations was the nmr, and the results are discussed in the following section.

Discussion of Nmr Data.—The nmr spectra are quite definitive for the compounds proposed, and it is possible to divide them into four main classes (see Table V). In all cases the two α protons of pyridine gave resonance peaks at δ 8.3–8.6 ppm, and the two β-proton peaks were located at δ 6.95–7.2 ppm. Since these four pyridine protons were always present, they were taken as internal standards for integration and will not be further discussed.

TABLE II

PENTENYLATION OF 4-ETHYL- AND 4-*n*-PROPYLPYRIDINE

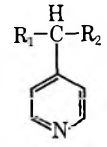


R	Catalyst	Sample no.	Time, hr	Conversion of alkylpyridine, %	Yield,[a] % Monoaddition 18 + 19 or 27 + 28	Diaddition 20 or 29	Diaddition 21 or 30	Diaddition 22 or 31
CH_3	Sodium	1[b]	0.5	30	100[c]	..	..	...
		2	1.0	66	96	2	2	...
		3	1.5	93	84	9	7	Trace
		5	3.5	100	52	27	19	2
	Potassium	1[b]	0.5	46	95[d]	2	3	...
		2[b]	1.0	70	87	6	7	...
		5	2.5	100	70	14	15	1
		6	5.3	100	15	40	40	5
C_2H_5	Sodium	1[b]	0.5	45	100[e]	..	..	...
		3[b]	1.5	82	100	..	..	...
		4	2.0	100	100	..	..	...
		5	3.0	100	98	2	..	...
		6	21.0	100	77	20	3	...
	Potassium	1[b]	0.5	8	100[e]	..	..	...
		3	1.5	55	100	..	..	...
		4	2.0	78	100	..	..	...
		5	2.5	100	91	6	2	...
		7	5.8	100	80	15	5	...
		10	20.0	100	59	28	13	Trace

[a] Compounds **18–22** and **27–31** are the products of pentenylation of 4-ethypyridine and 4-*n*-propylpyridine, respectively. [b] Reaction was run at 0° for these samples and then warmed to 20–25° for subsequent samples. [c] From nmr it was found that 68% of the monoadduct was **18** and 32% was **19**. [d] From nmr it was found that 55% of the monoadduct was **18** and 45% was **19**. [e] From nmr it was estimated that about 60–70% of the monoadduct was **27** and 30–40% was **28**.

TABLE III

PENTENYLATION OF 4-ISOPROPYL- AND 4-*sec*-BUTYLPYRIDINE



R_1	R_2	Catalyst	Sample no.	Time, hr	Conversion of alkylpyridine, %	Yield,[a] % Monoaddition 36 or 39	Monoaddition 37 or 40	Ratio of 37/37 or 39/40
CH_3	CH_3	Sodium	1	0.5	39	73	27	2.7
			2	1.0	57	72	28	2.6
			3	2.0	84	77	23	3.3
			5	20.5	100	77	23	3.3
		Potassium	1	0.5	15	58	42	1.4
			3	1.5	40	57	43	1.3
			4	2.5	75	56	44	1.3
			5	6.5	100	57	43	1.3
CH_3	C_2H_5	Sodium	1	0.5	23	89	11	8.1
			4	2.0	47	91	9	10.1
			5	3.5	60	90	10	9.0
			8	8.0	84	89	11	8.1
			12	12.0	95	90	10	9.0
			14	18.0	99+	90	10	9.0
		Potassium	1	0.5	12	90	10	9.0
			3	1.5	39	88	12	7.3
			5	3.3	52	85	15	6.7
			7	7.3	86	87	13	6.7
			11	12.0	95	86	14	6.1
			13	15.0	99+	86	14	6.1

[a] Compounds **36–37** and **39–40** are the products of pentenylation of 4-isopropylpyridine and 4-*sec*-butylpyridine, respectively.

Table V gives the approximate values found for the chemical shifts of the four classes of compounds produced. When diaddition compounds were formed, it was, of course, possible to have two classes present in the same nmr spectrum. Compounds of class I and II gave very predictable spectra. For class I, the most noticeable peaks are the unsplit methyl peaks, one being *trans* to the side chain and showing resonance at *ca.* δ 1.50 ppm and the other being *cis* to the side chain and giving a resonance peak at *ca.* δ 1.61 ppm. The class II compounds gave an unresolved mass of peaks a δ 0.9–1.9 ppm owing to the saturated side chain.

TABLE IV

PHYSICAL CONSTANTS FOR PRODUCTS OF ALKENYLATION OF 4-ALKYLPYRIDINES WITH ISOPRENE

Compd	Bp, °C (mm)	$n^{20}D$	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Relative retention times[a]
1	118–120 (15)	1.5116	$C_{11}H_{15}N$	...	...	...	...	0.46
2	76–77 (2)	1.5122	$C_{11}H_{15}N$	81.93	9.38	81.66	9.60	0.50
3[b]	125–128 (3)	1.5150	$C_{16}H_{23}N$	83.79	10.10	84.04	10.14	1.44
4[b]	125–128 (3)	1.5150	$C_{16}H_{23}N$	83.79	10.10	84.04	10.14	1.44
5[b]	125–128 (3)	1.5150	$C_{16}H_{23}N$	83.79	10.10	84.04	10.14	1.44
6	162–165 (3)	1.5257	$C_{21}H_{31}N$	...	...	...	...	2.61
7	162–165 (3)	1.5270	$C_{21}H_{31}N$	...	...	...	...	2.84
8[c]	162–165 (3)	1.5284	$C_{21}H_{31}N$	84.78	10.51	84.61	10.51	3.12
9[c]	162–165 (3)	1.5286	$C_{21}H_{31}N$	...	...	...	...	3.48
10	78–79 (3.5)	1.4874	$C_{11}H_{17}N$	80.92	10.50	80.81	10.80	0.40
11	78–79 (3.5)	1.4907	$C_{11}H_{17}N$	80.92	10.50	80.62	10.73	0.42
12[b]	...	1.4850	$C_{16}H_{27}N$	...	...	...	...	1.02
13[b]	...	1.4850	$C_{16}H_{27}N$	...	...	...	...	1.02
14[b]	...	1.4850	$C_{16}H_{27}N$	...	...	...	...	1.02
15	...	1.4858	$C_{21}H_{37}N$	83.10	12.29	83.31	12.49	2.05
16	...	1.4979	$C_{21}H_{35}N$	83.65	11.70	83.55	11.86	2.60
17[d]	...	...	$C_{21}H_{33}N$	...	...	...	...	...
18[b]	85–86 (3)	1.5098	$C_{12}H_{17}N$	...	...	...	...	0.53
19[b]	85–86 (3)	1.5098	$C_{12}H_{17}N$	...	...	...	...	0.53
20	117–118 (1.5)	1.5213	$C_{17}H_{25}N$	...	...	...	...	1.82
21	117–118 (1.5)	1.5220	$C_{17}H_{25}N$	83.89	10.35	83.73	10.53	2.01
22[c]	130–134 (4)	1.5229	$C_{17}H_{25}N$	83.89	10.35	83.91	10.31	2.22
23[b]	98–100 (8)	1.4877	$C_{12}H_{19}N$	81.30	10.80	81.11	10.91	0.43
24[b]	98–100 (8)	1.4877	$C_{12}H_{19}N$	81.30	10.80	81.11	10.91	0.43
25	...	1.4890	$C_{17}H_{29}N$	82.53	11.81	82.66	11.84	1.37
26	...	1.5042	$C_{17}H_{27}N$	...	...	...	...	1.75
27[b]	112–115 (4)	1.5062	$C_{13}H_{19}N$	82.48	10.12	82.25	10.25	0.65
28[b]	112–115 (4)	1.5062	$C_{13}H_{19}N$	82.48	10.12	82.25	10.25	0.65
29	146–148 (4)	1.5229	$C_{18}H_{27}N$	83.98	10.58	83.77	10.64	2.30
30	146–148 (4)	1.5238	$C_{18}H_{27}N$	83.98	10.58	84.09	10.65	2.55
31[c]	146–148 (4)	1.5243	$C_{18}H_{27}N$	83.98	10.58	84.11	10.37	2.76
32[b]	...	1.4875	$C_{13}H_{21}N$	...	...	...	...	0.53
33[b]	...	1.4875	$C_{13}H_{21}N$	...	...	...	...	0.53
34	...	1.4902	$C_{18}H_{31}N$	...	...	...	...	1.71
35	...	1.5065	$C_{18}H_{29}N$	...	...	...	...	2.28
36	130–134 (15)	1.5119	$C_{13}H_{19}N$	...	...	...	...	0.67
37	130–134 (15)	1.5132	$C_{13}H_{19}N$	82.48	10.12	82.77	10.14	0.74
38	...	1.4917	$C_{13}H_{21}N$	81.61	11.07	81.43	11.09	0.56
39	110–112 (3)	1.5133	$C_{14}H_{21}N$	82.70	10.41	83.04	10.56	0.92
40	110–112 (3)	1.5144	$C_{14}H_{21}N$	82.70	10.41	82.53	10.38	1.05
41	...	1.4938	$C_{14}H_{23}N$	...	...	...	...	0.80

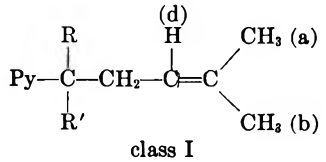
[a] Retention times were obtained using a 3.2 m × 0.25 in. column packed with 15% Versamid 900 on 60–80 mesh Gas-Pack WAB. Conditions used were 200° for monoadducts, 225° for diadducts, 245° for triadducts, and a flow rate of 70–75 ml/min. Internal standard was 1,1-diphenylbutane = 1.00 retention time. [b] The compounds within each group were inseparable and the physical constants given are for the mixture. [c] These compounds were isolated from reactions run in a different system; the procedure is given by H. Pines and W. M. Stalick, *Tetrahedron Lett.*, 3723 (1968). [d] This compound was not isolated.

There is an interesting feature in class III compounds due to steric crowding. The spectra of *cis*- or *trans*-3-methyl-2-pentene is quite similar to that described in Table V, as are the spectra of compounds **2**, **4**, **5**, **19**, and **28** (R = H, R′ = H, alkyl, alkenyl). However, when examining the spectra of other class III compounds where R and R′ are alkyl or alkenyl groups, a noticeable upfield shift is observed for the internal methyl group (b). This methyl group, which has previously been found in the region of δ 1.65 ppm, has now shown a diamagnetic shift to *ca.* δ 1.15 ppm, or an upfield shift of 0.5 ppm. From examination of space-filling molecular models of these compounds, it becomes clear that, in the compounds where R = H and R′ = H, alkyl, or alkenyl, the most stable position for the pentenyl group is away from the pyridine ring. However, for the other compounds in this class (R = R′ ≠ H), the pentenyl side chain must frequently reside over the pyridine ring owing to steric crowding. When this occurs, the internal methyl group (b) is much closer to the pyridine ring than is the external methyl group (a). When the methyl group is crowded into the π cloud above the ring, its shielding is increased, since the induced magnetic field of the ring and the applied magnetic fields are opposed.[20] Therefore, an upfield shift is noted for the internal methyl group, but virtually no shift is observed for the terminal methyl group. Owing to the hydrogenation procedure used (above), class IV is composed of only five compounds, **11**, **13**, **14**, **24**, and **33**. The spectra show resonance peaks for the terminal methyl group (a) at about δ 0.90 ppm, and for the internal methyl group (b) at about δ 0.94 ppm, but the peaks are not very well resolved from one another.

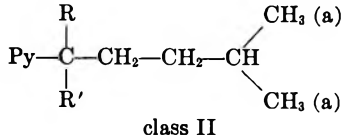
(20) D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists," Academic Press Inc., New York, N. Y., 1967, p 34.

TABLE V

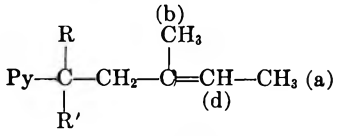
NMR DATA FOR GENERAL COMPOUND STRUCTURES



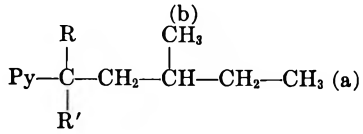
class I



class II



class III



class IV

Compd class	Group	δ ppm	Multiplicity
I	a	1.50	Singlet
	b	1.61	Singlet
	d	4.90	Multiplet
II	a	0.85	Doublet
III[a]	a	1.58	Doublet
	b	1.66	Singlet
	d	5.10	Quartet
IV	a	0.90	Triplet
	b	0.94	Doublet

[a] See discussion in text about this class of compound.

As was stated earlier, the following compounds were inseparable from one another: **3** and **4** from **5**; **18** from **19**; **27** from **28**; and the hydrogenation products of these compounds. The ratios given in Tables I–III for these compounds were determined by nmr in the following way. A peak at *ca.* δ 1.45 ppm was due to the head-addition isomer, and in the case of compounds **18** and **19** this peak allowed a good approximation of the relative amounts of these two compounds to be made. The ratios of **27**/**28** and of **3**/**4**/**5** were estimated in this same manner, but owing to some overlapping by a peak from the side-chain methylene group the ratios cannot be determined so accurately.

Experimental Section

Reagents.—4-Picoline, 4-ethylpyridine, 4-isopropylpyridine, and 4-*n*-propylpyridine were purchased from Reilly Tar and Chemical Co. The synthesis of 4-*sec*-butylpyridine is described in the following paper.[18] The alkylpyridines were distilled, dried over Linde 5A Molecular Sieves, and then redistilled immediately before use. Ethyl-, *n*-butyl-, and *sec*-butylcyclohexane, used as internal standards for vpc analyses, were obtained by catalytic hydrogenation of the corresponding alkylbenzenes. Isoprene (Aldrich 1-1955-1) was dried over Linde 3A Molecular Sieves and distilled just before use. Analyses by vpc of the above materials indicated them to be of >99.5% purity.

Preparation of Catalyst Solution and General Reaction Procedure.—The equipment used was that described previously.[8] The catalyst solution was prepared and the reaction procedure was performed as described in previous papers.[11,12] Dispersion was accomplished at room temperature and the reaction products were separated by distillation. The physical constants of the products thus produced can be found in Table IV.

Catalytic Hydrogenation.—In all cases the mono-, di-, and tripentylated compounds were separated from each other by distillation on a 6-in. Vigreux column. The hydrogenations were carried out by diluting the alkylpyridines with four parts of ethanol and adding 10% of a palladium black catalyst (Englehard, from Sargent No. SC13906) followed by reaction at room temperature and atmospheric pressure. The reaction mixture was checked by vpc, and, when *ca.* 95% of the tail-addition product was hydrogenated, the reaction was quenched. This allowed the selective hydrogenation of the tail-addition product with little or no hydrogenation of the head-addition product. The ethanol was evaporated under a stream of nitrogen and the products were separated by vpc.

Analysis of Products.—The infrared spectra of the pure samples were taken with a Baird Model 4-55 spectrophotometer calibrated at 5.14 μ with a polystyrene film. The nmr spectra were taken with a Varian Model A-60 nmr spectrophotometer using tetramethylsilane as an internal standard. Microanalyses were performed by either MicroTech Laboratories, Skokie, Ill., or M-H-W Laboratories, Garden City, Mich. Vapor phase chromatographic analysis and separations were performed on a F & M Model 720 dual-column instrument equipped with a thermal-conductivity detector and using helium as a carrier gas. The separations and identifications of the various alkenylated pyridines were accomplished with various columns with diameters of $^1/_8$–$^3/_8$ in. and lengths of 2.3–16.1 m, packed with 5–15% Versamide 900 on 60–100 mesh Gas Pack WAB.

Registry No.—**1**, 22253-14-1; **2**, 22253-15-2; **3**, 22253-16-3; **4**, 22253-17-4; **5**, 22253-18-5; **6**, 22297-86-5; **7**, 22253-19-6; **8**, 22253-20-9; **9**, 22297-87-6; **10**, 22241-38-9; **11**, 22241-39-0; **12**, 22253-23-2; **13**, 22253-24-3; **14**, 22253-25-4; **15**, 22253-26-3; **16**, 22253-27-6; **18**, 22253-28-7; **19**, 22253-29-8; **20**, 22253-30-1; **21**, 22253-31-2; **22**, 22253-32-3; **23**, 22253-33-4; **24**, 22253-34-5; **25**, 22253-35-6; **26**, 22253-36-7; **27**, 22253-37-8; **28**, 22253-38-9; **29**, 22297-88-7; **30**, 22253-39-0; **31**, 22253-40-3; **32**, 22241-55-0; **33**, 22241-56-1; **34**, 22241-57-2; **35**, 22241-58-3; **36**, 22241-59-4; **37**, 22241-60-7; **38**, 22241-61-8; **39**, 22241-62-9; **40**, 22241-63-0; **41**, 22241-64-1; isoprene, 78-79-5.

Acknowledgment.—The authors wish to thank Dr. Janusz Oszczapowicz for preliminary studies performed in this laboratory.

Base-Catalyzed Reactions. XXXVII.[1] Relative Rates of Side-Chain Alkenylation of 4-Substituted Pyridines with Isoprene. Effects of the Side-Chain Double Bond on Reaction Rates

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Received June 11, 1969

The competitive side-chain alkenylation of various 4-alkyl and alkenylpyridines with isoprene catalyzed by alkali metals was investigated. Examination of the alkylpyridines used in the reaction shows that steric factors are important when substitution is made on the carbon β to the pyridine ring. The presence of a side-chain double bond increases the rate of alkenylation and this is ascribed to a complexation of the olefinic bond with the alkali metal catalyst. The relative increase in competitive rate varies with the catalyst used in the reaction, such that K > Na > Li. The changes in reactivity that occur when using different catalysts are explained by the principle of hard and soft acids and bases. A table identifying many new 4-substituted pyridine compounds is also given.

It was noted in the preceding paper[1b] that, when isoprene was added to 4-picoline, the diadducts were formed very rapidly, even though the monoadducts were in very small concentrations. Diaddition products became detectable when only *ca.* 2% of the 4-picoline had been converted into monoadducts. The same results were observed when butadiene was added to 4-picoline in a similar reaction.[3] The side-chain double bond in these cases increases the overall rate of addition of a second conjugated diene.

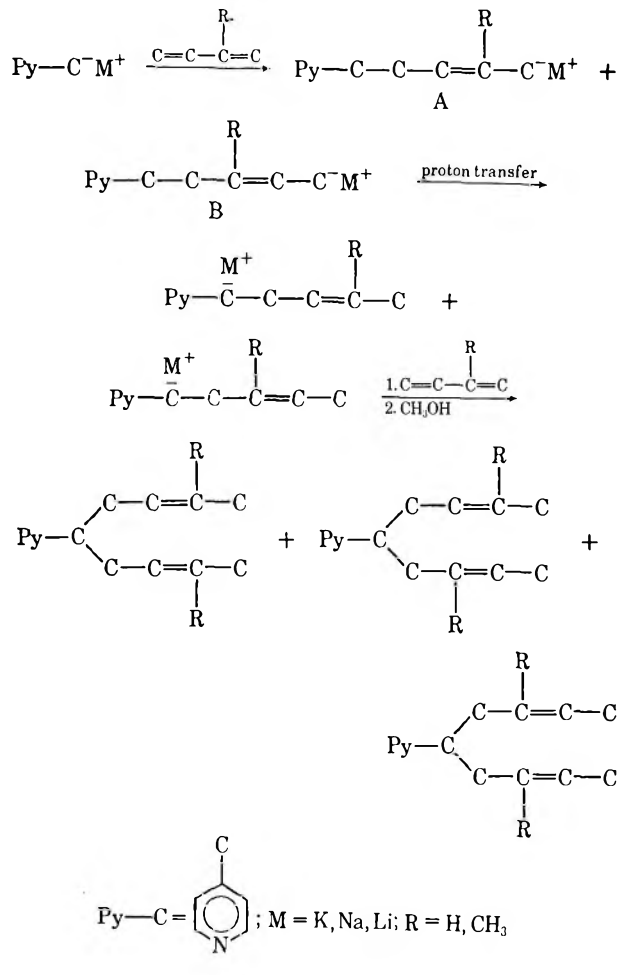
It was initially suggested[3] that this rate enhancement is due to a π-electron bonding of the picolyl[4] hydrogen with the double bond of the alkenyl group or aryl group, thus increasing the acidity of the alkenylated pyridines over that of the corresponding alkylpyridines. Similar increases in acidity of otherwise unactivated C–H bonds in camphenilone due to formation of homoenolate anions have also been noted.[5] Further studies now indicate that other factors may be of greater importance in the type of compounds presently being investigated. We now suggest that internal protonation of the anion formed by addition of a diolefin and complexation of the alkali metal with the side-chain double bond are the main contributors to the rate enhancement. Similar reports of the interaction of metals, such as lithium[6] and silver,[7] with olefinic bonds are known.

This study examines the reaction of isoprene at room temperature with various 4-alkyl- and alkenylpyridines. The steric effect of substitution is examined as well as the effect of changing the alkali metal catalyst.

Results and Discussion

The base-catalyzed alkenylation of 4-picoline with butadiene proceeds to only 1.5% completion before diaddition formation is noted.[3] When isoprene is added to 4-picoline, diaddition is found when the reaction has proceeded to about 2% completion.[1b] In these two cases the monoadducts react about 65 and 50 times faster, respectively, than does 4-picoline. Scheme I shows the general reaction of interest.

SCHEME I



In order to determine the effect of structure on reaction rate, a large number of 4-substituted pyridines were synthesized. These compounds are listed in Table I, along with their physical constants. All new compounds were identified by nmr. Competitive reactions were then carried out using isoprene as the diolefin, with either 4-picoline or 4-*n*-propylpyridine in

(1) (a) Paper VIII of the series Alkylation of Heteroaromatics. For paper VII and XXXVI of the series Base-Catalyzed Reactions, see ref 1b. (b) W. M. Stalick and H. Pines, *J. Org. Chem.*, **35**, 415 (1970).

(2) Monsanto Predoctoral Fellow, 1965–1966; Ethyl Corp. Predoctoral Fellow, 1967–1968.

(3) H. Pines and J. Oszczapowicz, *J. Org. Chem.*, **32**, 3183 (1967).

(4) Picolyl anion throughout the paper is defined as an anion on the α-carbon atom of the alkyl group on pyridine.

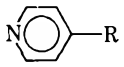
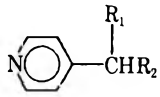
(5) (a) A. Nickon and J. L. Lambert, *J. Amer. Chem. Soc.*, **88**, 1905 (1966); (b) A. Nickon, J. L. Lambert, and J. E. Oliver, *ibid.*, **88**, 2787 (1966).

(6) J. P. Oliver, J. B. Smart, and M. T. Emerson, *ibid.*, **88**, 4101 (1966).

(7) D. Gray, R. A. Wies, and W. D. Closson, *Tetrahedron Lett.*, 5639 (1968).

TABLE I

SYNTHESIS OF 4-SUBSTITUTED PYRIDINES

Starting Materials		Products					
							
R	Alkylating agent	R_1	R_2	Registry no.	Isolated yield, %	Bp,[a] °C (mm)	$n^{20}D$
C_2H_5	C_2H_5Br	CH_3	C_2H_5		98[b,c]	128–130 (100)	1.4958
CH_3	i-C_3H_7Br	H	i-C_3H_7		79[d]	81 (15)	1.4896
C_2H_5	i-C_3H_7Br	CH_3	i-C_3H_7		98[c,d]	89 (15)	1.4930
CH_3	i-$C_5H_{11}Br$	H	i-C_5H_{11}	22241-38-9	85[c]	77–79 (3.5)	1.4874
CH_3	$CH_3CH(C_2H_5)CH_2Br$	H	$CH_2CH(CH_3)C_2H_5$	22241-39-0	92	78 (2.5)	1.4907
CH_3	C_4H_9Br	H	C_4H_9		93[e]	62–65 (2)	1.4920
CH_3	C_3H_7Br	H	C_3H_7		94[f]	84 (10)	1.4939
CH_3	i-C_4H_9Br	H	i-C_4H_9	4810-78-0	78	70 (3)	1.4903
CH_3	$(CH_3)_3C(CH_2)_2Br$	H	$(CH_2)_2C(CH_3)_3$	22241-41-4	90	89–90 (4)	1.4920
CH_3	$C_5H_{11}Br$	H	C_5H_{11}		87[g]	86–88 (4)	1.4891
CH_3	$H_2C{=}CH(CH_2)_2Br$	H	$(CH_2)_2CH{=}CH_2$	22241-42-5	80	102 (13)	1.5087
CH_3	$H_2C{=}CH(CH_2)_3Br$	H	$(CH_2)_3CH{=}CH_2$	22241-43-6	86	85–86 (3)	1.5052
C_2H_5	i-$C_5H_{11}Br$	CH_3	i-C_5H_{11}	22253-33-4	61[c]	98–100 (8)	1.4869
C_2H_5	$CH_3CH(C_2H_5)CH_2Br$	CH_3	$CH_2CH(CH_3)C_2H_5$	22253-34-5	70[c]	98–99 (8)	1.4895

[a] Boiling points are uncorrected. [b] Literature bp 197° (765 mm), $n^{20}D$ 1.49515 [C. T. Kyte, G. H. Jeffery, and A. I. Vogel, *J. Chem. Soc.*, 4454 (1960)]. [c] Yield calculated by vpc. [d] Previously synthesized in this laboratory [H. Pines and B. Notari, *J. Amer. Chem. Soc.*, **82**, 2209 (1960)]. [e] Literature bp 95° (6 mm), $n^{20}D$ 1.49196 (cited in *b*). [f] Literature bp 84° (8 mm), $n^{20}D$ 1.49387 (cited in *b*). [g] Literature bp 68.5° (0.1 mm), $n^{20}D$ 1.4886 [J. P. Wibaut and J. W. Hey, *Rec. Trav. Chim. Pays-Bas*, **72**, 513 (1953)].

competition with the synthesized pyridine. *Ca.* 5 g-atom % of metallic sodium was dispersed in an equimolar amount of the two 4-substituted pyridines to form the catalyst, and then about 10 mol % of isoprene was added to this mixture. Samples were removed periodically and the ratio of products was determined by vpc analysis; these competitive results were then corrected for variations in relative thermal conductivity and are summarized in Table II. The effect of anion stability on reaction rate can be inferred by examinination of expt 1 and 2. The secondary anion appears to be the most reactive; 4-picoline reacts more slowly owing to the stability of the anion, and the tertiary anion, although expected to be the most reactive, is slower, presumably because steric factors decrease the rate of addition to isoprene. Although the relative concentrations as well as the relative reactivities of the reactant anions contribute to the observed results, it appears that anion reactivity and steric hindrance effects are of major importance in the case of alkylpyridines. This assumption is further strengthened by the results discussed in the section dealing with solvent effects (see below). These results are in agreement with previous studies on the competitive rates of reaction of substituted aromatic hydrocarbons[8] and of 2- and 4-alkylpyridines[9,10] with ethylene carried out in an autoclave at elevated temperatures.

The relative rate of pentenylation of 4-*n*-propylpyridine is slower than that of 4-ethylpyridine by a factor of 2.5 (expt 5), probably owing to the increased bulk of the side chain. Further lengthening of the chain has only a slight effect on the rate of reaction, *n*-propyl-, *n*-butyl-, *n*-pentyl-, and *n*-hexylpyridine all being 3.5–4 times more reactive than 4-picoline (expt 3 and 7–9). Likewise, substitution for a hydrogen by a methyl group on a carbon atom γ or δ to the pyridine ring has little effect on the rate of reaction (expt 10–13). However, when the methyl substitution is on the carbon atom β to the pyridine ring, the rate of reaction decreases sharply within each series of anions (expt 1, 4, and 15 for tertiary anions and 2, 3, and 14 for secondary anions).

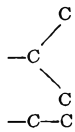
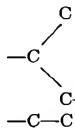
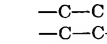
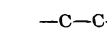
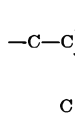
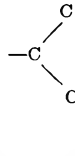
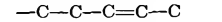
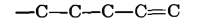
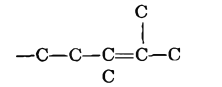
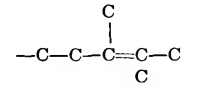
The effect of the side-chain double bond on the rate of isoprene addition can also be seen in Table II (expt 16, 19, and 20). The double bond of 4-(3-pentenyl)-pyridine (the butadiene adduct, expt 16) increases the rate of reaction with isoprene by a factor of *ca.* 10 over that of 4-picoline, while the isoprene monoadducts (expt 19 and 20) show a rate increase of about 7.5. The effect of the position of the double bond was examined in the case of 4-(3-pentenyl)-, 4-(4-pentenyl)-, and 4-(5-hexenyl)pyridine (expt 16–18), and it was found that the effect of the unsaturation decreases as the double bond is moved from the γ to the δ to the ϵ position with respect to the pyridine ring, the relative rates decreasing from 10 to 7 to 4, respectively. Unsaturation in the ϵ position has almost no effect on the reaction rate (expt 9 *vs.* 18).

In addition to sodium and potassium, it was found that lithium metal is also a catalyst for these reactions.[11] Changing the metal catalyst from potassium to sodium to lithium changes the competitive rate of pentenylation of 2-methyl-5-(4-pyridyl)-2-pentene *vs.* 4-*n*-propylpyridine from 2.6 to 2.2 and 1.9, respectively (expt 23, 19, and 25). However, no change in competitive reaction rates is noted when different metals are used as catalysts for the addition of isoprene to the saturated analog, 4-methyl-1-(4-pyridyl)pentane *vs.* 4-*n*-propylpyridine (expt 21, 10, and 24). The above results can be explained by applying the principle of hard and soft acids and bases.[12] An olefin is a soft base and as such is expected to form a more stable complex with the softest acid, potassium ion, and the least stable complex with lithium ion, which is the hardest acid in

(8) H. Pines and L. Schaap, *J. Amer. Chem. Soc.*, **80**, 3076 (1958).
(9) H. Pines and L. Schaap, *Advan. Catal.*, **12**, 117 (1960).
(10) B. Notari and H. Pines, *J. Amer. Chem. Soc.*, **82**, 2945 (1960).
(11) W. M. Stalick and H. Pines, *J. Org. Chem.*, in press.
(12) (a) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963); (b) R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

TABLE II

COMPETITIVE PENTENYLATION OF 4-SUBSTITUTED PYRIDINES[a]

Expt	4-Alkylpyridine 4-$C_5H_4NR_1$	4-Alkylpyridine 4-$C_5H_4NR_2$	Ratio of reacted $C_5H_4NR_1$/$C_5H_4NR_2$	Normalized ratio[b]
1			2.0	2.0
2			8.2	8.2
3			3.4	3.4
4			0.9	0.9
5			2.5	8.5
6			0.24	2.0
7			1.2	4.1
8			1.1	3.7
9			1.0	3.4
10			1.3	4.4
11			1.3	4.4
12			1.3	4.4
13			1.1	3.7
14			0.05	0.2
15			0	<0.01
16[c]			2.9	9.9
17			2.1	7.1
18			1.3	4.4
19			2.2	7.5
20			2.2	7.5
21[d]			1.2	4.1
22[d]			0.7	5.5
23[d]			2.6	8.8
24[e]			1.2	4.1
25[e]			1.9	6.5
26[f]			1.2	4.1
27[f]			1.1	9.0
28[f]			2.7	9.2
29[g]			2.7	9.2

[a] Sodium metal was used as the catalyst initiator, unless otherwise noted. [b] Ratio of reacted $C_5H_4NR_1$/4-picoline normalized to 4-picoline = 1. [c] Mixture of *cis-trans* was used in ratio of 1:2. [d] Potassium metal was used as the catalyst initiator. [e] Lithium metal was used as the catalyst initiator. [f] Reaction was run in a homogeneous system using dimethyl sulfoxide as a solvent and potassium *t*-butoxide as a catalyst. [g] Reaction was run in a homogeneous system using N-methyl-2-pyrrolidone as a solvent and potassium *t*-butoxide as a catalyst.

this study. As a consequence, the stronger the metal-to-olefin complex, the larger the amount of negative charge on the picolyl carbon; the picolyl carbon thus becomes more nucleophilic and reacts more rapidly. The metal–double-bond complex is assumed to be a monomer, in analogy with the case of benzyllithium in tetrahydrofuran.[13] The rate increase that is realized

in this case is even more significant when one considers that the metal not only complexes with the side-chain double bond but is probably also stabilized intermolecularly by the lone-pair electrons of neighboring pyridine molecules.

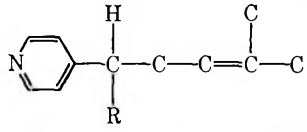
The second factor which appears to play an important role in increasing the rate of addition is the internal protonation of the monoaddition product (A and B in Scheme I). Since a rate increase of 50 to 65 times is noticed in the case of the isoprene or butadiene monoadduct over that of 4-picoline, and 7.5 and 10 are the respective rate increases due to double-bond complexation of the metal, the other factor of 6.5 is probably due to the intramolecular protonation of the side chain and subsequent metalation of the picolyl carbon. The following diagram illustrates the assumed cyclic structure containing five carbon atoms and a bridging hydrogen; examination of space-filling molecular models shows this to be a favorable situation.

This mechanism implies that the product formed from internal protonation must be of a *cis* conformation about the double bond. If an examination is made of

(13) P. West and R. Waack, *J. Amer. Chem. Soc.*, **89**, 4395 (1967).

TABLE III

CHARACTERIZATION OF NEW PRODUCTS FORMED DURING COMPETITIVE STUDIES[a]



Products from expt no.[b]	R[c]	Registry no.	$n^{20}D$	Calcd, % C	Calcd, % H	Found, % C	Found, % H
7	—C—C—C	22241-44-7	1.5042	82.70	10.41	82.52	10.35
8	—C—C—C—C	22241-45-8	1.5020	82.89	10.66	83.06	10.60
9	—C—C—C—C—C	22241-46-9	1.4996	83.05	10.89	82.84	10.78
10	—C—C—C—C (C)	22241-47-0	1.4990	83.05	10.89	83.06	10.78
11	—C—C—C—C (C)	22241-48-1	1.4998	83.05	10.89	82.72	10.78
12	—C—C—C (C) (C)	22241-49-2	1.5002	82.89	10.66	82.57	10.49
13	—C—C—C—C (C) (C)	22241-50-5	1.4960	83.20	11.09	83.47	10.99
14	—C (C) (C)	22241-51-6	1.5082	82.70	10.41	82.64	10.26
15	—C—C[d] (C)	12241-52-7	1.5149	82.89	10.66	83.09	10.68
16	C—C=C—C *trans*	22256-21-9	1.5148	83.66	9.83	83.76	9.63
16	C—C=C—C *cis*	22256-22-0	1.5178	83.66	9.83	83.60	9.92
17	—C—C—C=C	22241-53-8	1.5126	83.66	9.83	83.69	9.71
18	—C—C—C—C=C	22241-54-9	1.5102	83.78	10.11	83.52	10.06

[a] The physical constants of all products of the competitive reactions not given here are given in Table IV of the preceding paper (see ref 1b). [b] Experiment numbers refer to those given in Table II. [c] The isoprene adduct shown is the one formed by C-4 addition of isoprene. Nmr studies indicate that the product isolated contains about 60–70% C-4 and 30–40% C-1 addition products; therefore, the elemental analyses and refractive indices given here are for the mixture. [d] This product is made from 4-(2-isoamyl)pyridine, so that the hydrogen represented in the main structure in this case is replaced by a methyl group.

the diaddition products of butadiene to 4-picoline, a ratio of 3.1:3.3:1.0 is found for the distribution of *trans,trans/trans,cis/cis,cis*. Indeed, the ratio of product containing a *cis*-butene group is much larger than the thermodynamically predicted ratio.[14,15]

Solvent Effects.—Similar catalytic reactions occur in homogeneous media of dipolar aprotic solvents using potassium *t*-butoxide as a catalyst.[16] To determine the effect of solvent on the competitive rates of reaction, four experiments were performed using dimethyl sulfoxide or N-methyl-2-pyrrolidone as solvents (Table II, expt 26–29). It was found that the effect of solvent on the competitive rates is small. This result is not too surprising, for although the reactions in the presence of the alkali metal catalyst have been made without added solvent, they are, in actuality, in a similar polar medium of excess alkylpyridine. This type of reaction has been tried in less polar solvents, such as tetrahydrofuran and dimethoxyethane, but no evidence for reaction was found.[17]

The competitive rate of alkenylation of 4-isopropylpyridine increased upon changing the catalyst from sodium to potassium to potassium *t*-butoxide; the competitive ratio of 4-isopropylpyridine/4-ethylpyridine changes from 0.24:1 to 0.7:1 to 1.1:1, respectively, so that, in the homogeneous system, 4-isopropylpyridine is more reactive than 4-ethylpyridine, as would be predicted by anion reactivity. It appears that the relative rate of pentenylation of 4-isopropylpyridine increases as the anion becomes more loosely associated with the alkali metal; and finally, in the dipolar aprotic solvents, the cation is solvated and the anion of 4-isopropylpyridine adds to isoprene faster than does the anion of 4-ethylpyridine. This factor is important, because there should be little if any steric hindrance to addition by 4-ethylpyridine; but 4-isopropylpyridine should experience steric hindrance to addition if the ion pair is closely related. In the preceding paper[1b] it was also shown that the amount of head-addition product becomes larger as the catalyst is changed from sodium to

(14) The thermodynamic *cis/trans* ratio of 2-butenes at 27° was calculated to be about 1:3 (see ref 15). From this the calculated values expected for the diaddition product would be 9:6:1 for *trans,trans/trans,cis/cis,cis*.

(15) J. R. Kilpatrick, E. J. Prosen, K. S. Pitzer, and F. D. Rossini, *J. Res. Nat. Bur. Stand.*, **A36**, 559 (1946).

(16) H. Pines and W. M. Stalick, *Tetrahedron Lett.*, 3723 (1968).

(17) Unreported results from this laboratory.

potassium, which is in line with the increase in reactivity. Further substantiation of this point can be made by the fact that even with a sodium catalyst, the addition of these two alkylpyridines to ethylene was found to occur at the same rate when the reaction was run at elevated temperatures in an autoclave.[10]

Experimental Section

Synthesis of 4-Alkyl- and Alkenylpyridines.—The 4-substituted pyridines were prepared in liquid ammonia from 4-alkylpyridines, alkyl- or alkenylbromides, and sodium amide according to the general procedure described by Brown and Murphey.[18] Table I lists the products synthesized by this method along with their yields and physical constants.

Competitive Reactions.—The competitive reactions were carried out using the 4-substituted pyridines that had been dried over Linde 5-A Molecular Sieves and immediately redistilled before use. All materials were of >99.5% purity as determined by vpc. The following describes a typical competitive reaction: In a dry box, 0.025 mol of two 4-alkylpyridines were weighed and the alkylpyridines were then transferred to a three-necked flask of 20-ml capacity that had previously been flushed with nitrogen. The flask was equipped with a specially designed drum-shaped high-speed stirrer and a Dry Ice condenser to which a calcium chloride drying tube was attached. *Ca.* 2.5×10^{-3} g-atom of alkali metal was freshly cut and allowed to disperse in the combined alkylpyridines. After the metal was completely dispersed (2–3 hr), 5×10^{-3} mol of freshly distilled isoprene was added. Samples were withdrawn at 0.5-hr intervals for a total of 4 hr and decomposed with methanol. The products were then analyzed by vpc and the ratio of products was determined to calculate the relative rates of reaction. All products were synthesized individually and their physical constants and thermal conductivities were determined. All new products were identified by their nmr, ir, refractive indices, and elemental analyses. The new products are reported in Table III.

Homogeneous Catalyzed Reactions.—All of the needed reactants and solvents were distilled immediately before use. In a dry box, 0.025 mol of two 4-alkylpyridines were weighed and injected into a 30-dram vial containing 15 ml of a 0.5 *M* potassium *t*-butoxide in dimethyl sulfoxide or N-methyl-2-pyrrolidone solution. A rubber septum was inserted and the catalyst solutions were removed to the laboratory, where the reactions were carried out at room temperature following a procedure similar to that of Schriesheim and coworkers for the isomerization of olefins.[19] The samples from these reactions were quenched with methanol and the product ratios were determined by gas chromatography.

Analyses.—The infrared spectra of the pyridines were taken with a Baird Model 4-55 infrared spectrophotometer. Nmr analyses were performed on a Varian Model A-60 spectrophotometer using TMS as an internal standard. Refractive indices were measured on a Zeiss Opton refractometer thermostated at 20 ± 0.1°. Vpc separations and identifications were made using an F & M Model 720 dual-column gas chromatograph equipped with a thermal-conductivity detector using helium as a carrier gas. Separations, product compositions, and relative thermal conductivities were made using either 10% SE-30 silicone gum rubber on 60–80 Gas-Pack WAB columns or 15% Versamid 900 on 60–80 Gas-Pack WAB columns of various lengths and at appropriate temperatures. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich.

Registry No.—Isoprene, 78-79-5.

(18) H. C. Brown and W. A. Murphey, *J. Amer. Chem. Soc.*, **73**, 3308 (1951).

(19) S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, *ibid.*, **89**, 6897 (1967).

The Chemistry of Diazepines. The Photochemical Intramolecular 1,3-Dipolar Cycloaddition of Substituted 1-Ethoxycarbonyliminopyridinium Ylides[1]

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Received June 3, 1969

The photochemical intramolecular 1,3-dipolar cycloaddition of substituted 1-ethoxycarbonyliminopyridinium ylides produces 1H-1,2-diazepines. Structural elucidation of the diazepines was accomplished by spectral means and confirmed by Diels–Alder reactions with tetracyanoethylene (TCNE) and catalytic reduction.

Recently, increased attention has been paid to medium-sized cyclic nonbenzenoid heteroaromatic hydrocarbons such as azepines and oxepines.[2] Despite unabated interest in the theoretical and practical aspects of seven-membered heterocyclic chemistry, the diazepines have been incompletely defined, because until recently they have been known only in the form of condensed ring systems.[3] Recently, Streith, *et al.*,[4] reported the first synthesis of simple diazepines by the photochemical rearrangement of 1-ethoxycarbonyliminopyridinium ylides.

Independently, we have also reported the photochemical synthesis of 1H-1,2-diazepines by the same route.[1a] Since the photochemical behaviour of iminopyridinium ylides has not been so extensively investigated as that of aromatic amine oxides,[5] we have examined the solution-phase photolysis of α-, α,α′-, β-, and γ-substituted 1-ethoxycarbonyliminopyridinium ylides. This has led to a study of their catalytic reduction and their Diels–Alder reactions; the latter reactions appear to be the first in the diazepine series.

Results and Discussion

Syntheses of the Pyridinium Ylides.—The pyridinium ylides **3–11** were prepared by the reactions of α- and γ-pieoline, 2,4-lutidine, β-picoline, 2,5-, 3,5-, 3,4-, and

(1) (a) For the preliminary communication, see T. Sasaki, K. Kanematsu, and A. Kakehi, *Chem. Commun.*, 432 (1969). (b) Studies on Heteroaromaticity. XXXIII. Part XXXII of this series: T. Sasaki, T. Yoshioka, and Y. Suzuki, *Bull. Chem. Soc. Jap.*, **42**, 3335 (1969).

(2) For a recent brief review in the azepine field, see I. C. Paul, S. M. Johnson, L. A. Paquette, J. H. Barrett, and R. J. Haluska, *J. Amer. Chem. Soc.*, **90**, 5023 (1968); for the oxepin field, see E. Vogel, *et al.*, *Angew. Chem.*, **76**, 535 (1968).

(3) For a recent brief review, see T. Takase, *J. Syn. Org. Chem. Jap.*, **26**, 807 (1968).

(4) J. Streith and J.-M. Cassal, *Angew. Chem.*, **80**, 117 (1968); *Tetrahedron Lett.*, 4541 (1968); J. Streith, A. Blind, J.-M. Cassal, and O. Sigwalt, *Bull. Soc. Chim. Fr.*, 948 (1969).

(5) (a) P. L. Kumler and O. Buchardt, *Chem. Commun.*, 1321 (1968); (b) E. C. Taylor and G. G. Spence, *ibid.*, 1037 (1968); (c) C. Kaneko, I. Yokoe, and S. Yamada, *Tetrahedron*, **25**, 295 (1969).

TABLE I

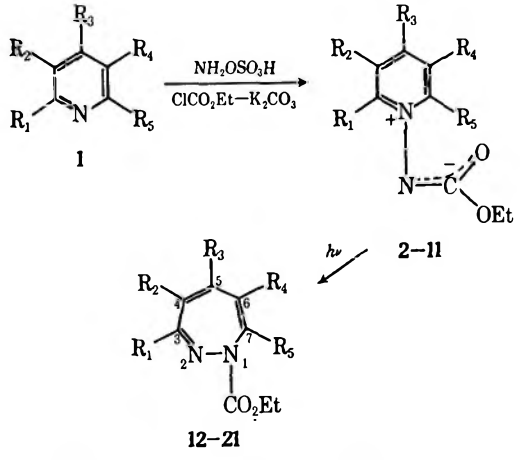
PHOTOISOMERIZATION OF YLIDES

Ylide	Solvent	Irradn time, hr	Method[a]	Diazepine[b]	Yield,[c] %	Mp, °C	$n^{22}D$	Appearance	$\nu_{C=O}^{KBr}$, cm^{-1}	λ_{max}^{EtOH} mμ (log ε)	
2	Acetone	8	A	12	95		1.5218	Red oil[d]	1710	228 (4.03)	355 (2.38)
	Dioxane	19	B		85						
	Benzene	50	B		44						
3	Acetone	5.5	A	13	80		1.4992	Red oil[d]	1715	220 (3.99)	325 (2.63)
	Dioxane	12	B		43						
4	Acetone	10	A	14	74	51–53		Yellow prisms[e]	1700	220 (3.87)[f]	368 (2.43)[f]
	Dioxane	12	B		53						
5	Benzene	65	B	15	77		1.5203[g]	Orange oil[d]	1707	221 (3.94)	338 (2.63)
6	Acetone	6	A	16	75		1.5200	Yellow oil[d]	1710	218 (4.00)	341 (2.55)
	Benzene	48	B		16						
7	Benzene	43	B	17	51	88–89		Yellow prisms[e]	1695	221 (4.19)	344 (2.50)
	Acetone	6	A		70						
8	Acetone	4	A	18	84	42–43		Yellow prisms[e]	1690	219 (4.05)	350 (2.52)
	Benzene	44	B		44						
9	Acetone	47	B	19	80	89–90		Yellow prisms[e]	1690	217 (3.98)	320 (2.74)
10	Benzene	50	B	20	47		1.5191[g]	Yellow oil[d]	1700	221 (3.95)	339 (2.61)
11	Benzene	45	B	21	76	110		Yellow prisms[e]	1705	220 (3.95)	274 (3.48)[g]
	Acetone	45	B		87						

[a] See Experimental Section. [b] C, H, and N analyses were within ±0.35% for all diazepines (Editor). [c] Based on weight of material isolated from silica gel chromatography. [d] Purification by short-path distillation at 120–180° (0.5–0.6 mm) after separation by column chromatography. [e] Temperature 19°. [f] *n*-Hexane. [g] Shoulder.

2,6-lutidine, and 2,4,6-collidine with hydroxylamine-O-sulfonic acid. These N-ylides showed strong carbonyl absorption in the range 1620–1640 cm^{-1} which shifted to 1730–1750 cm^{-1} in the corresponding picrates. The shift of the carbonyl absorption to lower wavenumber in the ylides may be due to the delocalization of the N lone pair, as shown in Scheme I. The uv spectra

SCHEME I

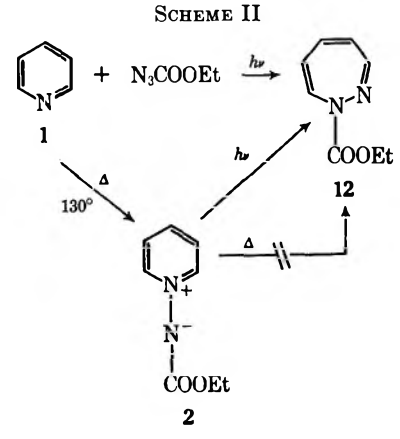


Ylide	Diazepine	R_1	R_2	R_3	R_4	R_5
2	12	H	H	H	H	H
3	13	CH_3	H	H	H	H
4	14	H	H	CH_3	H	H
5	15	CH_3	H	CH_3	H	H
6	16	H	CH_3	H	H	H
7	17	CH_3	H	H	CH_3	H
8	18	H	CH_3	H	CH_3	H
9	19	H	CH_3	CH_3	H	H
10	20	CH_3	H	H	H	CH_3
11	21	CH_3	H	CH_3	H	CH_3

of the ylides contained two maxima, one in the range of 228–243 mμ (log ε 3.3–4.0) and another at 304–318 mμ (log ε 3.0–3.7).

Photolysis of the N-Ylides and Structural Elucidation of the Products.—Irradiation of the ylides **2–11** in aprotic or protic solvents in Pyrex vessels using a 100-W high-pressure mercury lamp (>310 mμ) gave compounds **12–21** in 40–80% yields (Table I). When acetone was used as a solvent and irradiation was carried out with a 300-W high-pressure mercury lamp, the same products were obtained in 80–90% yields, suggesting that the photoisomerization may proceed *via* an excited triplet state. Irradiation of pyridine in acetone or in ethyl acetate in the presence of ethyl azidoformate at room temperature gave 1-ethoxycarbonyl-1H-1,2-diazepine in about 5% yield, while the thermal reaction of pyridine with ethyl azidoformate in ethyl acetate at 130° gave 1-ethoxycarbonyliminopyridinium ylide (**2**) in a yield of 60%. These findings indicate that 1-ethoxycarbonyl-1H-1,2-diazepine is formed only by the photochemical conversion of the ylide, as shown in Scheme II.

SCHEME II



In the uv spectral comparison between the ylides and their photoproducts **12–21**, the decrease in the molecular extinction of longer wavelength absorption and the increase in that of shorter wavelength absorption suggest that the photoproducts exist as nonplanar molecules. The nmr spectra, which show long-range coupling between ring protons and methyl

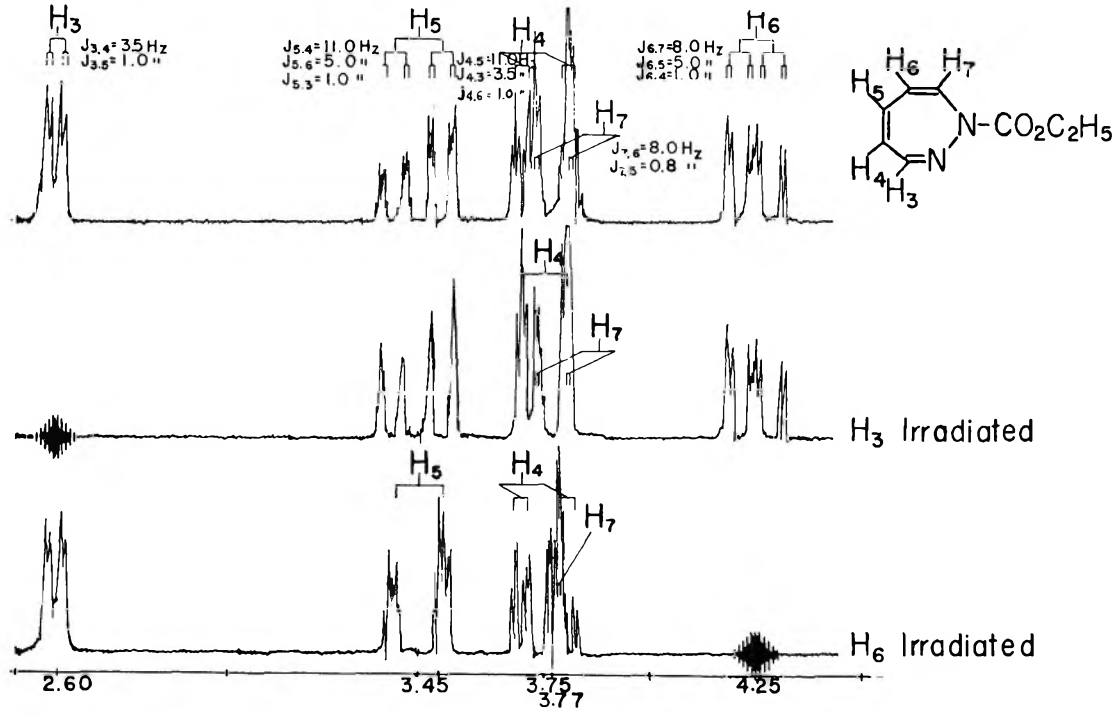


Figure 1.—100-Mc nmr spectra and spin decoupling of vinyl protons of 1-ethoxycarbonyl-1H-1,2-diazepine.

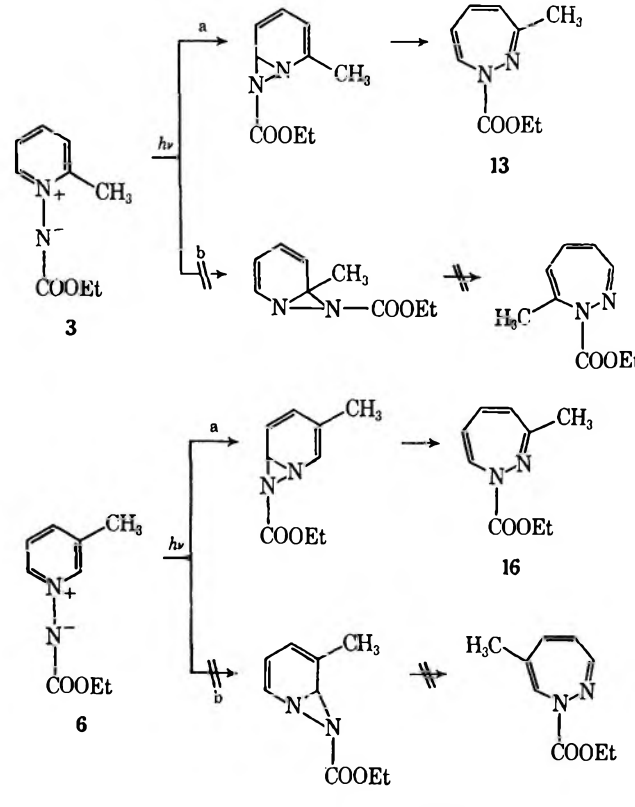
protons, confirm this conclusion. Recent studies on the molecular geometry of derivatives of 1H-azepine in the free and complexed state by X-ray analysis show that the molecule exists in a boat conformation (true polyenes).[2,6]

Structural elucidation of these photoproducts was accomplished by their nmr and mass spectral analyses. The spectral patterns of products **13**–**21** are grossly similar to each other, as seen from Table I. The nmr spectral and spin-decoupling data at 100 MHz for the parent diazepine **12** are shown in Figure 1.

Structural elucidation of the methyl-substituted diazepine derivatives was accomplished by the nmr spectral comparison with that of the parent compound **12**. Thus, compound **13** was assigned to be 1-ethoxycarbonyl-3-methyl-1H-1,2-diazepine from its nmr spectrum on the basis of absence of an absorption of the azomethine proton. Similarly, compound **16** was characterized as 1-ethoxycarbonyl-4-methyl-1H-1,2-diazepine on the basis of the nmr peaks which appeared at τ 2.69 (doublet, 1 H, H_3, J = 1.5 Hz owing to the azomethine proton, with the disposition of the C_3 and C_5 hydrogen atoms permitting long-range coupling), 3.63 (broad doublet, 1 H, H_5), 4.33 (broad triplet, 1 H, H_6), 3.78 (double doublets, 1 H, H_7), and 8.02 (doublet, 3 H, CH_3 at C_4, J = 1.5 Hz) in the ring protons. In particular, when acetone was used as a solvent and irradiation was carried out with a 300-W high-pressure mercury lamp (method A, see Experimental Section), the photoproduct **16** was obtained in 72.8% yield and no isomeric product could be detected by tlc or nmr analysis.

The mechanism by which these diazepines are produced is suggested to involve an intermediate diazabicyclo[4.1.0]heptadiene (Scheme III). On this basis, the results with ylide **3** indicate that initial 1,3-dipolar

SCHEME III



intramolecular cyclization on the less hindered α carbon is favored. This conclusion stands in contrast to results obtained by Okamoto[7a] and recently by us[7b] for the orientation of the ground-state 1,3-dipolar cycloaddition reactions of N-imines and the N-ylides with dipolarophiles (Scheme IV).

The above results are also interesting when com-

(6) X-Ray investigation of the iron–tricarbonyl complex of 1,2-diazepine has also been carried out by Professor Weiss; recent personal communication from Professor J. Streith.

(7) (a) T. Okamoto, M. Hirobe, Y. Tamai, and E. Yabe, *Chem. Pharm. Bull.* (Tokyo), **14**, 506 (1966); (b) T. Sasaki, K. Kanematsu, and Y. Yukimoto, unpublished work.

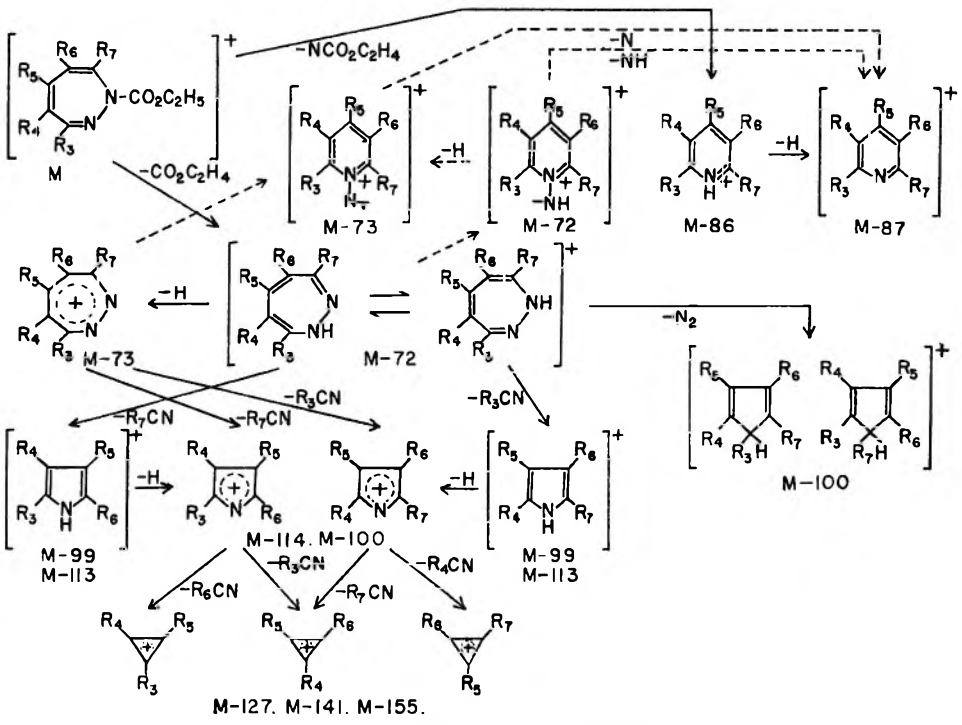
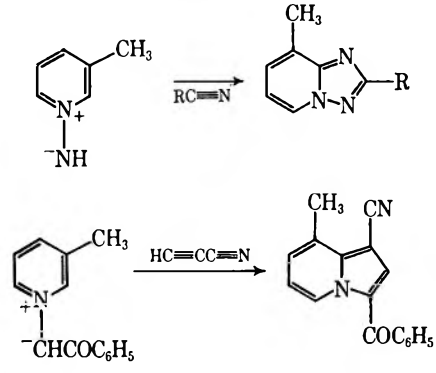
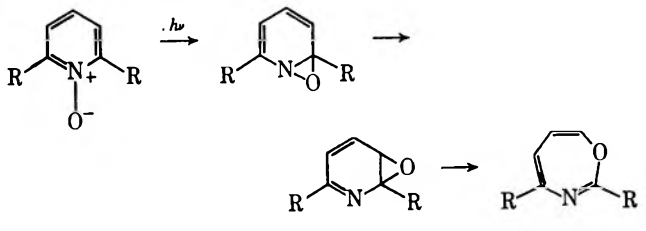


Figure 2.—Fragmentation paths of 1H-1,2-diazepines.

SCHEME IV



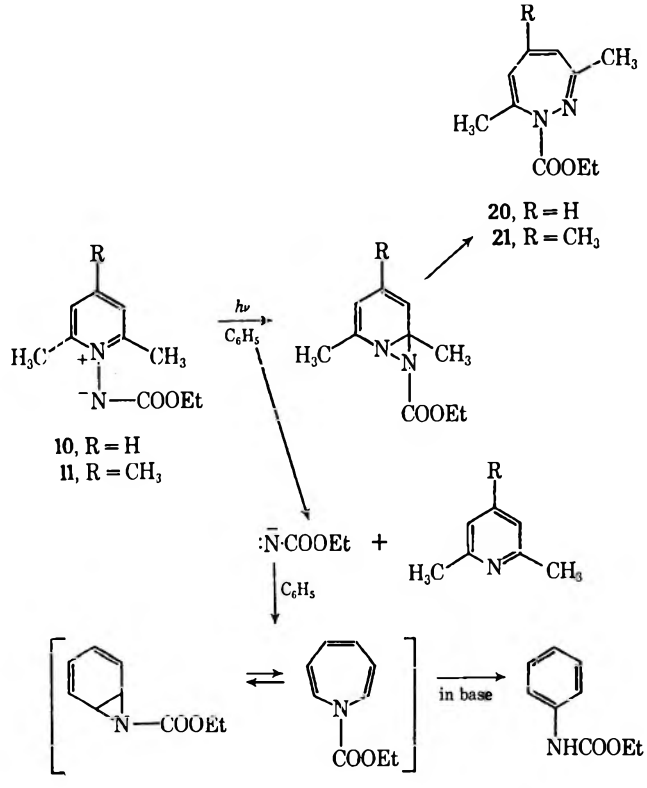
SCHEME V



pared with the formation of the 1,3-oxazepine ring system by photolysis of α,α'-substituted aromatic amine N-oxides and the mechanisms for their formation *via* oxaziridines and oxiranes[5] (Scheme V).

In contrast, in the case of 1-ethoxycarbonylimino derivatives of 2,6-lutidine and 2,4,6-collidine whose α and α' positions are occupied with methyl groups, the 1,3-dipolar intramolecular photocycloaddition reactions in benzene gave 1H-1,2-diazepine compounds **20** and **21**, and phenylurethan in yields of 47, 76, and *ca.* 2–5%, respectively. These findings suggest that ethoxycarbonyl nitrene is formed by photochemical cleavage of α,α'-disubstituted pyridinium ylides, which presumably add to benzene to give N-ethoxycarbonylazepine, which in turn rearranges to phenylurethan, since the azepine is known to rearrange to phenylurethan easily on treatment with base[8] (Scheme VI).

SCHEME VI



The structures of diazepines **20** and **21** were assigned on the basis of their nmr spectra. The nmr spectrum of **20** in deuteriochloroform exhibits signals at τ 3.60, 3.58, 4.15, and 7.82 with relative intensities of 1:1:1:6,

(8) (a) K. Hafner, D. Zinser, and K.-L. Moritz, *Tetrahedron Lett.*, 1733 (1964); (b) W. Lwowski, *Angew. Chem. Intern. Ed. Engl.*, **6**, 897 (1967).

TABLE II

NMR SPECTRA OF DIAZEPINES[a]

Diazepine	Ring protons and ring methyl protons, τ ($CDCl_3$)
13	3.60–3.67 (m, 3 H, H_4, H_5, H_7), 4.31 (dq, 1 H, H_6, $J_{6,7}$ = 7.5 Hz, $J_{6,5}$ = 4.5 Hz, $J_{6,4}$ = 2.0 Hz), 7.89 (s, 3 H, C_3 CH_3)
14	2.73 (br d, 1 H, H_3, $J_{3,4}$ = 3.0 Hz), 3.80 (d, 1 H, H_7, $J_{7,6}$ = 7.2 Hz), 3.95 (m, 1 H, H_4), 4.43 (dd, 1 H, H_6, $J_{6,7}$ = 7.2 Hz, $J_{6,4}$ = 2.0 Hz), 8.08 (d, 3 H, C_5 CH_3, J = 0.5 Hz)
15	3.73 (d, 1 H, H_7, $J_{7,6}$ = 7.5 Hz), 3.88 (br s, 1 H, H_4), 4.49 (dd, 1 H, H_6, $J_{6,7}$ = 7.5 Hz, $J_{6,4}$ = 1.5 Hz), 7.88 (s, 3 H, C_3 CH_3), 8.09 (d, 3 H, C_5 CH_3, J = 1.0 Hz)
16	2.69 (d, 1 H, H_3, $J_{3,5}$ = 1.5 Hz), 3.63 (br d, 1 H, H_5, $J_{5,6}$ = 5.0 Hz), 3.78 (dd, 1 H, H_7, $J_{7,6}$ = 8.0, $J_{7,5}$ = 0.8 Hz), 4.33 (br t, 1 H, H_6), 8.02 (d, 3 H, C_4 CH_3, J = 1.5 Hz)
17	3.63 (br s, 2 H, H_4, H_5), 3.86 (br s, 1 H, H_7), 7.90 (s, 3 H, C_3CH_3), 8.18 (d, 3 H, C_6 CH_3, J = 1.5 Hz)
18	2.89 (s, 1 H, H_3), 3.80 (br s, 1 H, H_5), 4.06 (br s, 1 H, H_7), 8.09 (d, 3 H, C_4 CH_3, J = 1.5 Hz), 8.23 (d, 3 H, C_6 CH_3, J = 1.5 Hz)
19	2.88 (s, 1 H, H_3), 3.84 (d, 1 H, H_7, $J_{7,6}$ = 7.5 Hz), 4.49 (d, 1 H, H_6, $J_{6,7}$ = 7.5 Hz), 8.16 (s, 6 H, C_4 and C_5 CH_3)
20	3.42–3.75 (m, 2 H, H_4, H_5), 4.15 (m, 1 H, H_6), 7.82 (br s, 6 H, C_3 and C_7 CH_3)
21	3.87 (br s, 1 H, H_4), 4.33 (br s, 1 H, H_6), 7.87 (br s, 6 H, C_3 and C_7 CH_3), 8.07 (s, 3 H, C_5 CH_3)

[a] Multiplicity is indicated as follows: s, singlet; d, doublet; dd, double doublet; m, multiplet; t, triplet; q, quartet; br, broad.

while that of **21** appears at τ 3.87, 4.33, 7.87, and 8.07 with relative intensities of 1:1:6:3, as shown in Table II. In addition, chemical-shift values of methyl protons at τ 7.82 ($2CH_3$) in **20**, and 7.87 ($2CH_3$) and 8.07 in **21** could be correlated with those of methyl-substituted 1H-1,2-diazepines **13–19**. Here, isomeric structures, 2-methyl-1H-1,3-diazepine derivatives for these products, are ruled out, since methyl protons attached to C_2 of the 1,3-diazine skeleton would appear at lower fields, as in 2-methylimidazole (τ 7.58).[9]

Mass Spectra of Diazepines.—Since the mass spectra of the diazepines have yet not been reported, the spectra of compounds **12–21** were examined and are characterized by fragment ion peaks at M − 72, M − 73, M − 86, M − 87, M − 99, M − 100, M − 113, M − 114, M − 127, and M − 141, as shown in Table III, and mechanisms for some of these fragmentation processes are proposed in Figure 2. Striking differences were observed in the base peaks between the spectra of the parent diazepine **12** and the methyl-substituted diazepines **13–21**. Base peaks (relative intensity 100) appear at *m/e* 166 (M^+), 67, 80, 29, 80, 29, 29, 29, 28, and 29 in the diazepines **12–21**, respectively. The ions at M − 72 and M − 73 are readily formed from the molecular ion and fragment to M − 99 and M − 113 ions. Apparently, the presence of the methyl group at C_3 or C_7 favors major fragmentation to the pyrrole ions at M − 113 and M − 114. In comparison, compound **12** and the methyl-substituted diazepines at C_4, C_5, and C_6 lose HCN, as observed by appearance of intense peaks at M − 99 and M − 100. The peaks at M − 127 or M − 141 presumably arise from loss of HCN or CH_3CN depending on the substitution pattern.

Diels–Alder Reactions of Diazepines.—For further structural elucidation, the diene reactivity of diazepines **12–21** was studied. The additions of dienophiles to medium-sized ring polyenes such as cycloheptatriene, oxepine, and azepine frequently lead to abnormal products.[10] Thus, cycloheptatriene and dimethyl acetylenedicarboxylate give rise to the tricyclic adduct formally derived from norcaradiene, and, similarly, oxepine and maleic anhydride also give a tricyclic adduct. Recently, a bicyclic 1,4-cycloaddition structure has been assigned to the product for the reaction between 1H-azepines and tetracyanoethylene.[11] More recently, the unusual 1,6-cycloaddition reaction of N-ethoxycarbonylazepine with nitrosobenzene was reported by Murphy and McCarthy.[12] A thermally induced, 6 + 2 cycloaddition is not permissible according to the Hoffmann–Woodward correlations.[13] The diazepines **12–15**, **17**, and **19** proved to be inert to reaction with maleic anhydride, dimethylacetylene dicarboxylate, or diethyl azodicarboxylate, but they did react readily with tetracyanoethylene (TCNE) in benzene solution even at room temperature to give

TABLE III

MASS SPECTRAL FRAGMENTATION IN DIAZEPINES

Ion	Rel intensity 12	13	14	15	16	17	18	19	20	21[a]
M	100	21	5	59	54	44	42	50	53	35[a]
M − 72	96	59	42	40	64	29	31	42	20	19
M − 73	42	31	12	32	33	40	46	33	21	35
M − 86	74	26	20	24	18	12	14	15	13	11
M − 87	39	50	20	27	20	21	17	21	16	11
M − 99	61	60	39	27	79	29	35	36	11	32
M − 100	56	95	100	50	100	49	66	69	12	36
M − 113	17	100	9	30	14	15	11	14	18	48
M − 114	17	41	13	56	8	31	22	22	29	37
M − 127	91	85	69	15	60	14	21	21	4	18
M − 141	...	38	10	48	42	42	30	31	14	24
77	...	92	31	27	19	21	17	20	8	11

[a] In this case, "M" refers to a fragment ion 14 mass units ($-CH_2$) below the molecular ion; the latter had a relative intensity of 4%.

(9) Chemical shifts of methyl protons of imidazoles are given in the literature; see G. S. Reddy, R. T. Hobgood, Jr., and J. H. Goldstein, *J. Amer. Chem. Soc.*, **84**, 336 (1962).

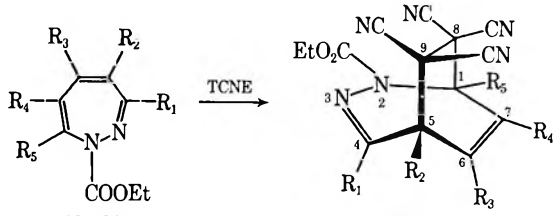
(10) A. S. Kende, P. T. Izzo, and J. E. Lancaster, *ibid.*, **87**, 5044 (1965).

(11) J. H. van den Hende and A. S. Kende, *Chem. Commun.*, 384 (1965).

(12) W. S. Murphy and J. P. McCarthy, *ibid.*, 1155 (1968).

(13) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

TABLE IV



12–21 22–29

Diazepine	Adduct[a]	R_1	R_2	R_3	R_4	R_5	Temp,[b] °C	Time, hr	Yield, %	Mp, °C
12	22	H	H	H	H	H	80	6	56	148.5–150.5
							25	72	10	
13	23	CH_3	H	H	H	H	25	72	53	177–179
14	24	H	H	CH_3	H	H	80	3	64	161–164
15	25	CH_3	H	CH_3	H	H	25	24	54	210 dec
16	26	H	CH_3	H	H	H	80	5	7	161–163
17	27	CH_3	H	H	CH_3	H	25	24	46	188–189
18	28	H	CH_3	H	CH_3	H	80	6	1.5	167–170
19	29	H	CH_3	CH_3	H	H	25	24	55	164–165

[a] C, H, and N analyses were within ±0.3% for all compounds (Editor). [b] 80° was refluxing benzene temperature; 25° was room temperature.

TABLE V

NMR DATA OF DIELS–ALDER ADDUCTS

Adduct	Ring protons and ring methyl protons, τ (DMSO-d_6)
22	2.98 (d, 1 H, H_4, $J_{4,5}$ = 6.0 Hz), 3.09 (br t, 1 H, H_6, $J_{5,6}$ = 8.0 Hz, $J_{6,7}$ = 8.0 Hz), 3.43 (br t, 1 H, H_7, $J_{7,1}$ = 7.0 Hz, $J_{7,6}$ = 8.0 Hz), 3.94 (dd, 1 H, H_1, $J_{1,7}$ = 7.0 Hz, $J_{1,6}$ = 1.5 Hz), 5.70 (m, 1 H, H_5)
23	3.10 (br t, 1 H, H_6, $J_{6,5}$ = 7.0 Hz, $J_{6,7}$ = 8.0 Hz), 3.41 (br t, 1 H, H_7, $J_{7,6}$ = 8.0 Hz, $J_{7,1}$ = 7.5 Hz), 3.91 (dd, 1 H, H_1, $J_{1,7}$ = 7.5 Hz, $J_{1,6}$ = 1.5 Hz), 5.64 (dd, 1 H, H_5, $J_{5,6}$ = 7.0 Hz, $J_{5,7}$ = 1.0 Hz), 7.88 (s, 3 H, C_4 CH_3)
24	3.00 (d, 1 H, H_4, $J_{4,5}$ = 6.5 Hz), 3.69 (m, 1 H, H_7), 4.06 (d, 1 H, H_1, $J_{1,7}$ = 8.0 Hz), 5.72 (dd, 1 H, H_5, $J_{5,4}$ = 6.5 Hz, $J_{5,7}$ = 1.0 Hz), 7.97 (d, 3 H, C_6 CH_3, J = 1.5 Hz)
25	3.80 (m, 1 H, H_7), 4.03 (d, 1 H, H_1, $J_{1,7}$ = 8.0 Hz), 5.67 (d, 1 H, H_5, $J_{5,7}$ = 2.0 Hz) 7.88 (s, 3 H, C_4 CH_3), 7.95 (d, 3 H, C_6 CH_3, J = 1.5 Hz)
26	3.19 (s, 1 H, H_4), 3.46 (dd, 1 H, H_6, $J_{6,7}$ = 8.0 Hz, $J_{6,1}$ = 1.5 Hz), 3.94 (t, 1 H, H_7, $J_{7,1}$ = 8.0 Hz, $J_{7,6}$ = 8.0 Hz), 4.16 (dd, 1 H, H_1, $J_{1,7}$ = 8.0 Hz, $J_{1,6}$ = 1.5 Hz), 8.27 (s, 3 H, C_5 CH_3)
27	3.48 (m, 1 H, H_6), 4.13 (d, 1 H, H_1, $J_{1,6}$ = 1.5 Hz), 5.73 (d, 1 H, H_5, $J_{5,6}$ = 8.0 Hz), 7.92 (s, 3 H, C_6 CH_3), 7.95 (d, 3 H, C_7 CH_3, J = 1.5 Hz)
28	3.19 (s, 1 H, H_4), 3.72 (m, 1 H, H_6), 4.11 (d, 1 H, H_1, $J_{1,6}$ = 1.5 Hz), 7.99 (d, 3 H, C_7 CH_3, J = 1.5 Hz), 8.33 (s, 3 H, C_5 CH_3)
29	3.22 (s, 1 H, H_4), 3.66 (m, 1 H, H_7), 4.03 (d, 1 H, H_1, $J_{1,7}$ = 8.0 Hz), 7.98 (d, 3 H, C_6 CH_3, J = 1.5 Hz), 8.23 (s, 3 H, C_5 CH_3)

the crystalline 1:1 adducts **22–25**, **27**, and **29**, respectively, in *ca.* 50% yields (Table IV). On the other hand, compounds **16** and **18** reacted with TCNE in benzene only on heating, to afford the corresponding 1:1 adducts **26** and **28** in very low yields, and **20** and **21** were inert to the Diels–Alder reaction. The nmr data are summarized in Table V; spectral assignments were derived by comparison with those of the carbethoxyazepine–tetracyanoethylene adduct.[10,14] Each adduct displayed characteristic ir bands for C=O (1700–1718 cm^{-1}), C≡N (2280 cm^{-1}), and C=C (1620–1638 cm^{-1}). Furthermore, the mass spectra of these adducts showed a molecular ion and strong peak at M − 128 by the loss of a C_6N_4 molecule from the molecular ion; this fragment may arise from a retro Diels–Alder fragmentation. As shown in Table VI, the fragment ion peaks at M − 128 for the adducts, with the exception of **26**, were observed as the base peaks.

(14) Computer-simulated analysis of the 100-MHz nmr spectrum of the adducts is now in progress.

TABLE VI

MASS SPECTRAL FRAGMENTATION IN DIELS–ALDER ADDUCTS

	Rel intensity						
Peak	**22**	**23**	**24**	**25**	**26**	**27**	**29**
Base	166	180	180	194	108	194	194
M	5	15	16	13	24	9	15
M − 128	100	100	100	100	89	100	100
128	28	17	37	74	76	18	27
76[a]	12	7	35	36	37	22	19

[a] A peak at *m/e* 76 might be assignable to the fragment TCNE − 2CN.

Catalytic Hydrogenation of Diazepines.—The diazepines **12–21** were hydrogenated over 5% palladium on carbon at atmospheric pressure. Reduction of compounds **14**, **18**, and **19** gave good yields of the corresponding hexahydro diazepines. These compounds showed ir absorption at 3340 cm^{-1} (NH). On the other hand, in agreement with Streith's observation,[4] the reduction of **12**, **13**, **15–17**, **20**, and **21** gave a mixture of the corresponding hexahydrodiazepines and tetrahydrodiazepines which could not be separated

by fractional distillation. These mixtures showed absorption owing to amino (3340 cm^{-1}) and imino bands (1630–1650 cm^{-1}) in their ir spectra.

Experimental Section[15]

Preparation of 1-Ethoxycarbonyliminopyridinium Ylides (2–11).[16] **1-Ethoxycarbonyliminopyridinium Ylide (2) (Method A).**—A solution of hydroxylamine-O-sulfonic acid (HAS) (5.7 g, 0.05 mol) in water (50 ml) was neutralized with aqueous potassium hydroxide (2.8 g, 0.05 mol, in 10 ml of water). To this solution was added pyridine (20 g, 0.25 mol). The solution was stirred at room temperature for 1 day and then potassium carbonate (6.9 g, 0.05 mol) was added. Water and unreacted pyridine were removed *in vacuo* below 50°. The residue was treated with ethanol (100 ml), and the insoluble precipitate was removed by filtration. To this filtrate ethyl chloroformate (5.4 g, 0.05 mol) and excess potassium carbonate (10 g, 0.07 mol) were added and the resulting solution was stirred at room temperature overnight. After filtration of the solution, the filtrate was concentrated *in vacuo*. Purification by chromatography (alumina) using benzene as an eluent followed by recrystallization from benzene gave **2** (3.4 g, 41%) as colorless crystals, mp 108–109° (lit.[8] mp 109°).

1-Ethoxycarbonylimino-2-methylpyridinium Ylide (3) (Method A).—From 14 g (0.15 mol) of α-picoline there was obtained 7.0 g (78%) of **3** as a pale yellow oil: picrate mp 145–147°, $\nu_{C=O}^{KBr}$ 1750 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}N_5O_9$ (picrate): C, 44.01; H, 3.69; N, 17.11. Found: C, 44.08; H, 3.71; N, 17.20.

When an aqueous solution of HAS and α-picoline was heated at 70–80° in a water bath for 1 hr, only 50% **3** was obtained.

3-Ethoxycarbonylimino-4-methylpyridinium Ylide (4) (Method A).—From 8 g (0.09 mol) of γ-picoline there was obtained 5.4 g (60%) of **4** as yellow crystals: mp 148–151°, $\nu_{C=O}^{KBr}$ 1640 cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.57; H, 6.82; N, 15.39.

When an aqueous solution of HAS and γ-picoline was heated at 70–80° for 1 hr, only 23% **4** was obtained.

1-Ethoxycarbonylimino-2,4-dimethylpyridinium Ylide (5) (Method A).—From 8 g (0.06 mol) of 2,4-lutidine there was obtained 6.1 g (63%) as a yellow oil, and this compound was used in the following reactions without further purification (one spot by tlc).

1-Ethoxycarbonylimino-3-methylpyridinium Ylide (6) (Method B).—A solution of HAS (5.7 g, 0.05 mol) in water (50 ml) was neutralized with aqueous potassium hydroxide (2.8 g, 0.05 mol, in 10 ml of water) under cooling. To this solution there was added β-picoline (10 g, 0.11 mol). The resulting solution was heated at 70–80° for 3 hr and cooled to room temperature with stirring. Potassium carbonate (6.9 g, 0.05 mol) was then added to the solution. Water and unreacted β-picoline were removed from the solution *in vacuo* below 50°. The residue was treated with chloroform (100 ml), and the insoluble precipitate was removed by filtration. To this filtrate ethyl chloroformate (5.4 g, 0.05 mol) and excess potassium carbonate (10 g, 0.07 mol) were added, and the resulting solution was stirred at room temperature overnight. After filtration the filtrate was concentrated *in vacuo*. Purification by chromatography (alumina) using benzene as an eluent followed by recrystallization from benzene gave **6** (4 g, 44%) as yellow crystals: mp 100–101°, $\nu_{C=O}^{KBr}$ 1630 cm^{-1}; picrate mp 141–143°, $\nu_{C=O}^{KBr}$ 1730 cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.83; H, 6.81; N, 15.50.

1-Ethoxycarbonyl-2,5-dimethylpyridinium Ylide (7) (Method B).—From 10 g (0.09 mol) of 2,5-lutidine there was obtained 3.3 g (34%) of **7** as hygroscopic yellow flakes after purification by chromatography (silica gel) using benzene as an eluent.

1-Ethoxycarbonyl-3,5-dimethylpyridinium Ylide (8) (Method B).—From 10 g (0.09 mol) of 3,5-lutidine there was obtained 4.4 g (45%) of **8** as colorless crystals: mp 132–134°, $\nu_{C=O}^{KBr}$ 1620 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 62.16; H, 7.46; N, 14.61.

1-Ethoxycarbonylimino-3,4-dimethylpyridinium Ylide (9) (Method B).—From 10 g (0.09 mol) of 3,4-lutidine there was obtained 4.5 g (46%) of **9** as yellow-brown crystals: mp 90–91°, $\nu_{C=O}^{KBr}$ 1625 cm^{-1}; picrate mp 154–155°.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.83; H, 7.27; N, 14.42. Found: C, 61.27; H, 7.30; N, 14.61.

1-Ethoxycarbonylimino-2,6-dimethylpyridinium Ylide (10) (Method A).—From 7.0 g (0.07 mol) of 2,6-lutidine there was obtained *ca.* 4.1 g (43%) of **10** as hygroscopic yellow needles. This compound was used for photolysis without further purification.

1-Ethoxycarbonylimino-2,4,6-trimethylpyridinium Ylide (11) (Method A).—From 6.0 g (0.06 mol) of 2,4,6-collidine there was obtained 1.5 g (14%) of **11** as colorless crystals, mp 137–140°.

Anal. Calcd for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.49. Found: C, 63.21; H, 7.55; N, 13.44.

However, this compound was not obtained by method B.

Preparation of the Diazepines (12–21). General Method.—A solution of the pyridinium ylides (**2–11**) in acetone or benzene was irradiated under nitrogen and cooling internally to 20–25° by a cold finger with (A) a 300-W high-pressure mercury lamp (volume 800 ml), or (B) a 100-W high-pressure mercury lamp (volume 400 ml). The solution was then concentrated *in vacuo* and purified by silica gel chromatography. Furthermore, the crude compound was purified by short-path distillation or recrystallization from *n*-hexane. These data are summarized in Table I. The crude products (strong pyridine odor)[17] from photolysis of compounds **11** and/or **12** were chromatographed using benzene as an eluent. After separation of the diazepine compounds **20** and **21**, elution with 10% benzene–chloroform solution yielded *ca.* 2–5% phenylurethan, characterized by identical ir and nmr spectra with those of an authentic sample.

Reactions of Pyridine with Ethyl Azidoformate. A. Photochemical.—A solution of ethyl azidoformate (6.0 g, 0.05 mol) and pyridine (15 g, 0.19 mol) in acetone (250 ml) was irradiated at room temperature for 36 hr by method A. The solution was concentrated *in vacuo*, and the residue was then purified by column chromatography (silica gel). 1-Ethoxycarbonyl-1H-1,2-diazepine (**12**)[4] was obtained in 5% yield. However, the yield when ethyl acetate was employed as a solvent instead of acetone was only 2%.

B. Thermal.—A mixture of ethyl azidoformate (2.0 g, 0.017 mol) and pyridine (10 g, 0.13 mol) was heated at 130° for 1 hr in a sealed tube. The reaction mixture was then purified by column chromatography (alumina) and recrystallized from benzene to yield 1.7 g (59%), mp 108–109°. This compound was found to be identical with 1-ethoxycarbonyliminopyridinium ylide (**2**), prepared by the method described above.

Diels–Alder Reactions of Diazepines (22–29).—The general procedure is illustrated for the preparation of **2-ethoxycarbonyl-8,8,9,9-tetracyano-2,3-diazabicyclo[3.2.2]nona-3,6-diene (22).** A solution of **12** (471 mg, 2.8 mmol) and TCNE (354 mg, 2.8 mmol) in dry benzene (30 ml) was refluxed for 6 hr and then cooled. The solution was concentrated *in vacuo* and the residue was recrystallized from ethanol to yield 471 mg (56.5%) of colorless crystals, mp 148.5–150.5°. However, when the reaction was carried out at room temperature for 3 days, the yield was only 9.7%.

Catalytic Hydrogenation of the Diazepines. General Method.—The diazepines in methanol (20 ml) were hydrogenated over 5% Pd–C with stirring at room temperature for 15-hr work-up in the normal way followed by short-path distillation at 70–100° (1–2 mm).

Registry No.—**3**, 22928-83-2; **3** picrate, 22928-84-3; **4**, 22928-85-4; **6**, 22928-86-5; **6** picrate, 22979-16-4;

(15) The melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were performed on a Yanagimoto C.H.N.-Corder, Model MT-1. The uv spectra were determined with a JASCO Model ORD/UV-5 recorder. The nmr spectra were taken with a Japan Electric Optics Laboratory Co., Ltd., Model JNM-MH-60 nmr spectrometer and with a Varian A-60 recording spectrometer with tetramethylsilane as an internal standard. The chemical shifts are expressed in τ values. The mass spectra were obtained on a Hitachi RMU-D double-focusing mass spectrometer operating at an ionization potential of 70 eV. The solid samples were ionized by electron bombardment after sublimation directly into the electron beam at 100–150°. The ir spectra were taken with a JASCO Model IR-S spectrophotometer. Thin layer chromatography (tlc) was carried out on alumina and silica plates by using benzene–methanol mixtues as developing solvents and iodine as a developing reagent.

(16) R. Gösl and A. Meuwsen, *Chem. Ber.*, **92**, 2521 (1959).

(17) 2,6-Lutidine and 2,4,6-collidine were characterized by glpc comparison with authentic samples.

8, 22928-87-6; **9**, 22979-17-5; **9** picrate, 22928-88-7; **11**, 22979-18-6; **12**, 17377-08-1; **13**, 22928-90-1; **14**, 22928-91-2; **15**, 22928-92-3; **16**, 22928-93-4; **17**, 22928-94-5; **18**, 22928-95-6; **19**, 22928-96-7; **20**, 22928-97-8; **21**, 22928-98-9; **22**, 22958-19-6; **23**, 22958-16-3; **24**, 22958-17-4; **25**, 22958-18-5; **26**, 22929-03-9; **27**, 22979-19-7; **28**, 22929-04-0; **29**, 22929-05-1.

Acknowledgment.—The authors are indebted to Dr. T. Nishida of the Nichiden Varian Co., Ltd., for the spin-decoupling experiments.

The Photoisomerization of 1-Iminopyridinium Ylides to 1(1H),2-Diazepines[1]

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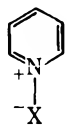
Received July 28, 1969

Irradiation of 1-iminopyridinium ylides **2a–f** and **4a** and **b** in methylene chloride solution produces 1(1H),2-diazepines **3a–f** and **5a** and **b** in good yields. The majority of the ylides were best prepared by a new method from the corresponding 1-aminopyridinium iodides and acylating agent. Structure **3a** was deduced from the first-order analysis of its 100-MHz nmr spectrum and was confirmed by its degradation to **9**. The second major photoproduct of the ylide **2d** was shown to be **10** by synthesis. Whereas ylide **2f** rearranged to **3f**, **2g** was photochemically stable; it is suggested that this may be due to large contributions of **13** and **14** to the respective excited states of the two ylides. Compound **15** was stable to irradiation at 3000 and 3500 Å.

Over the years, some of the most intriguing and fruitful heterocyclic chemistry has been associated with the three classes of compounds defined by structure **1** (X = O, CR_2, and NR). Although examples of each class have been known for over 50 years, their chemistry has been explored only relatively recently.[2] The isoelectronic nature of these systems has invited comparison of their ground-state chemical



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reactivity. A similar comparison in their photochemical reactivity is predicted to be instructive,[3] and thus it is not surprising that examples of all three types have been investigated from this point of view. Emphasis has been placed mainly on the irradiation of the readily available[2a] quinoline and pyridine N-oxides,[4-6] but more recently other aromatic amine N-oxides have received attention.[7] On the other hand, a single but interesting example of the pyridinium ylide **1** (X = CR_2) has been irradiated.[8] The corresponding N–N ylides remained unexplored[9] until Streith and Cassal made the important observation[10] that the irradiation of the system **1** (X = NCO_2Et) gives 1-ethoxycarbonyl-1(1H),2-diazepine (*vide infra*). More recently, the French workers[11] and a Japanese group[12] broadened the scope of this photochemical rearrangement. As part of a detailed investigation of the 1-iminopyridinium ylides **1** (X = NR), we have independently irradiated a series of ring-substituted 1-ethoxycarbonylimino- and 1-acetyliminopyridinium ylides **1** (X = NCO_2Et and $NCOCH_3$, respectively) as well as several related single examples. Preliminary observations concerning the system **1** (X = $NCOCH_3$) have appeared.[13] Herein we report on the photochemistry of the ylides **2a–g**, **4a**, **4b**, and **15**. Our results are complementary to the work of Streith[10,11] and Sasaki,[12] but differ in several aspects and extend the scope of the general photochemical synthesis of 1(1H),2-diazepines to include new functionalized derivatives of this largely unexplored class of compounds.[14] Furthermore, in view of the interest in the theoretical aspects of cycloaddition reactions as they apply to the related oxepin and azepine systems,[15] a detailed presentation of the preparation and physical properties of the new 1(1H),2-diazepines would seem to have timely utility. In this connection, it is to be noted that diazepine–tetracyanoethylene adducts have been described by Sasaki very recently.[12]

Whereas many complex 1-phenyliminopyridinium ylides have been known for some time,[16] only a few examples of simple 1-iminopyridinium ylides [com-

(1) Presented at the 52nd Meeting of the Chemical Institute of Canada, Montreal, May 25, 1969.

(2) Summaries follow. (a) **1** (X = O): E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1967. (b) **1** (X = CR_2): F. Krohnke, *Angew Chem.*, **75**, 317 (1963). (c) **1** (X = NR): T. Okamoto and M. Hirobe, *J. Syn. Org. Chem. Jap.*, **26**, 746 (1968).

(3) Such a comparison may be generalized; see H. Izawa, P. de Mayo, and T. Tabata, *Can. J. Chem.*, **47**, 51 (1969).

(4) (a) C. Kaneko, *J. Syn. Org. Chem. Jap.*, **26**, 758 (1968); (b) M. Ishikawa, C. Kaneko, I. Yokoe, and S. Yamada, *Tetrahedron*, **25**, 295 (1969), and references cited therein.

(5) O. Buchardt and P. L. Kumler, *Acta Chem. Scand.*, **23**, 159 (1969), and references cited therein.

(6) For a comprehensive list of references, see E. C. Taylor and G. G. Spence, *Chem. Commun.*, 1037 (1968).

(7) W. E. Dolbier, Jr., and W. M. Williams, *J. Amer. Chem. Soc.*, **91**, 2818 (1969), and references cited therein.

(8) J. Streith and J.-M. Cassal, *C. R. Acad. Sci., Paris, Ser. C.*, **264**, 1307 (1967); J. Streith, B. Danner, and C. Sigwalt, *Chem. Commun.*, 979 (1967).

(9) The photolyses of several unusual N–N ylides have been reported: P. de Mayo and J. J. Ryan, *Tetrahedron Lett.*, 827 (1967); P. de Mayo and J. J. Ryan, *Can. J. Chem.*, **45**, 2177 (1967); M. G. Pleiss and J. A. Moore, *J. Amer. Chem. Soc.*, **90**, 4738 (1968).

(10) J. Streith and J.-M. Cassal, *Angew. Chem. Intern. Ed. Engl.*, **7**, 129 (1968); experimental details have appeared recently in J. Streith, A. Blind, J.-M. Cassal, and C. Sigwalt, *Bull. Soc. Chim. Fr.*, 948 (1969).

(11) J. Streith and J.-M. Cassal, *Tetrahedron Lett.*, 4541 (1968); J. Streith and J.-M. Cassal, *Bull. Soc. Chim. Fr.*, 2175 (1969).

(12) S. Sasaki, K. Kanematsu, and A. Kaheki, *Chem. Commun.*, 432 (1969).

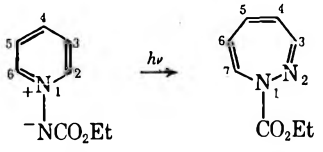
(13) V. Snieckus, *ibid.*, 831 (1969).

(14) Very few simple examples of the 1,2-diazepine system are known: F. D. Popp and A. C. Noble, *Advan. Heterocycl. Chem.*, **8**, 22 (1967); J. A. Moore and E. Mitchell, "Heterocyclic Compounds," Vol. 9, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 294 ff; see also T. Takase, *J. Syn. Org. Chem. Jap.*, **26**, 807 (1968).

(15) L. A. Paquette, J. H. Barrett, and D. E. Kuhla, *J. Amer. Chem. Soc.*, **91**, 3616 (1969), and references cited therein; see also J. R. Wiseman and B. P. Chong, *Tetrahedron Lett.*, 1619 (1969).

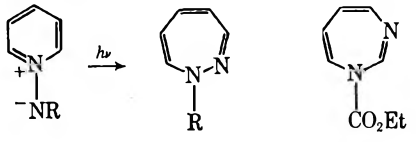
(16) K. Dimroth, G. Arnoldy, S. von Eicken, and G. Schiffler, *Justus Liebigs Ann. Chem.*, **604**, 221 (1957), and references cited therein.

pounds **1** (X = $NCOCH_3$) and ring-methylated derivatives,[17] **2a**,[18] **4a**,[19] and **4b**[20]] have been reported. In our attempts to prepare a series of simple ylides, application of the methods of Hafner[18] or Curtius[20] gave uniformly poor yields (Table I, method A), and a new procedure was therefore devised. Treatment of substituted 1-aminopyridinium iodides with potassium hydroxide and ethyl chloroformate produced the corresponding ylides **2a–f** in fair to good yields (Table I, method B). With the exception of the precursor to **2f**, the 1-aminopyridinium iodide derivatives were prepared by a literature method.[21] Ylide **2g** could not be synthesized by this procedure but was obtained *via* the Hafner route.[18] The ylides **4a** and **4b** were readily available from the reaction of 1-aminopyridinium iodide with benzoyl chloride and *p*-toluenesulfonyl chloride, respectively (see Experimental Section).



2a, unsubstituted
b, 2-CH_3
c, 4-CH_3
d, 3,5-diCH_3
e, 2,6-diCH_3
f, 4-$N(CH_3)_2$
g, 4-CO_2Et

3a, unsubstituted
b, 3-CH_3
c, 5-CH_3
d, 4,6-diCH_3
e, 3,7-diCH_3
f, 5-$N(CH_3)_2$



4a, R = COPh
b, R = $SO_2C_7H_7$

5a, R = COPh
b, R = $SO_2C_7H_7$

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The ir, uv, and nmr spectral data for these compounds are summarized in Tables I and II. Carbonyl absorption at 1630–1640 cm^{-1} in the infrared spectrum and ultraviolet maxima at >310 mμ were diagnostic for the characterization of these ylides and agreed with earlier reports of these properties for the related 1-acetyliminopyridinium systems.[17]

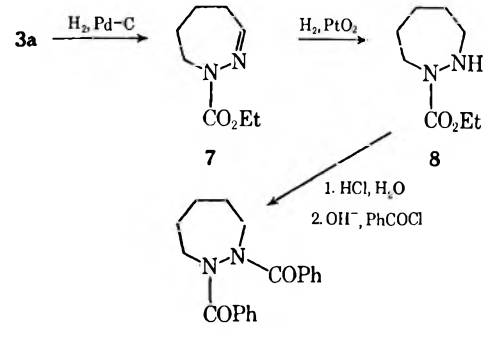
Photolysis of **2a** in methylene chloride solution at 3500 Å gave a single isomeric product. At this stage of our work, Streith and Cassal reported their preliminary results[10] and assigned structure **3a** to the photoproduct on the basis of spectral properties. Although our spectral data were in reasonable agreement with those presented by Streith, we had already undertaken a course of action initiated by the following analysis. As mentioned previously, a photochemical analogy between **2a** and the pyridine N-oxides could be drawn, and on this basis several possible structures could be formulated for the photoproduct. The spectral properties of the photoproduct, in particular the nmr spectrum, ruled out most of these and left structures **3a** and **6** for consideration.[22] The observed low-field signal at τ 2.56 could be associated with an azomethine proton in either of the two structures, but its multiplicity and coupling constants strongly favored the 1(1H),2-diazepine structure **3a** for the photoproduct. Determination of the 100-MHz nmr spectrum with appropriate decoupling experiments led to a complete first-order analysis in terms of the structure **3a** (Table III).[23] Confirmation was obtained by degradation of **3a** to the known[24] 1,2-dibenzoyl-1,2-hexahydrodiazepine **9** shown in Scheme I.

TABLE I
PREPARATION AND INFRARED AND ULTRAVIOLET SPECTRA OF PYRIDINIUM YLIDES

Ylide	Prepn method[a]	Yield, %	$\nu_{max}^{CHCl_3}$, cm^{-1} [b]	λ_{max}^{MeOH}, mμ (ε)[c]
2a	A	17	1641	228 (6600)
	B	48	1606	315 (5530)
2b	A	0	1632	242 (5300)
	B	47[d]	1610	270 (sh, 3810)
				277 (sh, 3350)
				310 (2050)
2c	A	3	1638	230 (5490)
	B	29	1620	245 (5880)
				312 (4620)
2d	A	9	1633	233 (5630)
	B	51	1611	282 (3420)
				311 (3670)
2e	B	49[d]	1632	243 (4960)
			1614	274 (4940)
				281 (sh, 4320)
				305 (sh, 970)
2f	B	53	1655	298 (23,460)
			1565	
2g	A	1	1720	231 (sh, 6460)
			1640	274 (4340)
			1610	350 (9900)
4a	B	83	1621 (w)	233 (13,530)
			1592	317 (4850)
			1551	
4b	A	14	1601 (w)	240 (14,000)
	B	57		317 (2180)

[a] See Experimental Section. [b] w = weak. [c] Liquid samples were handled by microtechniques described in P. L. Kirk, "Ultramicroanalysis," John Wiley & Sons, Inc., New York, N. Y., 1950. sh = shoulder. [d] Yield of picrate derivative.

SCHEME I



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(17) T. Okamoto, M. Hirobe, and A. Ohsawa, *Chem. Pharm. Bull.* (Tokyo), **14**, 518 (1966).
(18) K. Hafner, D. Zinser, and K.-L. Moritz, *Tetrahedron Lett.*, 1733 (1964).
(19) T. Okamoto, M. Hirobe, C. Mizushima, and A. Ohsawa, *Yakugaku Zasshi*, **83**, 308 (1963); *Chem. Abstr.*, **59**, 5130b (1963).
(20) T. Curtius and G. Kraemer, *J. Prakt. Chem.*, **125**, 303 (1930).
(21) R. Gosl and A. Meuwsen, *Chem. Ber.*, **92**, 2521 (1959).
(22) This point has been made recently by Kaneko; *cf.* ref 4a.
(23) Computer-simulated analysis of the nmr spectra of **3a** and related diazepines is in progress.
(24) G. Zinner and W. Deucker, *Arch. Pharm.* (Weinheim), **295**, 526 (1962). We thank Dr. Zinner for correspondence.

TABLE II

NMR SPECTRA OF PYRIDINIUM YLIDES[a]

Ylide	Aromatic and ring methyl protons	$CO_2CH_2CH_3$[b]	$CO_2CH_2CH_3$[b]
2a	1.34 (d, 2, J = 6 Hz, H_2, H_6), 2.14–2.59 (m, 3, H_{3-5})	5.85	8.68
2b	1.38 (br d, 1, J = 8 Hz, H_6), 2.02–2.61 (m, 3, H_{3-5}), 7.22 (s, 3, C_2 CH_3)	5.80	8.62
2c	1.54 (br d, 2, J = 6 Hz, H_2, H_6), 2.60 (br d, 2, J = 6 Hz, H_3, H_5), 7.41 (s, 3, C_4 CH_3)	5.80	8.62
2d	1.61 (br s, 2, H_2, H_6), 2.70 (br s, 1, H_4), 7.62 (s, 6, C_3, C_5 CH_3)	5.87	8.71
2e	1.70–2.60 (m, 2, H_{3-5}), 7.30 (s, 6, C_2, C_6 CH_3)	5.82	8.62
2f	1.84 (br d, 2, J = 7.5 Hz, H_2, H_6), 3.38 (br d, 2, J = 7.5 Hz, H_3, H_5), 6.83 [s, 6, $N(CH_3)_2$]	5.88	8.70
2g	1.05 (br d, 2, J = 6 Hz, H_2, H_6), 1.97 (br d, 2, J = 6 Hz, H_3, H_5)	5.69[c]	8.70[d]
4a	1.07 (br d, 2, J = 7 Hz, H_2, H_6), 1.77–2.67 (m, 8, H_{3-5}, COPh)		
4b	1.40 (br d, 2, J = 7 Hz, H_2, H_6), 2.73 (br d, 2, J = 8 Hz, $H_{2'}$, $H_{6'}$[e]), 1.92–2.45 (m, 3, H_{3-5}), 2.63 (br d, 2, J = 8 Hz, $H_{3'}$, $H_{5'}$[e]), 7.57 (s, 3, $C_{4'}$ CH_3[e])		

[a] Tabulation follows the order chemical shift (τ value), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), number, coupling constant, and assignment of protons. [b] J = 6–7 Hz. [c] Two overlapping quartets, 4 H. [d] Two overlapping triplets, 6 H. [e] Protons of the $-SO_2C_7H_7$ function.

TABLE III

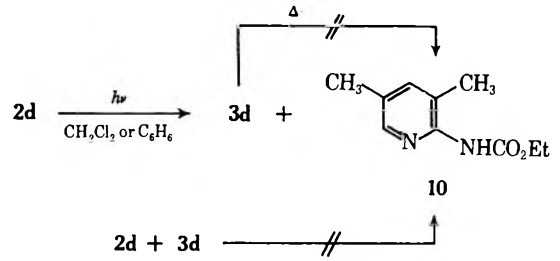
100-MHz NMR SPECTRUM OF 1-ETHOXYCARBONYL-1(1H),2-DIAZEPINE (3a)

Proton	τ	Multiplicity	Coupling constants, Hz
H_3	2.56	dd	$J_{3,4}$ = 3, $J_{3,5}$ = 1
H_4	3.70	m	$J_{4,3}$ = 3, $J_{4,5}$ = 11
H_5	3.40	m	$J_{5,3}$ = 1, $J_{5,4}$ = 11, $J_{5,6}$ = 5, $J_{5,7}$ = 1
H_6	4.20	m	$J_{6,4}$ = 1, $J_{6,5}$ = 5, $J_{6,7}$ = 7.5
H_7	3.71	m	$J_{7,5}$ = 1, $J_{7,6}$ = 7.5
$CO_2CH_2CH_3$	5.75	q	J = 7.0
$CO_2CH_2CH_3$	8.67	t	J = 7.0

Stepwise reduction to the hexahydro derivative **8** was followed by acid hydrolysis and Schotten–Baumann reaction with benzoyl chloride to yield compound **9**.

Irradiation of the ylides **2b**, **2c**, **2e**, **2f**, **4a**, and **4b** produced the corresponding diazepine derivatives **3b**, **3c**, **3e**, **3f**, **5a**, and **5b** in good yields (see Experimental Section). The structures of the photoproducts have been assigned by comparison of the spectral data with that of compound **3a**. In particular, the nmr spectra confirmed the structural assignments, although their complexity allowed calculation of coupling constants only in the cases of simple spin systems[23] (Table IV). The ir and uv data for these compounds are summarized in Table V (Experimental Section). It is to be noted that the unsymmetrical ylide **2b** rearranges exclusively to yield the diazepine **3b**; no isomeric product could be detected by tlc or nmr analysis.

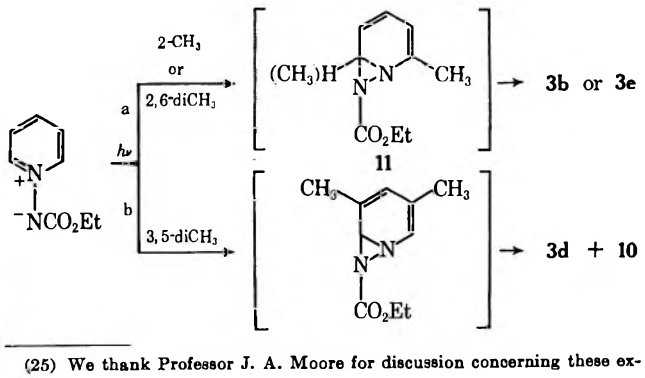
More interesting results were obtained when 3,5-dimethyl-1-carbethoxyiminopyridinium ylide **2d** was irradiated in methylene chloride solution. Besides the normal photoproduct **3d** (41%), characterized mainly by its nmr spectrum (Table IV), a 31% yield of 2-carbethoxyamino-3,5-dimethylpyridine (**10**) was obtained. The latter was identified by comparison with an authentic sample prepared by a known route. The same two products were produced by irradiation in benzene; however, the yields were different, **3d** (80%) and **10** (10%). It was shown that **10** did not arise from **3d** either by a thermal process or by a base-promoted rearrangement of **3d** (ylide **2d** acting as base) during the photolysis[25] (see Experimental Section). Therefore, compound **10** is a true photoproduct.



The effect of electronic factors on the photolytic process is illustrated dramatically by the behavior of ylides **2f** and **2g**. Whereas **2f** rearranged cleanly to **3f**, **2g** was stable to irradiation in methylene chloride or benzene solution.

The results may be summarized by the mechanism outlined in Scheme II. When dealing with a 2-methyl-substituted ylide (**2g**), rearrangement goes exclusively to the least hindered side, forming the hypothetical diaziridine intermediate **11** which then undergoes valence isomerization to the diazepine **3b**; however, 2,6-dimethyl substitution (**2e**) does not hinder the ring expansion to **3e** (path a). 3,5-Dimethyl substitution forces a cleavage process to compete with ring expansion (path b).

SCHEME II



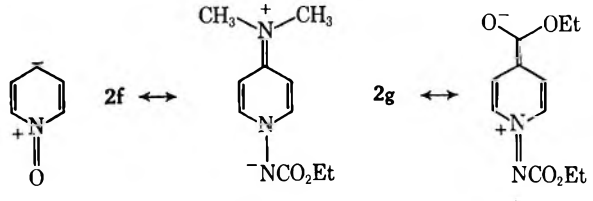
(25) We thank Professor J. A. Moore for discussion concerning these experiments.

TABLE IV
60-MHz NMR SPECTRA OF DIAZEPINES[a,b]

Diazepine	Aromatic and ring methyl protons	$CO_2CH_2CH_3$[c]	$CO_2CH_2CH_3$[c]
3b	3.44–3.74 (m, 3, H_4, H_5, H_7), 4.31 (m, 1, H_6), 7.90 (s, 3, C_3 CH_3)	5.70	8.67
3c	2.70 (d, 1, $J_{3,4}$ = 4 Hz, H_3) 3.73–4.07 (m, 2, H_4, H_7), 4.43 (dd, 1, $J_{6,4}$ = 1.5 Hz $J_{6,7}$ = 8 Hz, H_6), 8.10 (d, 3, C_5 CH_3)	5.67	8.67
3d	2.76 (d, 1, $J_{3,5}$ = 1.5 Hz, H_3), 3.73 (br s, 1, H_5), 3.99 (br s, 1, H_7), 8.07 (d, 3) and 8.21 (d, 3, C_4, C_6 CH_3)	5.70	8.68
3e	3.43–3.76 (m, 2, H_4, H_5), 4.17 (m, 1, H_6), 7.83 (s, 6, C_3, C_7 CH_3)	5.72	8.65
3f	2.75 (d, 1, $J_{3,4}$ = 5.5 Hz, H_3), 3.77 (d, 1, $J_{7,6}$ = 8.5 Hz, H_7), 4.35 (dd, 1, $J_{6,7}$ = 8.5 Hz, $J_{6,4}$ = 2.5 Hz, H_6), 5.20 (q, 1, $J_{4,3}$ = 5.5 Hz, $J_{4,6}$ = 2.5 Hz, H_4), 7.13 [s, 6, $N(CH_3)_2$],	5.72	8.67
5a	2.23–2.70 (m, 6, H_3, $COPh$), 3.15–3.80 (m, 3, H_4, H_5, H_7), 4.12 (m, 1, H_6)		
5b	2.16 (d, 2, J = 8 Hz, $H_{2'}$, $H_{6'}$[d]), 2.69 (d, 2, J = 8 Hz, $H_{3'}$, $H_{5'}$[d]), 2.74 (d, 1, hidden H_3), 3.24–3.92 (m, 2) and 4.06–4.49 (m, 2, H_{4-7}), 7.55 (s, 3, $C_{4'}$ CH_3[d])		

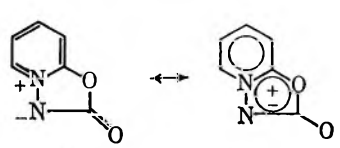
[a] See footnote *a*, Table II. [b] See ref 23. [c] J = 7.0 Hz. [d] See footnote *e*, Table II.

The results with ylides **2f** and **2g** are partially understood if reference may be made to the thoroughly investigated ultraviolet spectral characteristics of the isoelectronic pyridine N-oxides.[1a] In these systems, evidence is available which indicates that contributing resonance forms in which oxygen has lost most of its negative charge, *e.g.*, **12**, are important in excited-state considerations. Assuming that these considerations apply to the N–N ylides, the excited states of **2f** and **2g** may be described by the resonance forms **13** and **14**, respectively. Thus photochemical lability (**2f**) and stability (**2g**) may be associated with the amount of negative charge on exocyclic nitrogen. Information concerning the detailed mechanism, in particular evidence for the diaziridine intermediate **11**, is not yet available, although the attention of Streith toward the solution of this problem is to be noted.[10,11]



12 **13** **14**

Finally, the very similar uv spectrum [uv max (CH_2Cl_2) 271, 308 mμ] of an unusual, rigid carboxypyridinium ylide, pyrido[2,1-*b*]-1,3,4-oxadiazolone-2 (**15**),[26]



15

to that of the simple case **2a** led to a brief investigation of its photochemical behavior. It was found that compound **15** was stable to irradiation at 3500 and 3000 Å in methylene chloride solution for at least 24 hr. Sensitization with benzophenone also proved fruitless in that starting material was recovered unchanged after lengthy irradiation times at 3500 Å. The stability of **15** may be due to its inability to form a (strained) diaziridine intermediate which, in turn, is possibly associated with the highly delocalized (aromatic) nature of the compound.[26]

(26) K. Hoegele, *Helv. Chim. Acta*, **41**, 548 (1958).

Experimental Section

Microanalyses were performed by A. B. Gygli, Microtech Laboratories, Toronto, and Uniroyal Laboratories, Guelph. Melting points were measured on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were determined with Beckmann IR-5A, -9, and -10 instruments in chloroform solution unless otherwise indicated. Ultraviolet spectra were recorded on Hitachi EPS-3T and Beckman DB-G spectrophotometers in methanol solution. Nuclear magnetic resonance spectra were obtained with JEOL C-60, Varian T-60, and Varian HA-100 spectrometers in deuteriochloroform solution using tetramethylsilane as internal standard. Column, thin layer, and thick layer chromatography was carried out with silica gel obtained from Brinkmann (Canada) Ltd.; Woelm alumina (basic, grade III) was used for the purification of the ylide picrates. Solvents were reagent grade and distilled before use; unless otherwise indicated, petroleum ether of boiling range 60–80° was used. A Rayonet photochemical reactor equipped with sixteen 3500-Å lamps was used; photolyses were carried out in Pyrex vessels and cooled internally to 10–20° by a cold finger.

The Preparation of 1-Ethoxycarbonyliminopyridinium Ylides (2a–g). 1-Ethoxycarbonyliminopyridinium Ylide (2a). Method A.—A three-necked round-bottom flask equipped with a condenser and an addition funnel was charged with 70 g of freshly distilled pyridine and 10 g of ethyl azidoformate. The condenser was attached to a gas buret in order to measure the nitrogen evolution. The reaction was initiated by immersing the flask into an oil bath at 105° and stirring. In 12 hr, 1.9 l. of nitrogen were evolved (theoretical: 1.94 l.). Excess pyridine was removed *in vacuo* and the dark residue was taken up in 75 ml of boiling chloroform and treated with charcoal. The filtrate was concentrated and recrystallized twice from benzene and twice from tetrahydrofuran to yield 2.50 g (17.4% based on ethyl azidoformate) of **2a**, mp 108–109° (lit.[18] mp 109°).

Method B.—To a stirred solution of 1.60 g (7.55 mmol) of 1-aminopyridinium iodide[21] in 50 ml of ethanol were added dropwise and concurrently from two addition funnels solutions of 0.69 g (15.0 mmol) of potassium hydroxide in 50 ml of ethanol and 1.61 g (14.7 mmol) of ethyl chloroformate in 10 ml of ethanol. The additions were carried out in such a manner as to maintain a basic solution, indicated by the persistence of a purple color in the reaction mixture. After the additions, the resulting pale yellow solution was further stirred for 70 min. Evaporation to dryness yielded a yellow residue which was dissolved in 20 ml of a 10% aqueous sodium carbonate solution and extracted with methylene chloride. The extracts were dried (Na_2SO_4) and concentrated to yield 761 mg of crystalline material. Recrystallization from tetrahydrofuran gave colorless flakes of **2a**, 575 mg (48%), identical with material prepared by method A.

The following compounds were prepared by methods A and B as indicated in Table I.

2-Methyl-1-ethoxycarbonyliminopyridinium Ylide (2b).—A pale yellow, hygroscopic oil was obtained. Further purification was accomplished *via* the picrate. Recrystallization from benzene–

methanol gave yellow needles, mp 139–142.5°. For the purpose of photolysis, the ylide **2b** was regenerated by passing a chloroform solution of the picrate through a short column of basic alumina. Purity was established by ir and uv spectroscopy and tlc homogeneity in several solvent systems.

The picrate was recrystallized from benzene for the analytical sample, mp 141–142°.

Anal. Calcd for $C_{15}H_{15}N_5O_9$: C, 44.02; H, 3.69; N, 17.11. Found: C, 44.12; H, 3.92; N, 17.04.

4-Methyl-1-ethoxycarbonyliminopyridinium Ylide (2c).—Method A was modified in that toluene was used as a solvent for the reaction and the w/w ratio of pyridine derivative to ethyl azidoformate was reduced to 3:1. Recrystallization from tetrahydrofuran and benzene yielded **2c**. Further recrystallization from carbon tetrachloride furnished an analytical sample, mp 151.5–152.5°.

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.66; H. 6.80; N, 15.57.

3,5-Dimethyl-1-ethoxycarbonyliminopyridinium Ylide (2d).—Method A was modified as in the case of **2c**. Three recrystallizations from benzene gave colorless crystals of **2d**, mp 138–140°.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.71; H, 7.31; N, 14.46.

2,6-Dimethyl-1-ethoxycarbonyliminopyridinium Ylide (2e).—The picrate, mp 153–155° from ethanol, was treated as in the case of **2b**. Recrystallization from petroleum ether–benzene gave **2e** as pale yellow needles, mp 101–102°.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N; 14.42. Found: C, 61.93; H, 7.28; 6, 14.49.

4-Dimethylamino-1-ethoxycarbonyliminopyridinium Ylide (2f).—4-Dimethylamino-1-aminopyridinium iodide was prepared in 13% yield according to the procedures of Gosl[21] and Okamoto.[27] Two recrystallizations from ethanol gave colorless needles, mp 201.5–202.5°.

Anal. Calcd for $C_7H_{12}N_3I$: C, 31.72; H, 4.57; N, 15.85; I, 47.87. Found: C, 31.73; H. 4.63; N, 15.84; I, 47.71.

The above compound, when treated with ethyl chloroformate according to method B, gave **2f**. Three recrystallizations from benzene furnished colorless needles, mp 183–185°.

Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.31; H, 7.24; N, 20.31.

4-Ethoxycarbonyl-1-ethoxycarbonyliminopyridinium Ylide (2g).—Method A was modified as in the case of **2c**. Concentration *in vacuo* gave a viscous oil which was triturated with ether to yield pale yellow needles, mp 162–163.5°.

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H. 5.92; N, 11.76. Found: C, 55.19; H, 5.93; N, 11.62.

1-Benzoyliminopyridinium Ylide (4a).—In following method B, 2 equiv of benzoyl chloride instead of ethyl chloroformate was used. Recrystallization from benzene–petroleum ether gave tan needles of **4a**, mp 179–180.5° (lit.[19] mp 177.5°).

1-*p*-Toluenesulfonyliminopyridinium Ylide (4b).—Method B was followed except that 2 equiv of *p*-toluenesulfonyl chloride instead of ethyl chloroformate was used. Two recrystallizations from methanol yielded colorless rectangles, mp 215–217° (lit.[20] mp 210°).

Preparation of 1(1H),2-Diazepine Derivatives (3a–f). General Photolysis Procedure.—A 0.25% solution (w/v) of the ylide in methylene chloride was irradiated and the reaction was followed by the disappearance of the high-wavelength absorption in the uv spectrum (see Table I). In general, photolysis was complete in 10–12 hr for 100-mg samples. Evaporation of solvent *in vacuo*, chromatography over silica gel (elution with benzene and benzene–chloroform mixtures), and recrystallization or distillation yielded **3a–f**, **5a**, and **5b**. The yields of products and physical and analytical data are collected in Tables V and VI.

Photolysis of 1-Ethoxycarbonyliminopyridinium Ylide (2a) and Its Degradation to 1,2-Dibenzoyl-1,2-hexahydrodiazepine (9).—A solution of **2a** (399 mg, 2.5 mmol), in 90 ml of methylene chloride solution was photolyzed for 24 hr. The solvent was removed *in vacuo* and the resulting 370 mg of brown oil was hydrogenated at 1 atm in ethanol over 5% palladium on charcoal. After uptake of 101 ml (1.95 mmol) of hydrogen, the reaction was stopped and worked up in the usual way. A 130-mg portion of the crude product was chromatographed on silica gel (ether eluent) and yielded 60 mg of **1-ethoxycarbonyl-4,5,6,7-tetrahydrodiazepine (7)** as a pale yellow oil: ir (CCl_4) 1705 (C=O) and 1630 (C=N) cm^{-1}; nmr τ 2.92 (t, 1, C_3 H), 5.83 (q, 2, $CO_2CH_2CH_3$), 6.28 (br m, 2, C_4 H), 7.58 (br m, 2, C_7 H), 8.26 (br m, 4, C_5, C_6 H), and 8.68 (t, 3, $CO_2CH_2CH_3$). The remainder of the material was directly hydrogenated in ethanol over platinum oxide and yielded, after chromatography, 217 mg (55%) of oily **1-ethoxycarbonyl-1,2-hexahydrodiazepine (8)**: ir (CCl_4) 1700 cm^{-1} (C=O); nmr τ 5.80 (br, 1, NH, exchanged with D_2O), 5.87 (q, 2, $CO_2CH_2CH_3$), 6.53 (m, 2, C_7 H), 7.11 (m, 2, C_3 H), 8.36 (m, 6, C_4, C_5, C_6 H), and 8.73 (t, 3, $CO_2CH_2CH_3$).

Anal. Calcd for $C_9H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found: C, 55.71; H, 9.30; N, 16.66.

Compound **8** was dissolved in 7 ml of concentrated hydrochloric acid and the resulting solution was refluxed for 10 hr. Evaporation *in vacuo* gave a residue which was dissolved in alcoholic potassium hydroxide solution (10 g in 80 ml) and refluxed for 30 min. The solution was concentrated and extracted with large amounts of warm ether. Concentration of the ether extract to 25 ml was followed by additions of 50 ml of pyridine and 4 g of benzoyl chloride. After standing overnight, the mixture was concentrated *in vacuo* and the product was isolated in the usual way. Two recrystallizations from ethanol yielded **1,2-dibenzoyl-1,2-hexahydrodiazepine (9)**, mp 156–157°, which was characterized by identical ir spectrum, melting point, and mixture melting point with those of an authentic sample prepared according to Zinner and Deucker.[24]

Photolysis of 3,5-Dimethyl-1-ethoxycarbonyliminopyridinium Ylide (2d).—The crude product from photolysis in methylene chloride solution was chromatographed. After separation of **4,6-dimethyl-1-ethoxycarbonyl-1(1H),2-diazepine (3d)**, elution with 7% methanol–chloroform solution yielded 31% **10**, characterized by identical ir, uv, and nmr spectra, melting point, and mixture melting point with those of an authentic sample prepared as described below.

Preparation of 2-Carbethoxyamino-3,5-dimethylpyridine (10).—2-Amino-3,5-dimethylpyridine was prepared[28] in 20% yield: bp 98–100° (5–6 mm); ir (CCl_4) 3505, 3405, and 1616 cm^{-1}; uv max 235 mμ (ϵ 10,440) and 304 (5310); nmr τ 2.23 (br s, 1, H_6), 2.91 (br s, 1, H_4), 5.72 (br s, 2, NH_2, exchanged with D_2O), 7.84 (s, 3, C_5 CH_3), and 7.92 (s, 3, C_3 CH_3). This compound was treated with pyridine and ethyl chloroformate according to the procedure of Katritzky.[29] Compound **10** was obtained in 38% yield: mp 113–117.5°; ir (CCl_4) 3420, 3175 (NH), and 1740 cm^{-1} (C=O); uv max 226 mμ (ϵ 9200) and 274 (5000); nmr τ 1.93 (d, 1, J = 2 Hz, H_6), 2.44 (br, 1, NH, exchanged with D_2O), 2.63 (d, 1, J = 2 Hz, H_4), 5.98 (q, 2, $CO_2CH_2CH_3$), 7.70 (s, 6, C_3, C_5 CH_3), and 8.65 (t, 3, $CO_2CH_2CH_3$). Recrystallization from ethanol–water gave an analytical sample, mp 115.5–116.5°.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.93; H, 7.28; N, 14.49.

Methylene chloride solutions of **3d** and a mixture of **2d** with **3d** (1:1) were left standing at room temperature in the dark for 24 hr. In both cases, tlc analysis showed that no decomposition and no generation of **10** had occurred.

TABLE V

INFRARED AND ULTRAVIOLET SPECTRA OF DIAZEPINES

Diazepine	$\nu_{max}^{CHCl_3}$, cm^{-1} [a]	λ_{max}^{MeOH}, mμ (ϵ)[b]
3a	1700	221 (11,440)
	1609	255 (sh, 3560)
3b	1706	224 (12,380)
	1631	256 (sh, 3460)
3c	1711	220 (12,670)
	1633	242 (sh, 7260)
3d	1717	222 (8790)
	1632	250 (sh, 5840)
3e	1697	226 (8330)
	1641	242 (6990)
3f	1695	271 (14,200)
	1650	352 (3440)
5a	1651	227 (13,350)
	1611	285 (sh, 5400)
5b	1615 (w)	226 (16,050)
	1598 (w)	276 (sh, 1950)

[a] See footnote *b*, Table I. [b] See footnote *c*, Table I.

(27) T. Okamoto, M. Hirobe, and E. Yabe, *Chem. Pharm. Bull.* (Tokyo), **14**, 523 (1966).

(28) A. Albert and R. E. Willette, *J. Chem. Soc.*, 4063 (1964).

(29) A. R. Katritzky, *ibid.*, 2063 (1956).

TABLE VI
PHYSICAL AND ANALYTICAL DATA OF DIAZEPINES

Diazepine	Yield, %[a]	Physical state[b]	$n^{25}D$ or mp, °C	Molecular formula	Analysis,[c] % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
3a	97	Red oil	1.5400	$C_8H_{10}N_2O_2$	57.82	6.07	16.86	57.40	5.93	16.44
3b	84	Yellow oil	1.5276	$C_9H_{12}N_2O_2$	59.99	6.71	15.55	60.05	6.96	15.38
3c	98	Pale yellow needles[d]	55.5–56	$C_9H_{12}N_2O_2$	59.99	6.71	15.55	59.74	6.93	15.59
3d	41	Yellow oil	1.5065	$C_{10}H_{14}N_2O_2$	61.84	7.27	14.42	61.44	7.26	14.20
3e	72	Yellow oil	1.5140	$C_{10}H_{14}N_2O_2$	61.84	7.27	14.42	61.50	7.33	14.20
3f	65	Yellow needles[e]	90–91	$C_{10}H_{15}N_3O_2$	57.40	7.23	20.08	57.05	7.20	19.80
5a	64	Orange needles[e]	52–54	$C_{12}H_{10}N_2O$	72.71	5.08	14.13	72.71	5.23	14.00
5b	61	Pale yellow crystals[f]	173–175 dec	$C_{12}H_{12}N_2O_2S$[g]	58.06	4.87	11.28	58.37	4.77	11.06

[a] After chromatography. [b] Purification of the oily diazepines was achieved by short-path distillation at 45–60° (0.1–0.5 mm). [c] Owing to volatility and instability, analytical data on the oily compounds was difficult to obtain and the values given are the best of at least quadruplicate determinations. [d] From benzene–petroleum ether. [e] From ether–petroleum ether (bp 35–60°). [f] From benzene. [g] Calcd: S, 12.89. Found: S, 13.08.

Registry No.—**2a**, 23025-55-0; **2b**, 22928-83-2; **2b** picrate, 22928-84-3; **2c**, 22928-85-4; **2d**, 22928-87-6; **2e**, 23025-59-4; **2f**, 23025-60-7; **2g**, 23025-61-8; **3a**, 17377-08-1; **3b**, 22928-90-1; **3c**, 22928-91-2; **3d**, 22928-95-6; **3e**, 22928-97-8; **3f**, 23025-66-3; **4a**, 23031-08-5; **4b**, 23025-67-4; **5a**, 20169-43-1; **5b**, 23025-45-8; **7**, 20169-37-3; **8**, 20169-38-4; **10**, 22931-88-0.

Acknowledgments.—We express our gratitude to the National Research Council of Canada for the support of this work. Thanks are due to Mr. D. Burkholder and Mr. M. Stanton for able technical assistance and to Professor G. L. Lange for the use of the 3000-Å lamps and the nmr spectrometer in critical times. We are especially indebted to Mr. Brian Sayer for the 100-MHz nmr spectrum and to the Uniroyal Laboratories for analytical data on the oily diazepines. Finally, we wish to thank Professor T. Sasaki for an exchange of information and for graciously agreeing to simultaneous publication of results.

Synthesis of 4,5-Disubstituted Pyrimidines

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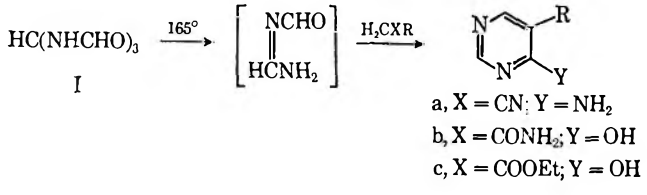
Received June 9, 1969

Several new 4-amino (or hydroxy) 5-substituted pyrimidines are prepared by the reaction of trisformylaminomethane with various substituted acetonitriles, acetamides, and corresponding esters, and the reaction results are discussed.

In a previous paper,[2] the synthesis of 4-amino (or hydroxy) 5-substituted pyrimidines by the reaction of trisformylaminomethane (I) with phenylacetonitriles (a) or *p*-nitrophenylacetamide (b) having an active methylene group was reported.



I

a, X = CN; Y = NH_2
b, X = $CONH_2$; Y = OH
c, X = COOEt; Y = OH

Pyrimidines of similar structure, with different substituent R, have been prepared by other workers.[3-7]

In this paper, the possibility of synthesis of 4-hydroxy-5-phenylpyrimidine from phenylacetamide, having a less active methylene group than *p*-nitrophenylacetamide, as well as the synthesis of 4-hydroxypyrimidines from the corresponding esters (c), were studied. Furthermore, in order to prepare new 4-amino (or hydroxy) 5-substituted pyrimidines and to extend the application of this synthetic method, substituted acetonitriles, acetamides, and the corresponding esters, with both electron-attracting and -releasing substituents, were used.

The reactions were carried out under the same conditions, using formamide as a solvent and *p*-toluenesulfonic acid as a catalyst.[8] However, the presence of formamide and the catalyst has been found to be unnecessary. The results of these reactions are presented in Table I.

Some 4-hydroxypyrimidines were also prepared by acid hydrolysis of the corresponding 4-aminopyrimidines. The results of the replacement reactions are summarized in Table II.

(1) Abstracted in part from the Ph.D. dissertation of A. H. K., University of Thessaloniki, Greece, 1967.
(2) G. Tsatsaronis and F. Effenberger, *Chem. Ber.*, **94**, 2876 (1961).
(3) H. Bredereck, G. Simchen, and H. Traut, *ibid.*, **98**, 3883 (1965).
(4) W. H. Davies and H. A. Piggot, *J. Chem. Soc.*, 347 (1945).
(5) W. H. Davies, A. W. Johnson, and H. A. Piggot, *ibid.*, 352 (1945).
(6) K. Huffman, F. Schaefer and G. Peters, *J. Org. Chem.*, **27**, 551 (1962).
(7) E. C. Taylor and J. G. Berger, *ibid.*, **32**, 2376 (1967).
(8) H. Bredereck, R. Gompper, and B. Geiger, *Chem. Ber.*, **93**, 1402 (1960).

TABLE I

SYNTHESES OF 4,5-DISUBSTITUTED PYRIMIDINES

Starting material RCH₂X		Reaction conditions	Product		Pure yield, %	Formula	Calcd, %			Found, %		
R	X		Compd	Y			C	H	N	C	H	N
α-$C_{10}H_7$	CN	A	II	NH_2	28	$C_{14}H_{11}N_3$	75.99	5.01	18.99	76.08	5.13	19.03
2-C_5H_4N	CN[a]	A	III	NH_2	54	$C_9H_9N_4$	62.77	4.68	32.54	62.73	4.54	31.99
3-C_5H_4N	CN[b]	A	IV	NH_2	52	$C_9H_8N_4$	62.77	4.68	32.54	62.51	4.60	32.28
4-C_5H_4N	CN[c]	A	V	NH_2	52	$C_9H_8N_4$	62.77	4.68	32.54	62.18	4.45	32.47
2-C_9H_6N	CN[d]	A[e]	VI	NH_2	38	$C_{13}H_{10}N_4$	70.25	4.54	25.21	69.71	4.48	25.36
4-C_9H_6N	CN[f]	A[e]	VII	NH_2	36	$C_{13}H_{10}N_4$	70.25	4.54	25.21	70.53	4.21	25.37
6-C_9H_6N	CN[g]	A[e]	VIII	NH_2	7	$C_{13}H_{10}N_4$	70.25	4.54	25.21	69.96	4.40	24.96
8-C_9H_6N	CN[h,i]	A[e]	IX	NH_2	10	$C_{13}H_{10}N_4$	70.25	4.54	25.21	70.13	4.49	25.15
CH_3	CN	A[j]	X	NH_2	1.8	$C_5H_7N_3$[k]	55.03	6.47	38.51	54.43	6.07	38.37
C_6H_5	$CONH_2$	A[l]	XI	OH	9	$C_{10}H_8N_2O$[m]	...	...	...	...	...	...
C_6H_5	COOEt	A[l]	XI	OH	0.3	$C_{10}H_8N_2O$	...	...	...	...	...	...
α-$C_{10}H_7$	$CONH_2$[n]	A	XII	OH	5	$C_{14}H_{10}N_2O$	75.65	4.54	12.61	75.36	4.25	12.60
α-$C_{10}H_7$	COOEt	A	No pyrimidine		...	...	...	...	...	...	...	...
3-C_5H_4N	$CONH_2$[o]	A	XIII	OH	25	$C_9H_7N_3O$	62.42	4.07	24.27	62.06	3.80	23.97
4-C_5H_4N	$CONH_2$[p]	A	XIV	OH	40	$C_9H_7N_3O$	62.42	4.07	24.27	62.50	3.82	24.40
p-$O_2NC_6H_4$	COOEt	A	XV	OH	40	$C_{10}H_7N_3O_3$[q]	...	...	...	...	...	...
C_3H_7	CN	A[r]	No pyridine		0.4	Bisformyl aminomethane						
C_5H_{13}	CN	A[s]	No pyrimidine		0.6	Bisformyl aminomethane						

[a] N. Sperber, *et al.*, *J. Amer. Chem. Soc.*, **73**, 5752 (1951). [b] Obtained from K & K Laboratories, Inc. [c] Prepared analogously to 2-pyridylacetonitrile, yield 58%. [d] W. Borsche and R. Manreuffel, *Chem. Abstr.*, **31**, 406 (1937); *Chem. Zentr.*, I, 2971 (1937). [e] Half quantities of reactants were used. [f] H. Lettré, *et al.*, *Chem. Ber.*, **85**, 397 (1952). [g] Prepared analogously to 2-pyridylacetonitrile from the 6-quinolylacetamide, yield 55%, mp 80–81°. [h] R. G. Jones, Q. F. Soper, O. K. Behrens, and J. W. Corse, *J. Amer. Chem. Soc.*, **70**, 2843 (1948). [i] B. Prijs, *et al.*, *Helv. Chim. Acta*, **37**, 90 (1954). [j] In a glass sealed tube heated in an autoclave. [k] R. R. Williams, A. E. Ruehle, and J. Finkelstein, *J. Amer. Chem. Soc.*, **59**, 526 (1937). [l] Without catalyst. [m] Reference 4. [n] W. Wenner, *Chem. Abstr.*, **44**, 9374c (1950). [o] A. Burger and C. Walter, *J. Amer. Chem. Soc.*, **72**, 1988 (1950). [p] A. Burger, *et al.*, *ibid.*, 74, 3175 (1952). [q] Reference 2. [r] Fivefold quantities of reactants were used. [s] Tenfold quantities of reactants were used.

TABLE II

REPLACEMENTS OF THE SUBSTITUENT Y

Starting material			Product		Pure yield, %	Formula	Calcd, %			Found, %		
Compd	R	Y	Compd	Y			C	H	N	C	H	N
II	α-$C_{10}H_7$	NH_2	XII	OH	45	...	...	...	...	...	...	...
III	2-C_5H_4N	NH_2	XVI	OH	43	$C_9H_7N_3O$	62.42	4.07	24.27	62.13	3.90	24.13
IV	3-C_5H_4N	NH_2	XII	OH	50	...	...	...	...	...	...	...
XII	α-$C_{10}H_7$	OH	XVII	Cl	76	$C_{14}H_9N_2Cl$	69.82	3.77	11.63	69.42	3.40	11.77
XVII	α-$C_{10}H_7$	Cl	II	NH_2	54	...	...	...	...	...	...	...
XVII	α-$C_{10}H_7$	Cl	XVIII	$NHNH_2$	80	$C_{14}H_{12}N_4$	71.16	5.12	23.72	71.29	5.05	23.53

On the basis of the yields (Table I), it is found that the reactivity of RCH_2X, for the same substituent R, decreases in the order nitrile > amide > ester (X = CN, $CONH_2$, and COOEt, respectively). This is attributed to the higher electron-attracting effect of the CN group with respect to the $CONH_2$ and the COOEt group, with the result that the methylene group of nitrile becomes more active.

In addition, for the same substituent X, as the electron-attracting effect of the substituent R is increased, higher yields are obtained, provided that the hindrance effect of R is almost the same. This is evident from the reaction yields with α-naphthyl- and 4-quinolylacetonitrile, 3-pyridyl- and 4-pyridylacetamide, and phenyl- and *p*-nitrophenylacetic ethyl ester and from the reactions with propio-, valero-, and caprylonitrile, where R is an electron-releasing substituent. Thus no pyrimidine was obtained with valero- and caprylonitrile, although larger quantities of reactants were used to make possible the isolation of the expected pyrimidine, even in small amounts. However, from these reactions, bisformylaminomethane, in very small yield, was isolated. It was identified by mixture melting point and by comparison of the ir spectra with that of an authentic sample.[9] The mechanism of formation of bisformylaminomethane is under further investigation.

The yield also depends significantly on the steric bulk of the substituent R. Thus, in spite of the more electron-attracting effect, the yields with α-naphthyl- and 2-quinolylacetonitrile were, respectively, less than with phenyl- and 2-pyridylacetonitrile. The considerably smaller yield with 8-quinolyl- or 6-quinolylacetonitrile compared with α-naphthylacetonitrile is due to the formation of resinous by-products.

The ratio of the yields with amide and corresponding nitrile becomes greater as the electron-attracting effect

(9) C. W. Sauer and R. J. Bruni, *J. Amer. Chem. Soc.*, **77**, 2559 (1955).

of the substituent R increases. Thus for R = α-naphthyl, 3-pyridyl, and 4-pyridyl, the ratio of yields is increased, respectively. Consequently, for a more electron-attracting substituent R, the reaction yield with an amide would be expected to approach the yield with the corresponding nitrile. A similar increase of the ratio of yields with ester and corresponding amide is also observed.

The compound obtained by Novelli[10,11] by reaction of α-naphthylacetonitrile with formamide and described as α-naphthylmethyl-1,3,5-triazine was shown in this work to be the isomeric 4-amino-5-α-naphthylpyrimidine (II). The identification was based on mixture melting point and ir spectra. The aminopyrimidines showed the characteristic absorptions of the amino group[12-15] (1620–1670, 3100–3170, and 3288–3360 cm^{-1}).

Experimental Section

Melting points were taken on a Kofler hot-stage apparatus and are corrected. The melting point of 4-amino-5-methylpyrimidine (X) was obtained in a closed capillary tube because of its sublimation. All ir spectra were obtained as Nujol mulls on a Beckman IR-4 spectrophotometer.

Reaction Conditions (A, Table I).—A mixture of 0.05 mol of starting material (nitrile, amide, or ester), 14.5 g (0.1 mol) of trisformylaminomethane[16] (I), 8 ml (0.2 mol) of formamide, and 1 g of *p*-toluenesulfonic acid was heated with stirring for 7 hr at 170°.

4-Amino-5-α-naphthylpyrimidine (II).—The dark reaction mixture was acidified with 10% hydrochloric acid, diluted with water, treated with active carbon, and filtered, and the aminopyrimidine (II) was precipitated by basification with 8% sodium hydroxide and crystallized from benzene (charcoal). It is very soluble in chloroform and warm alcohol, and soluble in warm benzene and water. Recrystallizations from benzene (charcoal) gave white crystals, yield 3 g, mp 194–195°.

4-Amino-5-(pyridyl-2)-pyrimidine (III).—The reaction mixture was allowed to crystallize overnight. The product was filtered with suction, washed with a small amount of water, dried, and, after treatment with active carbon, crystallized from benzene, yield 4.9 g, mp 173–175°. From the filtrate, by basification, with 8% sodium hydroxide and extraction with benzene for 24 hr, an additional 0.5 g of III was obtained. Recrystallization from benzene (charcoal) gave white crystals, yield 4.7 g, mp 175–176°.

4-Amino-5-(pyridyl-3)-pyrimidine (IV).—In the same manner as above, white crystals of IV were obtained, yield 4.5 g, mp 196–197°.

4-Amino-5-(pyridyl-4)-pyrimidine (V).—As above, crude V was obtained, yield 5.4 g, mp 225–227°. Recrystallization from chloroform (charcoal) gave white crystals, yield 4.5 g, mp 228–229°.

4-Amino-5-(quinolyl-2)-pyrimidine (VI).—The reaction mixture was allowed to stand overnight. The crystalline product was separated and treated as in the case of II, giving, after crystallization from benzene (charcoal), crude VI, yield 2.9 g, mp 196–200°. Recrystallizations from benzene (charcoal) gave bright plates, yield 2.1 g, mp 201–201.5°.

4-Amino-5-(quinolyl-4)-pyrimidine (VII).—In the same manner as previously, crude VII was obtained, yield 2.5 g, mp 243–246°. Recrystallization from chloroform (charcoal) gave white crystals, yield 2 g, mp 246–247°.

4-Amino-5-(quinolyl-6)-pyrimidine (VIII).—The dark, viscous reaction mixture was extracted with benzene for 24 hr. The benzene solution was treated with active carbon and the formed resin, on cooling, was separated by decantation. The solution was then concentrated, affording a crystalline product which dissolved in 10% hydrochloric acid. The solution was treated with active carbon and the product was precipitated by basification of the filtrate with 8% sodium hydroxide. The precipitate was crystallized from water, giving crude VIII as pale yellow crystals, yield 1.9 g, mp 163–171°. It was chromatographed on basic alumina by using 4:1 chloroform–benzene as eluent to yield a product, mp 186–193°. Recrystallizations from ligroin (bp 100–120°) gave white crystals of pure VIII, yield 0.4 g, mp 194–195°.

6-Quinolylacetamide.—In a flask with stopper, 21.5 g (0.1 mol) of 6-quinolylacetic ethyl ester[17] and 100 ml of ammonium hydroxide (27%) were shaken for 8 hr. The formed amide was separated and crystallized from alcohol as white crystals, yield 13 g (70%), mp 207–208°.

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.71; H, 5.80; N, 15.10.

4-Amino-5-(quinolyl-8)-pyrimidine (IX).—The resinous reaction mixture was treated as in the case of II. The resin formed was removed and the alkaline solution was extracted with benzene for 24 hr to yield crude IX as pale yellow crystals, yield 0.8 g, mp 174–180°. Recrystallization from benzene (charcoal) gave white needles, yield 0.6 g, mp 186–187°.

4-Amino-5-methylpyrimidine (X).—The reaction mixture was treated with water, made alkaline with 8% sodium hydroxide, and extracted with benzene for 30 hr. Crude X was obtained from the benzene extract as pale yellow crystals, yield 0.2 g. Recrystallization from benzene (charcoal) gave white needles, yield 0.1 g, mp 178–179° (lit.[18] mp 175–176°).

4-Hydroxy-5-phenylpyrimidine (XI). A. Synthesis with Amide.—The reaction mixture was treated with a small amount of water and 8% sodium hydroxide and the unreacted amide was separated and regained after recrystallization, yield 22%. The alkaline filtrate was treated with active carbon, filtered, cooled, and saturated with carbon dioxide to pH 7–8 to precipitate XI, yield 0.9 g, mp 125–140°. The new filtrate was extracted with chloroform for 10 hr and the extract, after removal of chloroform and formamide [bp 95° (10 mm)], was dried on a plate, yield 1.8 g, mp 136–167°. The totally received crude XI was warmed on a steam bath with 10 ml of 36% hydrochloric acid for 1 hr to hydrolyze any unreacted amide. The residue, after evaporation, was dissolved in 8% sodium hydroxide and the solution was saturated with carbon dioxide to give XI, yield 1 g, mp 170–173°. Recrystallization from water gave white crystals, yield 0.8 g, mp 173–174° (lit.[4] mp 173–174°).

B. Synthesis with Ester.—The reaction mixture gave two layers. The upper layer, by distillation *in vacuo* [bp 120–121° (20 mm)], gave the unreacted ester, yield 50%. The lower layer was made alkaline with 8% sodium hydroxide, treated with active carbon, filtered, saturated with carbon dioxide, and extracted with chloroform for 10 hr. The hydroxypyrimidine XI was separated and purified as above. Recrystallization from water, after cooling in a refrigerator, gave white crystals, yield 0.03 g, mp 172–174°.

4-Hydroxy-5-α-naphthylpyrimidine (XII).—The unreacted amide was recovered in 45% yield as in procedure A for XI. The alkaline filtrate was treated with active carbon and saturated with carbon dioxide to precipitate XII, which was redissolved in 8% sodium hydroxide and reprecipitated with carbon dioxide. Recrystallization from benzene (charcoal) or alcohol gave white crystals, yield 0.6 g, mp 203–205°.

Attempted Reaction of I with α-Naphthylacetic Ethyl Ester.—In an analogous manner to procedure B for XI, no hydroxypyrimidine XII was obtained and the ethyl ester was recovered in 50% yield.

4-Hydroxy-5-(pyridyl-3)-pyrimidine (XIII).—The reaction mixture was allowed to stand overnight. The crystalline product was filtered,[19] dissolved in a small amount of 35% sodium hydroxide, and treated with active carbon. The filtrate was saturated with carbon dioxide and cooled overnight in a refrigerator, and the separated, crude XIII was crystallized from alcohol (charcoal) as pale yellow crystals, yield 3.3 g, mp 235–238°.

(10) A. Novelli, *Anales Assoc. Quim. Arg.*, **31**, 23 (1943).
(11) D. J. Brown, "The Pyrimidines," John Wiley & Sons, Inc., New York, N. Y., 1962, p 92.
(12) L. N. Short and H. W. Thompson, *J. Chem. Soc.*, 168 (1952).
(13) D. J. Brown and L. N. Short, *ibid.*, 331 (1953).
(14) J. A. Brownlie, *ibid.*, 3062 (1950).
(15) J. A. Montgomery, *J. Amer. Chem. Soc.*, **78**, 1928 (1956).
(16) H. Bredereck, R. Gompper, H. Rempfer, K. Klemm, and H. Keck, *Chem. Ber.*, **92**, 329 (1959).
(17) R. G. Jones, Q. F. Soper, O. K. Behrens, and J. W. Corse, *J. Amer. Chem. Soc.*, **70**, 2843 (1948).
(18) R. R. Williams, A. E. Ruehle, and J. Finkelstein, *ibid.*, **59**, 526 (1937).
(19) From the filtrate, after distillation of formamide and extraction of the residue with boiling chloroform, unreacted amide was recovered in 6% yield.

Recrystallization from alcohol gave white crystals, yield 2.2 g, mp 238–239°.

4-Hydroxy-5-(pyridyl-4)-pyrimidine (XIV).—In the same manner as above, crude XIV was obtained as pale yellow needles, yield 4.4 g, mp 280–283°. Recrystallizations from alcohol gave white needles, yield 3.5 g, mp 282–283°.

4-Hydroxy-5-*p*-nitrophenylpyrimidine (XV).—The reaction product was separated, dissolved in warm 8% sodium hydroxide, and treated with active carbon, and the filtrate after saturation with carbon dioxide, yielded XV as a yellow powder, yield 6 g, mp 330–332° dec. By redissolving the product in 8% sodium hydroxide and reprecipitation with carbon dioxide, pure XV was obtained as yellow needles, yield 4 g, mp 335–337° dec (lit.[2] mp 337° dec).

Attempted Reaction of I with Valeronitrile. Isolation of Bisformylaminomethane.—The reaction mixture was distilled to recover the unreacted nitrile in 71% yield. (The nitrile was purified from the distilled *s*-triazine by freezings and redistillations). The solid residue, after the distillation of formamide, was dissolved in water, made alkaline with sodium carbonate, and extracted with chloroform for 3 days to give a crystalline product, yield 0.5 g, mp 132–139°. Recrystallization from toluene (charcoal) gave white crystals of bisformylaminomethane, yield 0.3 g mp 140–141° (lit.[9] mp 142–143°).

Attempted Reaction of I with Caprylonitrile. Isolation of Bisformylaminomethane.—The reaction mixture gave two layers. The upper layer gave the unreacted nitrile, bp 205°. (The purification of the nitrile from *s*-triazine was obtained as previously.) The lower layer was made alkaline with 8% sodium hydroxide and the resultant oily layer of unreacted nitrile was removed (88% of the nitrile was totally recovered). The solution was then extracted with ether for 4 days to give a mixture of two layers. The upper layer was ether. The lower was distilled in vacuo to remove formamide, and the residue was treated with boiling methanol to yield a crystalline product, yield 1.4 g, mp 127–134°. Recrystallization from acetic ethyl ester (charcoal) gave white needles of bisformylaminomethane, yield 0.9 g, mp 140–141°.

4-Hydroxy-5-α-naphthylpyrimidine (XII) by Hydrolysis of II.—A solution of 11.1 g (0.05 mol) of II in 35 ml of 36% hydrochloric acid was heated on a steam bath in a stream of hydrogen chloride for 20 hr. The reaction mixture was made alkaline with 35% sodium hydroxide and the unreacted II was recovered in 18% yield by filtration. The filtrate was diluted with 50 ml of water and saturated with carbon dioxide to precipitate XII. Crystallization from water or alcohol gave white needles, yield 5 g, mp 204–205°. The yield of XII was increased to 56% when the hydrolysis time was 40 hr.

4-Hydroxy-5-(pyridyl-2)-pyrimidine (XVI) by Hydrolysis of III.—Compound III (8.6 g, 0.05 mol) was hydrolyzed as previously for 20 hr. The reaction mixture was evaporated on a steam bath under reduced pressure to remove the hydrogen chloride. The residue was dissolved in sodium hydroxide solution and extracted with benzene for 12 hr to remove unreacted III (0.5 g). The alkaline solution was then saturated with carbon dioxide and extracted with chloroform for 48 hr, yielding crude XVI. Recrystallization from acetic ethyl ester (charcoal) gave white crystals, yield 3.8 g, mp 181–183°.

4-Hydroxy-5-(pyridyl-3)-pyrimidine (XIII) by Hydrolysis of IV.—In the same manner as previously, crude XIII was obtained on the saturation of the alkaline solution with carbon dioxide, yield 4.1 g, mp 234–238°. An additional amount (1.5 g) of XIII was obtained by extraction of the filtrate with chloroform for 36 hr. Recrystallization from alcohol gave white crystals, yield 4.3 g, mp 238–239°.

4-Chloro-5-α-naphthylpyrimidine (XVII).—A mixture of 11.1 g (0.05 mol) of XII in 40 ml of freshly distilled phosphorus oxychloride was refluxed for 1 hr and then the excess of oxychloride was removed under reduced pressure. The residual resinous product was treated with ice–water and the crude XVII was separated as yellow powder. Crystallization from petroleum ether (bp 60–80°) with active carbon gave white crystals, yield 9.2 g, mp 99–100°.

4-Amino-5-α-naphthylpyrimidine (II) by Transformation of XVII.—A mixture of 0.5 g of XVII and 5 ml of alcohol saturated with ammonia gas was heated in a sealed tube for 4 hr at 150–160°. The alcohol was removed by evaporation under reduced pressure and the residue was extracted with boiling benzene to give, after recrystallization, II, yield 0.25 g, mp 195°.

4-Hydrazino-5-α-naphthylpyrimidine (XVIII).—To a slightly warm solution of 2.4 g (0.01 mol) of XVII in 50 ml of methanol, 10 ml of hydrazine hydrate was added and the solution was allowed to stand for 24 hr. Rhomboid crystals of XVIII were separated. Recrystallization from methanol (charcoal) gave white crystals, yield 1.9 g, mp 181–182°.

Registry No.—II, 22433-62-1; III, 22487-56-5; IV, 22433-63-2; V, 22433-65-4; VI, 22433-66-5; VII, 22433-67-6; VIII, 22487-57-6; IX, 22487-58-7; X, 22433-68-7. XI, 22433-69-8; XII, 22433-70-1; XIII, 22433-71-2; XIV, 22433-72-3; XV, 22433-73-4; XVI, 22433-74-5; XVII, 22487-59-8; XVIII, 22433-75-6; 6-quinolylacetamide, 22433-76-7.

The Photocyclization of 1-(α-Indolyl)-2-(β-pyridyl)acrylonitrile

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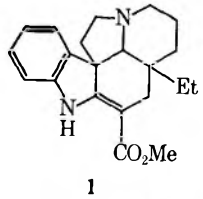
Received June 18, 1969

The photolysis of an ethanol solution of the title compound in the presence of ferric chloride or iodine has yielded 6-cyano-7H-pyrido[3,2-*c*]carbazole and 6-cyano-7H-pyrido[3,4-*c*]carbazole. A similar photolysis in the absence of oxidizing agents has led to 1-cyano-3-(β-formylvinyl)carbazole.

One of the many conceivable routes of synthesis of *Aspidosperma* alkaloids, *e.g.*, vincadifformine (**1**), involves the construction of a tetracyclic nucleus, such as **4**, and later introductions of the angular two-carbon substituent and the β-indolyl–N_b ethano bridge. In pursuit of this goal, the synthesis of nitrile **4** was attempted. It was assumed that the photolysis of 1-(α-indolyl)-2(β-pyridyl)acrylonitrile (**2**) would yield **4** in analogy to the photochemical conversion of the dicyanostilbene **5** into the dihydrophenanthrene **6**.[1-3] While this proved not to be the case, an interesting new rearrangement was encountered.



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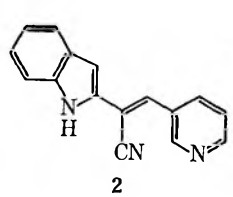

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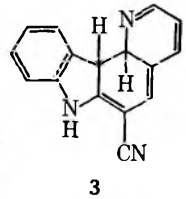

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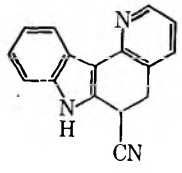

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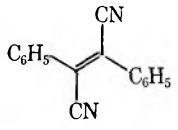

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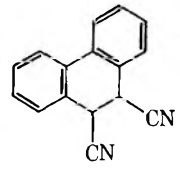
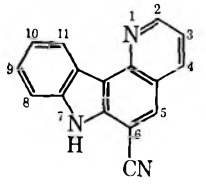


6

Methoxide-induced condensation of α-indolylacetonitrile[4] with nicotinaldehyde yielded a single product **2** (or its geometric isomer).[5] Determination of its stereochemistry could be avoided, since its subsequent photocyclization was expected to be preceded by photoisomerization of its central double bond. The photolysis of **2** was first executed in an oxidative manner, in order to ascertain the ease and direction of cyclization and to avoid possible complications during the desired isomerization of the anticipated, sensitive intermediate **3** into **4**. Irradiation of an ethanolic solution of **2** with a high-pressure Hanau lamp in the presence of ferric chloride or iodine led to two products, **7** and **8**, in 5 and 30% yields, respectively. The spectral characteristics of the pyridocarbazoles were in consonance with their assigned structures, the most striking features being the deshielding of the C-11 proton by the nonbonded electron pair of N-1 in the proton magnetic resonance spectrum of the less polar substance **7** and the deshielding of the C-4 proton by the central benzene ring in the spectrum of **8** (see Experimental Section). The heterocycle **7**, containing a highly hindered pyridine nitrogen, was unreactive toward methylation, whereas **8** yielded a pyridinium salt on treatment with methyl iodide, which could be converted into the piperidine derivative **9** on sodium borohydride reduction. The mass spectrum of the latter product revealed an M − 43 peak, characteristic of the $CH_2{=}NCH_3$ moiety and indicative of the lack of attachment of the piperidine nitrogen to the carbazole nucleus.



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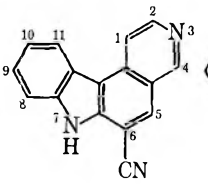

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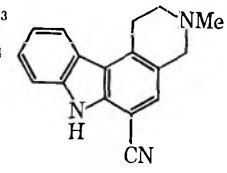
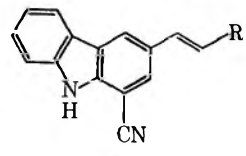
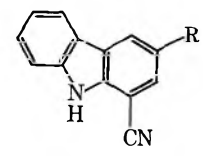


9

Irradiation of an ethanolic solution of **2** under nitrogen with a high-pressure Hanau lamp yielded a complex mixture from which a product to which structure **10a** was assigned could be isolated in 30% yield. Its reduction with sodium borohydride gave the alcohol **10b** whose acetylation afforded the ester **10c**, while its oxidation with osmium tetroxide and thereafter with sodium periodate yielded 1-cyano-3-formylcarbazole (**11a**). Borohydride reduction of the latter led to the alcohol **11b**, whereas condensation with malonic acid gave the cinnamic acid derivative **10d**, the reduction of whose acid chloride with lithium tri-*t*-butoxyaluminum hydride produced an alcohol identical with the product (**10b**) of reduction of the photolysis product. The last set of experiments verified the *trans* configuration of the side chain of **10a**, already discernible from its pmr spectrum.



10a, R = CHO
b, R = CH_2OH
c, R = CH_2OAc
d, R = CO_2H
e, R = CO_2Me



11a, R = CHO
b, R = CH_2OH

The formation of **10a** from the photolysis of **2** implicates **3** and **12** as consecutive intermediates. While

(1) M. V. Sargent and C. J. Timmons, *J. Amer. Chem. Soc.*, **85**, 2186 (1963); *J. Chem. Soc.*, 5544 (1964).

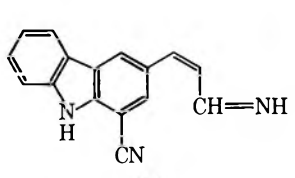
(2) For reviews of the photochemical transformation of stilbenes into dihydrophenanthrenes or phenanthrenes, see (a) R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, pp 219–222; (b) F. R. Stermitz in "Organic Photochemistry," Vol. 1, O. L. Chapman, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 247; (c) A. Schönberg, "Preparative Organic Photochemistry," Springer-Verlag, New York, N. Y., 1968, Chapters 13 and 14, pp 126–145; (d) K. A. Muszkat and E. Fischer, *J. Chem. Soc., B*, 662 (1967).

(3) For examples of the conversion of stilbazoles into azodihydrophenanthrenes or azophenanthrenes, see ref 2a–c and (a) C. E. Loader and C. J. Timmons, *J. Chem. Soc., C*, 1078 (1966); 1457 (1967); 330 (1968); (b) V. M. Clark and A. Cox, *Tetrahedron*, **22**, 3421 (1966); (c) E. Winterfeldt and H. J. Altmann, *Angew. Chem.*, 486 (1968).

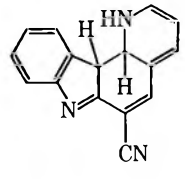
(4) W. Schindler, *Helv. Chim. Acta*, **40**, 2156 (1957).

(5) This compound was synthetized initially by Dr. T. Oishi (E. Wenkert and T. Oishi, unpublished observations).

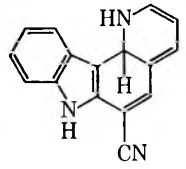
the unravelling of the pyridine ring is unprecedented,[6] it represents an elimination–aromatization reminiscent of the spontaneous formation of phenanthrenes from dihydrophenanthrene intermediates possessing leaving groups at central bridgehead positions in the photocyclization of *o*-halo- or *o*-methoxystilbenes.[7] Alternatively, **3** in ethanol solution can be expected to be in equilibrium with its tautomers **13** and **14**, of which the latter can undergo an electrocyclic transformation into **12**. The available experimental facts were insufficient to differentiate these reaction routes or to discern the sequence of events in the hydrolytic isomerization of **12** into **10a** (photolysis or work-up).



12



13



14

Experimental Section

Melting points were determined on a Kofler block. Ultraviolet spectra were measured on a Unicam Model SP 700 spectrometer and infrared spectra (Nujol) were measured on a Perkin-Elmer Model 257 spectrometer. Mass spectra were recorded on an A. E. I. Model MS 9 spectrometer. Proton magnetic resonance spectra of deuteriodimethyl sulfoxide solutions were taken on a Varian Model A-60A instrument.

1-(α-Indolyl)-2-(β-pyridyl)acrylonitrile (2).—Nicotinaldehyde, 6 ml, was added to a solution of 8.00 g of α-indolylacetonitrile[4] and sodium methoxide (from 1.20 g of sodium) in 300 ml of methanol. The mixture was kept at room temperature for 1 hr, diluted with water, and saturated with sodium chloride. The resultant precipitate was filtered and crystallized from acetone, leading in 80% yield to the nitrile **2**: mp 206°; ir (Nujol) 2220 cm^{-1} (C≡N); λ_{max} (EtOH) 270 mμ (log ε 4.14) and 380 (4.46); λ_{max} ($EtOH_2^+$) 269 (4.14) and 389 (4.42); λ_{max} (EtOH–NaOH) 264 (shoulder, 4.57) and 374 (4.60); mass spectrum *m/e* 245 (M^+).

Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.23; H, 4.50; N, 16.91.

6-Cyano-7H-pyrido[3,2-*c*]carbazole (7) and 6-Cyano-7H-pyrido[3,4-*c*]carbazole (8).—A solution of 600 mg of **2** and 100 mg of iodine in 250 ml of ethanol under nitrogen was irradiated by a high-pressure Hanau Q 81 lamp for 5 hr. Enough sodium thiosulfate was added to decolorize the solution. The mixture was concentrated and then diluted with water. Filtration of the resultant precipitate yielded 520 mg of a solid. Several repetitions of the operation gave 3.80 g of crude product. A solution of the product in a minimum amount of methanol was mixed with 30 g of Florisil (60–100 mesh), the solvent was eliminated, and the remaining powder was added to a chromatography column of 140 g of the same Florisil. The benzene and 100:1 benzene–chloroform eluates led to 275 mg of solid whose crystallization from chloroform gave 150 mg of yellow needles of nitrile **7**: mp >260°; λ_{max} (EtOH) 222 mμ (log ε 4.52), 250 (4.54), 284 (4.46), 350 (3.95), and 386 (shoulder, 3.74); λ_{max} ($EtOH_2^+$) 221 (4.50), 250 (4.50), 282 (4.39), 312 (3.94), 351 (3.85), and 386 (3.74); λ_{max} (EtOH–NaOH) 250 (4.46), 278 (4.34), 320 (4.25), and 385 (3.82); nmr δ 7.55 (q, 1, *J* = 8, 4.5 cps, H-3), 8.51 (q, 1, *J* = 8, 2 cps, H-4), 8.56 (s, 1, H-5), 8.90 (m, 1, H-11), and 9.15 ppm (q, 1, *J* = 4.5, 2 cps, H-2); mass spectrum *m/e* 243 (M^+).

Anal. Calcd for $C_{16}H_9N_3$: C, 78.99; H, 3.73; N, 17.28. Found: C, 78.80; H, 3.99; N, 17.27.

The chloroform eluates gave a solid whose crystallization from 2:1 chloroform–methanol yielded 1.22 g of yellow crystals of nitrile **8**: mp >260°; λ_{max} (EtOH) 220 mμ (shoulder, log ε 4.54), 255 (shoulder, 4.54), 271 (4.59), 286 (4.50), and 347 (4.03); λ_{max} ($EtOH_2^+$) 236 (4.47), 260 (4.51), 268 (4.51), and 321 (4.55); λ_{max} (EtOH–NaOH) 267 (4.49) and 322 (4.65); nmr δ 7.41 (d, 1, *J* = 6 cps, H-1), 8.55 (m, 1, H-11), 8.70 (s, 1, H-5), 8.75 (d, 1, *J* = 6 cps, H-2), and 9.41 ppm (s, 1, H-4); mass spectrum *m/e* 243 (M^+).

Anal. Calcd for $C_{16}H_9N_3$: C, 78.99; H, 3.73; N, 17.28. Found: C, 78.77; H, 3.89; N, 17.08.

Irradiation of a solution of 500 mg of **2** and 500 mg of ferric chloride in 250 ml of ethanol as above, concentration of the solution, dilution with water and addition of potassium carbonate until the mixture reached pH 6, extraction with chloroform, and further work-up as above gave similar yields of **7** and **8**.

1,2,3,4-Tetrahydro-3-methyl-6-cyano-7H-pyrido[3,4-*c*]carbazole (9).—Methyl iodide, 5 ml, was added to a solution of 200 mg of **8** in a minimum amount of methanol and the mixture was kept at 40° for 48 hr. Three additional 5-ml portions of methyl iodide were added during this period. Filtration of the resultant precipitate, 193 mg, and crystallization from methanol yielded **8** methiodide, mp >270°.

Anal. Calcd for $C_{17}H_{12}N_3I$: C, 52.98; H, 3.11; N, 10.90. Found: C, 52.37; H, 3.12; N, 10.50.

Sodium borohydride, 100 mg, was added in small portions to a suspension of 92 mg of the methiodide in 25 ml of 9:1 methanol–water. The starting material dissolved and the solution assumed a green fluorescence. After 15 min a precipitate appeared. The mixture was diluted with aqueous saturated brine solution and the precipitate, 50 mg, was filtered. Crystallization of the solid from 1:1 methanol–acetone gave the base **9**: mp 250°; λ_{max} (EtOH) 222 mμ (log ε 4.66), 252 (4.22), 278 (4.35), 306 (4.09), and 364 (3.86); λ_{max} ($EtOH_2^+$) 222 (4.66), 251 (4.44), 277 (4.46), 310 (4.09), and 364 (3.84); λ_{max} (EtOH–NaOH) 252 (4.28), 278 (4.18), 304 (4.06), and 364 (3.69); nmr δ 2.38 (s, 3, CH_3), 2.75 (m, 2, C-2 CH_2), 3.31 (s, broad, 2, C-1 CH_2), and 3.60 ppm (s, broad, 2, C-4 CH_2); mass spectrum *m/e* 261 (M^+), 260 (M − 1), and 218 (M − 43, CH_2=NCH_3).

Anal. Calcd for $C_{17}H_{15}N_3$: C, 78.13; H, 5.79; N, 16.08. Found: C, 78.10; H, 5.71; N, 15.92.

1-Cyano-3-(β-formylvinyl)carbazole (10a).—A solution of 600 mg of **2** in 250 ml of ethanol under nitrogen was irradiated by a high-pressure Hanau Q 81 lamp for 15 hr. The solution was concentrated under reduced pressure. Three repetitions of the operation gave 1.80 g of crude product. A solution of the product in a minimum amount of methanol was mixed with 12 g of Florisil (100–200 mesh), the solvent was eliminated, and the remaining powder was added to a chromatography column of 42 g of the same Florisil. The 9:1 benzene–chloroform eluates yielded 405 mg of pure product, while the 4:1 eluates led to 280 mg of somewhat impure material. Sublimation at 150° (0.01 mm) gave **10a**: mp >264°; ir (Nujol) 2230 (C≡N) and 1660 cm^{-1} (C=O); λ_{max} (EtOH) 213 mμ (log ε 4.61), 309 (4.59), and 346 (4.36); λ_{max} (EtOH–NaOH) 301 (4.54), 319 (4.56), 354 (shoulder, 4.44), and 438 (4.47); nmr δ 6.98 (q, 1, *J* = 16, 7.5 cps, vinyl β H), 7.85 (d, 1, *J* = 16 cps, vinyl α H), and 9.71 ppm (d, 1, *J* = 7.5 cps, aldehyde H); mass spectrum *m/e* 246 (M^+).

Anal. Calcd for $C_{16}H_{10}ON_2$: C, 78.03; H, 4.09; O, 6.50; N, 11.38. Found: C, 77.68; H, 4.03; O, 6.42; N, 11.12.

1-Cyano-3-formylcarbazole (11a).—Osmium tetroxide, 20 mg, was added with stirring to a mixture of 200 mg of aldehyde **10a** in 4 ml of water and 30 ml of dioxane at room temperature. After the dark brown mixture had been left standing for 150 min, 50 mg of sodium periodate was added over a 1-hr period and the mixture was kept at room temperature for 90 min, concentrated under reduced pressure, diluted with water, and extracted with chloroform. The extract was washed with water, filtered twice through 2 g of Florisil, and evaporated. Crystallization of the residue, 165 mg, from methanol yielded aldehyde **11a**: mp 206–208°; ir (Nujol) 2230 (C≡N) and 1680 cm^{-1} (C=O);

(6) The photoinduced hydration of pyridine has been reported: J. Joussot-Dubien and J. Houdard, *Tetrahedron Lett.*, 4389 (1967), and references cited therein.

(7) F. B. Mallory, C. S. Wood and J. T. Gordon, *J. Amer. Chem. Soc.*, **86**, 3094 (1964), and references cited therein.

λ_{max} (EtOH) 225 mμ log (ε 4.37), 291 (4.66), and 357 (3.89); λ_{max} (EtOH–NaOH) 312 (4.45) and 375 (4.00); nmr δ 8.36 (d, 1, J = 2 cps, H-4), 8.95 (d, 1, J = 2 cps, H-2), and 10.09 ppm (s, 1, aldehyde H); mass spectrum m/e 220 (M^+).

Anal. Calcd for $C_{14}H_8ON_2$: C, 76.36; H, 3.66; O, 7.27; N, 12.72. Found: C, 76.58; H, 3.81; O, 7.55; N, 12.16.

1-Cyano-3-hydroxymethylcarbazole (11b).—Reduction of aldehyde **11a** followed the procedure for the conversion of **10a** into **10b** (*vide infra*). Crystallization of the product from 1:1 chloroform–methanol gave **11b**: mp 150°; λ_{max} (EtOH) 222 mμ (log ε 4.59), 253 (4.31), 278 (4.33), and 366 (3.77); λ_{max} (EtOH–NaOH) 250 (4.38), 278 (4.36), 294 (shoulder, 4.22), 366 (3.54), and 417 (3.14); mass spectrum m/e 222 (M^+).

Anal. Calcd for $C_{14}H_{10}ON_2$: C, 75.65; H, 4.54. Found: C, 74.42; H, 4.90.

1-Cyano-3-(β-hydroxymethylvinyl)carbazole (10b).—Sodium borohydride, 50 mg, was added in small portions to a solution of 50 mg of aldehyde **10a** in 15 ml of methanol. After 2 hr the mixture was diluted with water and extracted with chloroform. Evaporation of the extract and crystallization of the residue, 50 mg, from methanol yielded alcohol **10b**, mp 204°, mass spectrum m/e 248 (M^+).

Anal. Calcd for $C_{16}H_{12}ON_2$: C, 77.40; H, 4.87; O, 6.44; N, 11.28. Found: C, 77.28; H, 4.82; O, 6.64; N, 11.39.

Alcohol **10b** was acylated by dissolution in a mixture of acetic anhydride and pyridine at room temperature. The usual work-up and crystallization of the crude product from 1:1 acetone–hexane gave acetate **10c**, mp 185°.

Anal. Calcd for $C_{18}H_{14}O_2N_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.26; H, 4.70; N, 9.56.

1-Cyano-3-(β-carbomethoxyvinyl)carbazole (10e).—A solution of 200 mg of aldehyde **11a**, 160 mg of malonic acid, and a few drops of piperidine in 8 ml of pyridine was kept at 80° for 1 hr and then at 100° for 2 hr, refluxed for 0.5 hr, and poured into a 10% hydrochloric acid solution. Crystallization of the resultant precipitate, 197 mg, from 3:2 methanol–acetone yielded acid **10d**, mp >260°, nmr δ 6.70 (d, 1, J = 16 cps, olefinic H) and 7.83 ppm (d, 1, J = 16 cps, olefinic H). A solution of 50 mg of the acid and 3 drops of concentrated sulfuric acid in 10 ml of methanol was refluxed for 18 hr and poured into saturated brine solution. Crystallization of the precipitate, 38 mg, from methanol yielded ester **10e**, mp 250°, mass spectrum m/e 276 (M^+).

Anal. Calcd for $C_{17}H_{12}O_2N_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.87; H, 4.20; N, 10.10.

A solution of 30 mg of acid **10d** and a few drops of oxalyl chloride in 10 ml of tetrahydrofuran was stirred at room temperature for 90 min. The solvent and excess reagent were evaporated under reduced pressure. The residue was redissolved in 10 ml of anhydrous tetrahydrofuran and mixed with a solution of 20 mg of lithium tri-*t*-butoxyaluminum hydride in 10 ml of tetrahydrofuran. The mixture was stirred at room temperature for 1 hr, diluted with saturated brine solution, and extracted with chloroform. Evaporation of the extract and crystallization of the residue from methanol yielded a crystalline alcohol, identical in all respects with **10b** (*vide supra*). Its treatment with acetic anhydride yielded an acetate, identical in all respects with **10c** (*vide supra*).

Registry No.—**2**, 22433-55-2; **7**, 22433-56-3; **8**, 22433-57-4; **8** methiodide, 22433-61-0; **9**, 17517-71-4; **10a**, 22487-48-5; **10b**, 22430-80-4; **10c**, 22430-81-5; **10d**, 22430-82-6; **10e**, 22430-83-7; **11a**, 22433-59-6; **11b**, 22433-60-9.

Aziridines. XXII. The Reactions of Some 1-Substituted Aziridines with Carbethoxymethylenetriphenylphosphorane and Carbethoxyethylidinetriphenylphosphorane

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Received December 23, 1968

1-Aroylaziridines and related systems have been shown to react with carbethoxymethylenetriphenylphosphorane and carbethoxyethylidinetriphenylphosphorane. The products of reaction arise from intermediates formed by the carbanionic center of the ylide attacking the aziridinyl carbon.

Reactions of nucleophiles or reagents possessing nucleophilic sites with either 1-aroylaziridines or aziridines bearing other unsaturated 1 substituents have been well studied in recent years.[1-7] The products resulting from these reactions may be rationalized, usually, as arising from intermediates formed by an attack of the nucleophile at the 2 position of the aziridine ring. A new and potentially useful reaction that follows this general pattern, namely, the reaction of 1-aroylaziridines and related systems with carbethoxymethylenetriphenylphosphorane (**1**) and carbethoxyethylidinetriphenylphosphorane (**8**), has now been observed.

Results

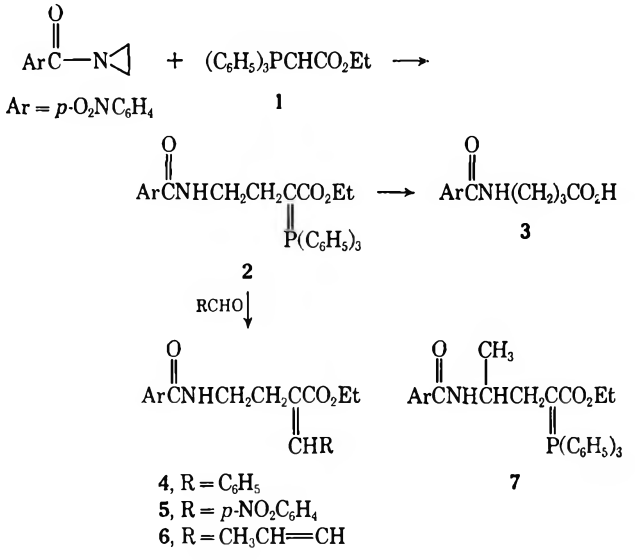
Carbethoxymethylenetriphenylphosphorane (**1**) and 1-*p*-nitrobenzoylaziridine in refluxing toluene formed the new and isolable ylide **2** (Scheme I). The structure of **2** was demonstrated by spectral data and conversion into 4-(*p*-nitrobenzamido)butanoic acid (**3**). The ir spectrum of **2** showed NH absorption and no carbonyl absorption below 6.15 μ, evidence that the ester carbonyl group was participating in charge delocalization. Heating of **2** with benzaldehyde and *p*-nitrobenzaldehyde gave the corresponding ethyl 2-benzylidine-4-(*p*-nitrobenzamido)butanoates **4** and **5**, respectively, and similar heating of **2** with 2-butenal gave compound **6**.

Compound **1** also reacts with 1-*p*-nitrobenzoyl-2-methylaziridine to produce ethyl 4-(*p*-nitrobenzamido)-2-triphenylphosphoranylpentanoate (**7**). Compound **7** was hydrolyzed to 4-(*p*-nitrobenzamido)pentanoic acid. The structure of this acid was authenticated by an alternate preparation involving the reaction of 4-aminopentanoic acid with *p*-nitrobenzoyl chloride and by mass spectroscopy.

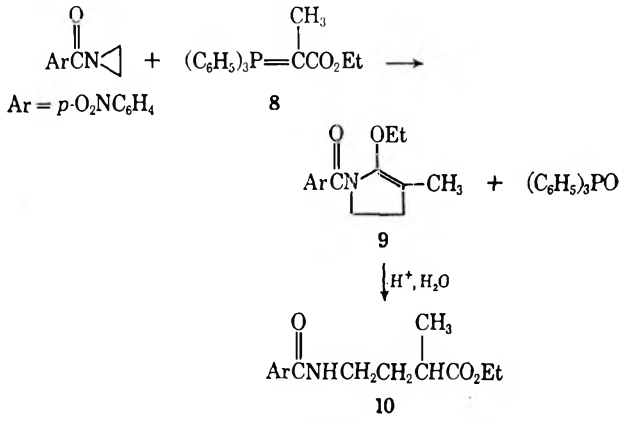
Reaction of carbethoxyethylidinetriphenylphosphorane (**8**) in refluxing toluene formed triphenylphosphine oxide and 1-(*p*-nitrobenzoyl)-2-ethoxy-3- methyl- 2-pyrroline (**9**) (Scheme II) as well as a small quantity (8%) of 2-*p*-nitrophenyl-2-oxazoline. The structure of

(1) H. W. Heine, *Angew. Chem. Intern. Ed. Engl.*, **1**, 528 (1962).
(2) J. E. Dolfini and J. D. Simpson, *J. Amer. Chem. Soc.*, **87**, 4381 (1965).
(3) P. Thyrum and A. R. Day, *J. Med. Chem.*, **8**, 107 (1965).
(4) G. E. Ham, U. S. Patent 3,247,220; *Chem. Abstr.*, **64**, 19622*h* (1966).
(5) H. W. Heine and T. Newton, *Tetrahedron Lett.*, 1859 (1967).
(6) H. W. Heine and M. S. Kaplan, *J. Org. Chem.*, **32**, 3069 (1967).
(7) S. Fujita, T. Hiyama, and H. Nozaki, *Tetrahedron Lett.*, 1677 (1969).

SCHEME I



SCHEME II

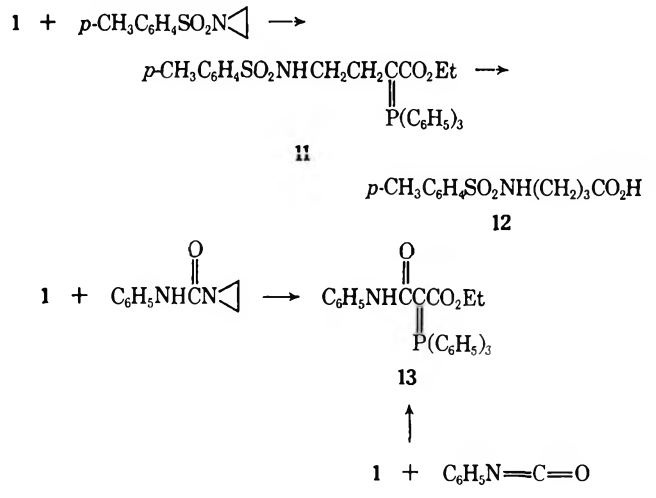


the novel enamide **9** was deduced from elemental analyses, nmr spectroscopy, and the mild acid hydrolysis of **9** at room temperature to ethyl 2-methyl 4-(*p*-nitrobenzamidobutanoate (**10**), the structure of which was verified by nmr and mass spectroscopy. The nmr spectrum of **9** taken in deuteriochloroform shows (a) the four hydrogens of the *p*-nitrophenyl group as two doublets at *ca.* 8.24 and 7.61 ppm, (b) the characteristic splitting pattern of the ethyl group with the methylene and methyl moieties absorbing at 3.40 and 0.68 ppm, respectively; (c) the 3-methyl group as a singlet at 1.68 ppm; and (d) the protons at C-4 and C-5 of the ring as triplets centered at *ca.* 2.42 (2 H) and 4.00 ppm (2 H).

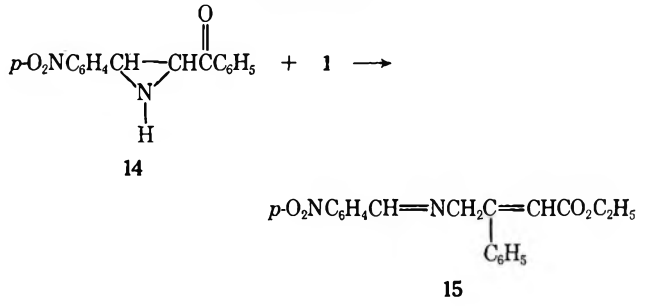
Reaction of 1-*p*-tolylsulfonylaziridine with **1** formed the ylide **11** (Scheme III). The structure of **11** was confirmed by elemental analyses and conversion into the known 4-(*p*-tolylsulfonamido)butanoic acid (**12**). As with compound **2**, the ester carbonyl absorption of **11** was at *ca.* 6.15 μ. Compound **1** with 1-aziridinecarboxanilide in refluxing toluene did not open the aziridine ring but instead displaced it to form the ethyl ester of 2-(triphenylphosphoranylidene)malonanilic acid (**13**), a known compound[8] prepared by reaction of **1** with phenyl isocyanate (Scheme III).

Carbethoxymethylenetriphenylphosphorane (**1**) and *trans*-2-*p*-nitrophenyl-3-benzoylaziridine (**14**) in refluxing chloroform formed the Schiff base **15** (Scheme IV). The structure of **15** was deduced by elemental analyses, nmr spectroscopy, and the formation of the *p*-nitrobenzaldehyde 2,4-dinitrophenylhydrazone when **15** was treated with 2,4-dinitrophenylhydrazine. The nmr spectrum of **15** in $CDCl_3$ with TMS as an internal standard showed the methylene group as a sharp singlet at 4.13 ppm and the ethyl group with its characteristic splitting pattern as a quartet centered at about 4.08 ppm and a triplet centered at 1.18 ppm. The two vinylic hydrogens absorbed in the same region as the two aromatic moieties (6.8–7.9 ppm). A control run of **14** in refluxing chloroform resulted in the recovery of the starting reagent.

SCHEME III



SCHEME IV



Discussion

It seems that, in the reactions of 1-*p*-nitrobenzoylaziridine and 1-*p*-tolysulfonylaziridine with **1**, the carbanionic center of the ylide attacks the aziridinyl carbon and opens the ring to form **2** and **11**, respectively. Compound **1** reacts in a similar fashion at the methylene carbon rather than the methine carbon of 1-*p*-nitrobenzoyl-2-methylaziridine to produce ethyl 4-(*p*-nitrobenzamido)- 2- triphenylphosphoranylpentanoate (**7**). This result is akin to the selective isomerizations by iodide ion of 1-*p*-nitrobenzoyl-2-methylaziridine to 2-*p*-nitrophenyl-4-methyl-2-oxazoline[9] and 1-*p*-nitrophenylazo-2-methylaziridine (**16**) to 1-*p*-nitrophenylazo-4-methyl-Δ^2-1,2,3-triazoline (**17**).[10,11]

(8) S. Tripett and D. M. Walker, *J. Chem. Soc.*, 3874 (1959).

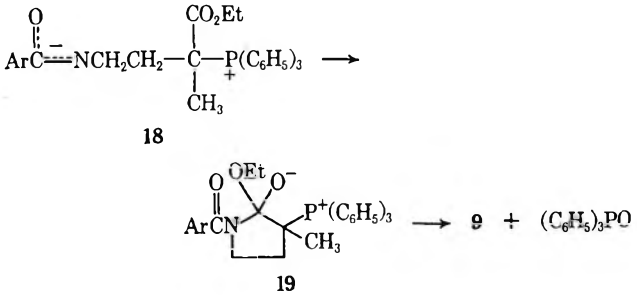
(9) H. W. Heine, W. G. Kenyon, and E. M. Johnson, *J. Amer. Chem. Soc.*, **83**, 2570 (1961).

(10) H. W. Heine and D. A. Tomalia, *ibid.*, **84**, 993 (1962).

(11) R. Huisgen and G. Szeimies, personal communication. These investigators proved unequivocally that the product of isomerization of **16** was **17** by oxidation of **17** to the corresponding triazole, which was synthesized by an alternate route.

The reaction of **8** with 1-*p*-nitrobenzoylaziridine probably proceeds *via* a ring opening of the aziridine by the ylide to give **18**. Intermediate **18** could undergo an internal nucleophilic addition by the benzamido nitrogen to the ester group to yield a typical Wittig intermediate **19**, which could form triphenylphosphine oxide and **9** (Scheme V). The small quantity of 2-*p*-nitrophenyl-2-oxazoline (8%) formed in this reaction may arise by the well known pyrolysis of 1-acylaziridines to 2-oxazolines.

SCHEME V



18

19

All of the above reactions of aziridines with ylides involve nucleophilic displacement at the aziridinyl carbon. In contrast, it appears that the carbonyl carbon of 1-aziridinecarboxanilide is the site of attack by **1**. Reactions taking place at the carbonyl group of 1-acylaziridines are not unknown. Examples are the easy methanolysis of 1-*p*-nitrobenzoylaziridine catalyzed by iodide ion[12] and the reaction of 1-acylaziridines with lithium aluminum hydride to yield aldehydes.[13]

It is also conceivable that the ylide **1** reacts with 1-aziridinecarboxanilide to give phenyl isocyanate, which, as previously shown by Tripett,[8] could react with the ylide to form **13**.

The formation of **15** from **1** and **14** involves cleavage of the carbon–carbon bond of the aziridine ring and a Wittig reaction with the carbonyl group of the aziridine. Isomerizations of 2,3-disubstituted aziridines into Schiff bases have been reported. Thus at 225° 2,3-diphenylaziridine isomerizes into benzalbenzylamine,[14] and at 205° 2,2-diphenyl-3-methylaziridine is converted into ethyliminobenzophenone.[15] *trans*-2-phenyl-3-benzoylaziridine and **14** have been shown to add to dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate, respectively, by carbon–carbon scission of the aziridine ring.[16,17] Our experimental results indicate that **1** plays a role in the isomerization, but do not permit a conclusion as to whether the Wittig reaction precedes or follows the isomerization.

Experimental Section

Ethyl 4-(*p*-Nitrobenzamido)-2-triphenylphosphoranylbutanoate (2).—A mixture of 348 mg of carbethoxymethylenetriphenylphosphorane and 192 mg of 1-*p*-nitrobenzoylaziridine[12] in 25 ml of dry toluene was refluxed for 2 hr. The solvent was evaporated and the 529 mg of crude **2** that remained was recrystallized three times from equal portions of benzene and petroleum ether (bp 90–115°) to give crystals, mp 191–192°.

Anal. Calcd for $C_{31}H_{29}N_2O_5P$: C, 68.88; H, 5.41; N, 5.18. Found: C, 68.92; H, 5.26; N, 5.04.

4-(*p*-nitrobenzamido)butanoic Acid (3) was obtained by dissolving 540 mg of **2** in 25 ml of hot 10% aqueous methanol. A solution containing 56 mg of KOH in 25 ml of aqueous methanol (1:1) was added and the entire mixture was refluxed for 1 hr. The reaction mixture was cooled and then poured into 500 ml of water. The solvent was evaporated to 50 ml and the precipitated triphenylphosphine oxide was filtered. The filtrate was adjusted to a pH of 1–3 with 10% H_2SO_4. Evaporation of the filtrate gave 201 mg of **3**. Recrystallization from acetone–CCl_4 and then 95% ethanol formed **3**, mp 165–167°. Compound **3** was also prepared by the reaction of 4-aminobutanoic acid with *p*-nitrobenzoyl chloride.

Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.55; H, 5.03; N, 11.01.

Ethyl 4-*p*-nitrobenzamido-2-benzylidenebutanoate (4) was prepared by refluxing a mixture of 540 mg of **2** and 15 ml of benzaldehyde for 24 hr. Evaporation of the excess benzaldehyde and dissolution of the residual oil in 15 ml of C_6H_6 followed by the addition of 20 ml of petroleum ether gave 211 mg of **4**. Four recrystallizations from 95% ethanol gave **4**, mp 137–138°.

Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.17; H, 5.64; N, 7.46.

Ethyl 4-(*p*-Nitrobenzamido)-2-(*p*-nitrobenzylidene)butanoate (5).—A mixture of 540 mg of **5**, 151 mg of *p*-nitrobenzaldehyde, and 25 ml of $CHCl_3$ was refluxed for 2 hr. The solvent was evaporated and the residual oil was dissolved in 15 ml of C_6H_6. The addition of 15 ml of petroleum ether precipitated 342 mg of **5**. Three recrystallizations from $CHCl_3$ gave **5**, mp 175–177°.

Anal. Calcd for $C_{20}H_{19}N_3O_7$: C, 58.11; H, 4.63; N, 10.16. Found: C, 58.43; H, 4.87; N, 10.35.

Ethyl 4-(*p*-Nitrobenzamido)-2-(2-butenylidene)butanoate (6).—A mixture of 540 mg of **2** and 20 ml of crotonaldehyde was refluxed for 12 hr. The excess aldehyde was evaporated, the residual oil was dissolved in 15 ml of C_6H_6, and 156 mg of crude **6** was precipitated by the addition of 20 ml of petroleum ether. Five recrystallizations from 95% ethanol gave **6**, mp 145–147°.

Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.36; H, 5.99; N, 8.25.

Ethyl 4-(*p*-Nitrobenzamido)-2-triphenylphosphoranylpentanoate (7) was prepared by refluxing in 30 ml of toluene for 5 hr a mixture of 348 mg of **1** and 206 mg of 1-*p*-nitrobenzoyl-2-methylaziridine.[9] The solvent was evaporated and the residual oil was dissolved in 50 ml of ethyl ether. Slow evaporation gave 381 mg of crude **7**, which was recrystallized four times from ethyl ether to give **7**, mp 183–184°.

Anal. Calcd for $C_{32}H_{31}N_2O_5P$: C, 69.31; H, 5.63; N, 5.05. Found: C, 69.16; H, 5.65; N, 4.98.

1-(*p*-Nitrobenzoyl)-2-ethoxy-3-methyl-2-pyrroline (9).—A mixture of 1.45 g of **8** and 0.768 g of 1-*p*-nitrobenzoylaziridine in 70 ml of dry toluene was refluxed for 6 hr. The solvent was evaporated and 3–4 ml of dry Et_2O was added to the residual oil. The $(C_6H_5)_3PO$ that precipitated was filtered and the solvent was evaporated. The residue was dissolved in a minimum amount of dry C_6H_6 and the solution was chromatographed on a column of neutral alumina with C_6H_6. The first 50-ml fraction was evaporated to give 70 mg of crude 2-*p*-nitrophenyl-2-oxazoline. The next fraction of 150–200 ml eluent, when evaporated, gave 360 mg of **9**. Compound **9** was then dissolved in a minimum of DMF, and water was added until **9** precipitated; the compound was redissolved in DMF and precipitated again with H_2O. Pure **9** melted at 142.5–145.5°.

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.85; H, 5.85; N, 10.14. Found: C, 61.04; H, 5.91; N, 10.16.

Ethyl 2-Methyl-4-(*p*-nitrobenzamido)butanoate (10).—To 1 ml of acetone was added 39 mg of **9**, 0.4 ml of glacial acetic acid, and 0.4 ml of H_2O. In 10 min the initially bright yellow solution turned colorless. At this point 3.6 ml of H_2O was added and the solution was allowed to stand for 1–3 days. Crystals of **10** gradually appeared and were filtered. The yield of crude **10** was 30 mg. Four recrystallizations from petroleum ether (bp 100–115°) gave **10**: mp 65.5–66.5°; nmr ($CDCl_3$) δ 1.26 (t, 3, J = 6 Hz, CH_2CH_3), 1.22 (d, 2, J = 7 Hz, $CHCH_3$), 1.91 (m, 1, $CHCH_3$), 2.55 (quintet, 2, J = 7 Hz, CH_2CH), 3.52 (q, 2, J = 6 Hz, NCH_2), 4.23 (q, 2, J = 7 Hz, OCH_2), 7.05 (m, 1, NH), and

(12) H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Amer. Chem. Soc.*, **81**, 2202 (1959).

(13) H. C. Brown and A. Tsukamoto, *ibid.*, **83**, 2016, 4549 (1961).

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(15) B. K. Campbell and K. N. Campbell, *J. Org. Chem.*, **9**, 178 (1944).

(16) (a) A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965); (b) A. Padwa and L. Hamilton, *J. Heterocycl. Chem.*, **4**, 118 (1968).

(17) H. W. Heine, A. B. Smith, III, and J. D. Bower, *J. Org. Chem.*, **33**, 1097 (1968).

7.88–8.35 (m, 4, aromatic); mass spectrum *m/e* 294 (molecular ion), 248, 193, 179, 150, and 102.

Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.11; H, 6.16; N, 9.52. Found: C, 57.44; H, 6.02; N, 9.80.

Ethyl 4-(*p*-Tolylsulfonyl)-3-triphenylphosphoranylbutanoate (11).—A mixture of 197 mg of *p*-tolylsulfonylaziridine,[9] 348 mg of **1**, and 25 ml of dry toluene was refluxed for 15 min. On cooling, a white solid, mp 240–260°, precipitated and was filtered. Evaporation of the filtrate gave 166 mg of crude **11**. Four recrystallizations from 95% ethanol gave **11**, mp 184–186°.

Anal. Calcd for $C_{31}H_{32}NO_4PS$: C, 68.23; H, 5.91; N, 2.56. Found: C, 68.27; H, 6.21; N, 2.61.

Conversion of 11 into 12.—To 272 mg of **11** in 20 ml of 10% aqueous methanol was added a solution of 28 mg of KOH in 15 ml of 50% aqueous methanol. The mixture was refluxed for 1 hr, cooled, and added to 175 ml of H_2O. The volume of solvent was reduced to 25 ml by evaporation and the triphenylphosphine oxide that had precipitated was filtered. The pH of the filtrate was adjusted to *ca.* 2 by 10% H_2SO_4 and then the filtrate was evaporated to give 115 mg of **12**. Recrystallization three times from aqueous ethanol gave **12**, mp 132–134°. An authentic sample of **12** prepared according to a published method[18] melted at 133–134°; the ir spectra of the two samples were identical.

Compound 11 was prepared by refluxing a mixture of 348 mg of **3**, 192 mg of 1-aziridinecarboxanilide,[19] and 25 ml of dry toluene for 4 hr. The solvent was evaporated and 306 mg of crude **11** was obtained and recrystallized from CCl_4–hexane, mp 182–184°. An authentic sample was prepared by a published method.[5] This sample of **11** melted at 188–189° and had an ir spectrum identical with that of **11** prepared from the 1-aziridinecarboxanilide.

Ethyl 3-Phenyl-4-(N-*p*-nitrobenzylidene)amino-2-butenoate (15).—A mixture of 268 mg of 2-*p*-nitrophenyl-3-benzoylaziridine, 351 mg of **1**, and 30 ml of $CHCl_3$ was refluxed for 24 hr. The solvent was evaporated and the glassy residue was slurried with a small amount of 95% ethanol. The yellow crystals of **15** were filtered and recrystallized from 95% ethanol to give 150 mg of **15**, mp 113–115°.

Anal. Calcd for $C_{19}H_{18}N_2O_4$: C, 67.43; H, 5.36; N, 8.28. Found: C, 67.14; H, 5.46; N, 8.20.

Hydrolysis of 7 to 4-(*p*-nitrobenzamido)pentanoic acid was effected by adding 227 mg of **7** to 20 ml of CH_3OH–H_2O (1:1) and heating until **7** dissolved. A solution containing 28 mg of KOH in 20 ml of CH_3OH–H_2O (1:1) was added and the mixture was refluxed for 2 hr. Evaporation of the CH_3OH caused precipitation of Ph_3PO, which was filtered. The filtrate was acidified to pH 1–3 with 10% H_2SO_4. Evaporation of the filtrate gave 75 mg of 4-(*p*-nitrobenzamido)pentanoic acid. Recrystallization from aqueous ethanol gave material melting at 145–146°. Reaction of 4-aminopentanoic acid[20] with *p*-nitrobenzoyl chloride also formed 4-(*p*-nitrobenzamido)pentanoic acid in poor yield. The two samples gave identical ir spectra; mass spectrum molecular ion *m/e* 266, fragments *m/e* 249, 220, 193 [*p*-$O_2NC_6H_4CONHCHCH_3]^+$, 150, and 120.

Registry No.—**1**, 1099-45-2; **2**, 22487-52-1; **3**, 22433-20-1; **4**, 22433-21-2; **5**, 22433-22-3; **6**, 22433-23-4; **7**, 22433-24-5; **8**, 5717-37-3; **9**, 22433-26-7; **10**, 22433-27-8; **11**, 22433-28-9; **12**, 1213-42-9; **15**, 22487-54-3.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work and Mr. Richard Adams for the experiments dealing with *trans*-2-*p*-nitrophenyl-3-benzoylaziridine. The authors are also indebted to Professor Charles Sweeley for the mass spectrum of compound **10**.

(18) D. Todd and S. Teich, *J. Amer. Chem. Soc.*, **75**, 1895 (1953).
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Cyclization Reactions of Ninhydrin with Aromatic Amines and Ureas[1]

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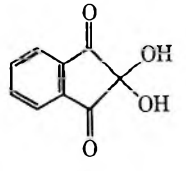
Received March 25, 1969

Ninhydrin (1,2,3-indantrione monohydrate, **1**) condenses with aromatic amines that contain an additional activating group in the *meta* position. The reaction proceeds with cyclization to give structures of type **5** (X = OH, OCH_3, or NH_2; R = H). These products are stable, show the appropriate number of aromatic protons in their nmr spectra, give strong parent peaks in their mass spectra, and yield well-characterized acetyl derivatives. These properties distinguish them from the products formed from **1** and less activated aromatic amines, in which reaction takes place only at the central carbonyl group of **1**. The reaction of **1** with urea and 1,3-dimethylurea also proceeds with cyclization, to give structures of type **6** (R = H or CH_3; R′ = H). 1,1-Dimethylurea does not react with ninhydrin.

In recent studies in this laboratory,[2,3] it was reported that ninhydrin reacted with the amino heterocycles guanine and cytosine to afford products which contained an additional heterocyclic ring. These results stood in contrast to earlier reports in the literature about the reactions of ninhydrin with simpler aromatic amines and ureas. Thus the reaction products of **1** with aniline,[4] *p*-chloroaniline,[4] *o*- and *m*-hydroxyaniline,[4] *p*-aminobenzoic acid,[5] 2-aminopyridine,[4] urea,[6,7] 1,1-dimethylurea,[6] and guanidine[7,8] were assigned structures of type **2**, while the corresponding dehydrated products (**3**) were obtained from *p*-hydroxyaniline and



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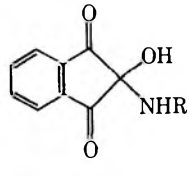
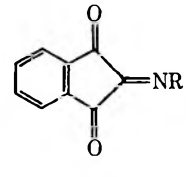


2a, R = C_6H_5
b, R = *p*-ClC_6H_4
c, R = *m*-HOC_6H_4
d, R = $CONH_2$



3

p-phenylenediamine.[5] Only in the reaction of *o*-phenylenediamine with ninhydrin was a cyclized structure (**4**) ascribed to the product.[9]

(1) This investigation was supported by a grant (GM-11437) from the U. S. Public Health Service.
(2) R. Shapiro and J. Hachmann, *Biochemistry*, **5**, 2799 (1966).
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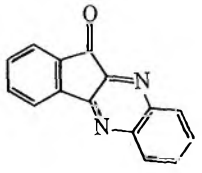
(9) S. Ruhemann, *ibid.*, **97**, 1438 (1910).

We have now reinvestigated these reactions and wish to report that aromatic amines with an electron-releasing group (hydroxy, methoxy, or amino) in the *meta* position react with ninhydrin to give the corresponding indeno[2,1-*b*]indole derivative (**5**). If the



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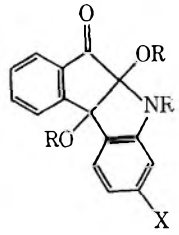
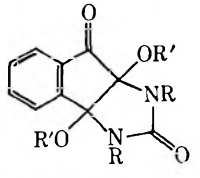


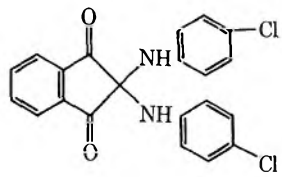
5a, X = OH; R = H
b, X = O_2CCH_3; R = $OCCH_3$
c, X = OCH_3; R = H
d, X = OCH_3; R = $OCCH_3$

activating group is not present, then cyclization does not occur, but rather simple addition to the central carbonyl group of ninhydrin takes place. Urea and 1,3-dimethylurea react with **1** to give cyclized products of structure **6**. No reaction occurs with 1,1-dimethylurea and ninhydrin.

The products of reaction of ninhydrin and aniline and *p*-chloroaniline were unstable. Unlike the cyclized products discussed below, they reverted to their components upon thin layer chromatography, gave acetanilide and *p*-chloroacetanilide upon attempted acetylation, and exhibited no molecular ion in the mass spectrum. Our analysis of the ninhydrin–aniline product agreed with that of Friedman,[4] and we agree with assignment of structure **2a** to this compound. The analysis and nmr spectrum of the product of reaction of ninhydrin and *p*-chloroaniline indicated that it contained one indandione residue and two amine molecules. Upon recrystallization of this from chloroform–hexane, a 1:1 adduct analogous to that of Friedman[4] was obtained. Inspection of the nmr spectrum of the 1:2 adduct in $(CD_3)_2SO$ revealed that it had decomposed, in that solvent, to an equal mixture of 1:1 adduct and *p*-chloroaniline. Similarly, the 1:1 adduct partially decomposed in $(CD_3)_2SO$ to ninhydrin and *p*-chloroaniline. In CH_3OD, both compounds decomposed completely to ninhydrin and *p*-chloroaniline. The infrared spectrum (KBr) of the 1:2 adduct was well defined and distinguishable from those of *p*-chloroaniline and the 1:1 adduct. On this basis, we believe it to represent a distinct compound as a solid (if not in solution) and have assigned structure **7** to it.



6a, R = R′ = H
b, R = R′ = $COCH_3$
c, R = CH_3; R′ = H
d, R = CH_3; R′ = $COCH_3$



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The product obtained from *m*-hydroxyaniline and ninhydrin has quite different properties from those of **2a** and **7**. It recrystallized well, gave a well-defined spot upon thin layer chromatography, and showed an intense molecular-ion peak in its mass spectrum. Its nmr spectrum in $(CD_3)_2SO$ revealed the presence of four indanone protons, three benzenoid protons (with the proton *meta* to nitrogen split by a single adjacent proton), and four exchangeable protons. Friedman[4] has assigned structure **2c** to the reaction product of *m*-hydroxyaniline and ninhydrin. This assignment was apparently made by analogy to the aniline reaction, as it was stated that the nmr spectra of the product in dimethyl sulfoxide-d_6 and CF_3CO_2H were too complex for unequivocal analysis. However, we feel that the properties of this compound are quite readily interpretable in term of structure **5a**. Further confirmation of this structure was provided by the conversion of **5a** into a stable tetracetyl derivative, **5b**. This product exhibited absorptions for four different CH_3CO groups in the nmr, as expected.

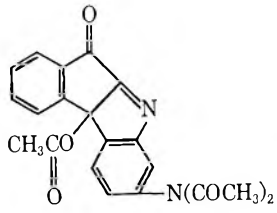
m-Anisidine gave with ninhydrin a product similar in its properties to **5a**. Its nmr spectrum was consistent with that expected from a cyclized product of structure **5c**. Acetylation of this substance afforded a triacetyl derivative, **5d**. An adduct prepared from *m*-phenylenediamine and ninhydrin crystallized well only from an acetone–water mixture. It crystallized with a molecule of acetone, but its properties and nmr spectrum were otherwise analogous to those of **5a** and **5c**. Structure **5e** was assigned to this adduct. Upon acetylation, it yielded a dehydrated, triacetyl derivative to which structure **8** has been assigned.

The ready formation of an adduct of urea and ninhydrin has been reported by several groups of workers.[6,7,10] Structure **2d** (or a tautomer involving the enol from of the urea moiety) was assigned to it.[6,7] This was supported largely by the observation that 1,1-dimethylurea gave an analogous adduct with **1**, but that 1,3-dimethylurea did not. In reexamining these results, however, we obtained the exact opposite result. Urea and 1,3-dimethylurea readily gave adducts with ninhydrin. No new product could be isolated when 1,1-dimethylurea and ninhydrin were brought together under a variety of conditions. Only unchanged ninhydrin was observed by tlc, and unchanged 1,1-dimethylurea was recovered from the reaction mixture. The urea–ninhydrin product ran as a well-defined spot on tlc, exhibited a peak for the molecular ion in the mass spectrum, and had absorptions for four different NH and OH protons in its nmr spectrum. It formed a well-characterized tetracetyl derivative, whose nmr spectrum confirmed the presence of four nonequivalent acetyl groups. On this basis, structures **6a** and **6b** were assigned to the urea–ninhydrin product and its tetraacetyl derivative, respectively. The properties of the product of 1,3-dimethylurea and ninhydrin were fully analogous, and in accord with the structure **6c**. A diacetyl derivative, **6d**, was prepared from this compound.

A reaction product of guanidine and ninhydrin was also reported by earlier workers.[7,8] We found this compound to be insoluble in most neutral solvents and to streak badly on tlc. Its nmr spectrum (CF_3CO_2H) showed one NH absorption which integrated as two protons, and another NH (one proton) absorption over-

(10) D. D. Van Slyke and P. B. Hamilton, *J. Biol. Chem.*, **150**, 471 (1943).

lapping the aromatic hydrogen peak. These results suggested structure **9**, or a tautomer, for this compound.



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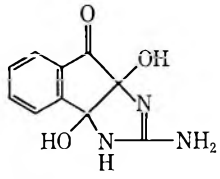

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However, the mass spectrum showed a number of peaks of *m/e* values higher than the expected molecular ion, and it seems likely that the substance is dimeric or polymeric. Only intractable mixtures were formed upon attempted acetylation.

Experimental Section

The general procedures used were similar to those already described,[3] with the following exceptions. Mass spectra were determined with a Varian M-66 mass spectrometer at 70 eV. Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., or on an automatic CHN analyzer (F & M Scientific Corp., Model 185). Thin layer chromatography was performed on plates prepared with Merck silica gel, except where otherwise noted.

2-Hydroxy-2-*N*-phenylamino-1,3-indandione (2a).—The procedure of Friedman was followed, using 1.85 g (10.4 mmol) of ninhydrin and 0.97 g (10.4 mmol) of aniline. A yield of 1.20 g (45%) of **2a** was obtained, as a yellow powder: mp 106–108° dec; the ir and uv were similar to those reported;[4] nmr (CD_3SOCD_3), τ 1.95 (s, 4, indandione H) and 2.80–3.65 (m, 7, aniline H, NH, and OH); after addition of D_2O, the peak at 2.80–3.65 integrated as five protons.

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.18; H, 4.05; N, 5.11.

2,2-Di-(*p*-chlorophenylamino)-1,3-indandione (7).—To a solution of 1.27 g (10 mmol) of *p*-chloroaniline in 200 ml of H_2O at 45° was added 0.89 g (5 mmol) of ninhydrin in 100 ml of H_2O. The reaction mixture was stirred for 1 hr at 25° and allowed to stand for 16 hr at 5°. The resulting yellow, crystalline precipitate was filtered and dried under vacuum for 2 days to yield 1.55 g (79%) of **7**. An analytical sample was prepared by recrystallization from ethanol–water: mp 119–121° dec; ir (KBr) 2.95, 5.71, 6.22 (shoulder), 6.28, and 6.70 μ; nmr (CD_3SOCD_3) τ 2.00 (s, 4, indandione H), 2.86 (s, 5, *p*-ClC_6H_4NH of **2b** and NH or OH of **2b**), 2.90, 3.04, 3.36, and 3.52 (q, 4, *p*-$ClC_6H_4NH_2$), 3.21 (s, 1, NH or OH of **2b**), and 4.83 (s, broad, 2, *p*-$ClC_6H_4NH_2$); nmr (CH_3OD) τ 2.00 (s, 4, ninhydrin aromatic H) and 2.86, 3.00, 3.25, and 3.40 (q, 4, *p*-$ClC_6H_4NH_2$).

Anal. Calcd for $C_{21}H_{14}N_2O_2 \cdot H_2O$: C, 60.74; H, 3.89; N, 6.75; Cl, 17.09. Found: C, 61.11; H, 3.96; N, 6.81; Cl, 17.48.

Attempts to remove the water of hydration resulted in decomposition of the compound.

Reaction of Ninhydrin with *m*-Hydroxyaniline. Formation of 5a.—A solution of 3.27 g (30 mmol) of *m*-hydroxyaniline and 5.34 g (30 mmol) of ninhydrin 300 ml of water was stirred for 30 min at 25°. The fluffy, yellow precipitate that formed was collected and dried under vacuum to yield 7.50 g (93%) of **5a**. An analytical sample, which did not melt below 340°, was prepared by recrystallization from ethanol: the ir and uv spectra were similar to those reported;[4] nmr (CD_3SOCD_3) τ 1.07 (s, 1, phenolic OH), 1.90–2.35 (m, 4, indanone H), 2.90 (d, 1, J = 8 Hz, H *meta* to NH), 3.37 (s, 1, NH), 3.65–4.08 (m, 2, H *ortho* and *para* to NH), and 4.70 (broad, 2, OH); the NH and OH protons disappeared upon addition of D_2O; nmr (CF_3CO_2H) τ 1.93–2.75 (m, 5, indanone H and H *meta* to NH) and 2.92–3.27 (m, 2, H *ortho* and *para* to NH); at 15° a broad peak at τ 1.16 appeared (NH or OH); tlc R_f 0.80 [1-butanol–water (86:14) on Avicel microcrystalline cellulose].

Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.12; N, 5.20; mol wt, 269. Found: C, 67.18; H, 3.95; N, 4.84; mol wt, 269 (mass spectrum).

Acetylation of 5a.—A mixture of 2.0 g (7.5 mmol) of **5a**, 100 ml of acetic anhydride, and 2 ml of pyridine was heated at reflux, with stirring, for 5 days. The solvents were removed under vacuum and the red-brown residue was treated with methanol and filtered. The filtrate was decolorized with charcoal and evaporated. The residue was washed with water and then recrystallized from methanol–water to afford 1.10 g (34%) of crude acetylated product **5b**. An analytical sample, mp 194–196°, was prepared by multiple recrystallizations from methanol: ir (KBr) 5.68 (shoulder), 5.75 (shoulder), 5.81, 5.88 (shoulder), 6.25, and 6.67 μ; uv max (MeOH) 244 mμ (ϵ 20,000), 294 (6490); nmr (CD_3SOCD_3) τ 2.02 (s, 4, indanone H), 2.23 (d, 1, J = 9 Hz, H *meta* to $NCOCH_3$), 2.72–2.96 (m, 2, H *ortho* and *para* to $NCOCH_3$), 7.90 (s, 3, CH_3CO), 7.99 (s, 6, CH_3CO), and 8.25 (s, 3, CH_3CO); tlc R_f 0.62 (ethyl acetate).

Anal. Calcd for $C_{23}H_{19}NO_8$: C, 63.16; H, 4.39; N, 3.20; mol wt, 437. Found: C, 63.22; H, 4.25; N, 3.21; mol wt, 437 (mass spectrum).

Reaction of Ninhydrin with *m*-Anisidine. Formation of 5c.—The preparation was analogous with that conducted with *m*-hydroxyaniline. A crude yield of 92% was obtained. An analytical sample, mp 212–214° dec, was prepared by several recrystallizations from ethanol: ir (KBr) 2.92, 2.99, 3.14, 5.71, 5.84, 6.20, 6.28, 6.66, and 6.84 μ; uv max (MeOH) 224 mμ (ϵ 50,000), 244 (24,100), and 288 (4080); nmr (CD_3SOCD_3) τ 2.00 (s, 4, indanone H), 2.65 (d, 1, J = 8 Hz, H *meta* to NH), 3.23 (s, 1, NH), 3.60–3.95 (m, 2, H *ortho* and *para* to NH), 4.85 (broad, 2, OH), and 6.85 (s, 3, OCH_3); tlc R_f 0.68 [benzene–methanol (80:20)].

Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94; mol wt, 283. Found: C, 68.26; H, 4.71; N, 4.92; mol wt, 283 (mass spectrum).

Acetylation of 5c.—A mixture of 2.0 g (7.1 mmol) of **5c** and 65 ml of acetic anhydride were heated with stirring at 95° for 139 hr. The solvent was removed under vacuum and the residue was recrystallized from methanol to yield 0.80 g (28%) of crude **5d**. An analytical sample, mp 179–180°, was prepared by several recrystallizations from methanol: ir (KBr) 5.72, 5.80, 5.91, 6.23, 6.30 (shoulder), 6.67, and 6.83 μ; uv max (MeOH) 227 mμ (ϵ 46,200), 252 (27,500), and 290 (6720); nmr (CD_3SOCD_3) τ 2.12 (s, 4, indanone H), 2.25 (d, 1, J = 8 Hz, H *meta* to $NCOCH_3$), 2.95–3.20 (m, 2, H *ortho* and *para* to $NCOCH_3$), 6.88 (s, 3, OCH_3), and 7.97 (s, 9, CH_3CO); tlc R_f 0.90 (ethyl acetate).

Anal. Calcd for $C_{22}H_{19}NO_7$: C, 64.54; H, 4.68; N, 3.42; mol wt, 409. Found: C, 64.71; H, 5.04; N, 3.36; mol wt, 409 (mass spectrum).

Reaction of Ninhydrin with *m*-Phenylenediamine. Formation of 5e.—The preparation was analogous to that conducted with *m*-hydroxyaniline. A yield of 65% **5e**, as a yellow solid, was obtained. An analytical sample, which had no melting point below 300°, was prepared by several recrystallizations from acetone–water: ir (KBr) 2.86, 2.98, 3.10 (shoulder) 5.88, 6.15, and 6.80 μ; nmr (CD_3SOCD_3) τ 2.00–2.45 (m, 4, indanone H), 2.88 (s, 1, NH), 3.00 (d, 1, J = 8 Hz, H *meta* to NH), 3.90–4.20 (m, 4, H *ortho* and *para* to NH; NH_2 or OH), 4.85 (broad, 2 NH_2 or OH), and 7.82 (acetone); upon addition of D_2O, the peaks at τ 2.88 and 4.95 disappeared and the multiplet at τ 3.90–4.20 integrated as two protons; tlc R_f 0.55 (ethyl acetate).

Anal. Calcd for $C_{15}H_{12}N_2O_3$–C_3H_6O: C, 66.25; H, 5.56; N, 8.59. Found: C, 66.54; H, 5.66; N, 8.39.

Acetylation of 5e.—A mixture of 1.2 g of **5e**, 100 ml of acetic anhydride, and 10 ml of pyridine was heated at reflux under N_2 for 48 hr. The resulting red solution was evaporated to dryness under vacuum. The residue was washed with water and triturated with acetone. The insoluble, crystalline material was recrystallized several times from alcohol (once with charcoal) and then from chloroform–hexane. This afforded 0.1 g of **8** as a yellow powder: mp 236–237.5°; ir (KBr) 5.65, 5.80, 5.90, 6.18, and 6.90 μ; uv max (MeOH) 238 mμ (ϵ 33,000), 278 (18,800), 289 (13,600), 302 (13,500), and 359 (7120); nmr ($CDCl_3$) τ 2.10–3.15 (m, 7, aromatic H), 7.50 (s, 3, CH_3CO), and 7.65 (s, 6, CH_3CO); tlc R_f 0.91 (ethyl acetate).

Anal. Calcd for $C_{21}H_{16}N_2O_5$: C, 67.02; H, 4.28; N, 7.44; mol wt, 376. Found: C, 66.50; H, 4.27; N, 7.35; mol wt, 376 (mass spectrum).

Reaction of Ninhydrin with Urea. Formation of 6a.—The reaction was conducted according to the published procedure.[10] The ultraviolet spectrum of the product has been reported.[7] The product, **6a**, had the following additional properties: ir (KBr) 2.98, 3.05, 5.80, 5.92, and 6.33 μ; nmr (CD_3SOCD_3)

τ 1.99 (s, 1, NH), 2.08–2.60 (m, 5, indanone H and 1 NH), 3.45 (s, 1, OH), and 3.58 (s, 1, OH); tlc R_f 0.14 (ethyl acetate).

Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72; mol wt, 220. Found: C, 54.41; H, 3.87; N, 12.84; mol wt, 220 (mass spectrum).

Acetylation of 6a.—A suspension of 2.0 g (9.1 mmol) of **6a** in 75 ml of acetic anhydride was heated with stirring, under N_2 for 3 hr. The temperature, initially 50°, was raised to 100° over this time. The mixture was poured into 500 ml of ice–water and allowed to stand for 16 hr. The mixture was extracted with an ether–benzene mixture, and the organic layer was washed several times with water and evaporated. The residue was washed with hot water, allowed to dry, and then crystallized from benzene–petroleum ether (bp 30–60°). A yield of 1.80 g (52%) of **6b** was obtained. An analytical sample, mp 186–188°, was prepared by recrystallization from benzene–petroleum ether: ir (KBr) 5.61, 5.70, 5.80, 6.22, and 6.82 μ; uv max (MeOH) 225 mμ (ϵ 8600), 250 (9000), and 286 (1000); nmr (CD_3SOCD_3) τ 1.95–2.40 (m, 4, indanone H), 7.62 (s, overlaps CD_3HSOCD_3 peak, $COCH_3$), 7.70 (s, 3, $COCH_3$), 7.97 (s, 3, $COCH_3$), and 7.99 (s, 3, $COCH_3$); tlc R_f 0.86 (ethyl acetate).

Anal. Calcd for $C_{18}H_{16}N_2O_8$: C, 55.67; H, 4.15; N, 7.21; mol wt, 388. Found: C, 55.98; H, 4.12; N, 7.43; mol wt, 388 (mass spectrum).

Reaction of Ninhydrin with 1,3-Dimethylurea. Formation of 6c.—A solution containing 2.42 g (13.6 mmol) of ninhydrin and 2.82 g (32 mmol) of 1,3-dimethylurea in 80 ml of 0.1 *N* H_2SO_4 was heated at 60° for 30 min. The reaction mixture was kept at 5° for 48 hr. The precipitate that formed was filtered, washed with water, and dried to afford 3.10 g (92%) of **6c**. An analytical sample, mp 259–261° dec, was prepared by recrystallization from methanol–chloroform: ir (KBr) 3.01, 3.20 (shoulder), 5.75, 5.95, 6.20, 6.74, and 6.83 μ (shoulder); uv max (MeOH) 248 mμ (ϵ 10,600) and 290 (1730); nmr (CD_3SOCD_3) τ 1.95–2.28 (m, 4, indanone H), 3.00 (s, 1, OH), 3.15 (s, 1, OH), 7.08 (s, 3, NCH_3), and 7.16 (s, 3, NCH_3); tlc R_f 0.49 (ethyl acetate).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28; mol wt, 248. Found: C, 57.77; H, 4.63; N, 11.03; mol wt, 248 (mass spectrum).

Acetylation of 6c.—A mixture of 0.5 g (2.0 mmol) of **6c**, 40 ml of acetic anhydride, and a small amount of sodium acetate was heated at reflux with stirring under N_2 for 90 min. The reaction was worked up by the procedure used for **6b** to afford 0.3 g (45%) of **6d**. An analytical sample, mp 191–193°, was prepared by several recrystallizations from benzene–petroleum ether: ir (KBr) 3.38, 5.64, 5.80, 6.22, 6.82, and 6.95 μ; uv max (MeOH) 250 mμ (ϵ 10,800) and 290 (1500); nmr (CD_3SOCD_3) τ 1.91–2.30 (m, 4, indanone H), 7.10 (s, 3, NCH_3), 7.17 (s, 3, NCH_3), 7.85 (s, 3, $COCH_3$), 7.88 (s, 3, $COCH_3$); tlc R_f 0.90 (ethyl acetate).

Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43; mol wt, 332. Found: C, 57.63; H, 4.81; N, 8.44; mol wt, 332 (mass spectrum).

Reaction of Ninhydrin with Guanidine.—A solution containing 1.78 g (10 mmol) of ninhydrin and 1.80 g (15 mmol) of guanidine carbonate in 150 ml of water was stirred at 25° for 30 min and kept at 5° for 16 hr. The precipitate that formed was filtered, washed with water, and dried under vacuum. This product, 2.0 g (91%), mp 215–218° dec, was used directly for analysis: ir (KBr) 2.90–4.0 (broad), 5.82, 5.90 (shoulder), 5.98, 6.02 (shoulder), 6.08 (shoulder), 6.12 (shoulder), 6.21, 6.40, and 6.86 μ; nmr (CF_3CO_2H) τ 2.30–2.80 (m, overlapping broad absorption, 5, indanone H + NH) and 3.50 (s, 2, NH). The mass spectrum showed numerous weak peaks beyond the expected molecular ion (m/e 219) up to about m/e 350.

Anal. Calcd for $C_{16}H_9N_3O_3$: C, 54.80; H, 4.14; N, 19.17. Found: C, 54.77; H, 4.12; N, 19.05.

Registry No.—**1**, 485-47-2; **2a**, 17438-16-3; **5a**, 22487-55-4; **5b**, 22433-31-4; **5c**, 22430-97-3; **5d**, 22430-98-4; **5e**, 22430-99-5; **6a**, 22431-00-1; **6b**, 22431-01-2; **6c**, 22431-02-3; **6d**, 22431-03-4; **7**, 22431-04-5; **8**, 22431-05-6; **9**, 22431-06-7.

Attempted Epoxidation of Triphenylcyclopropene[1a,b]

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Received May 5, 1969

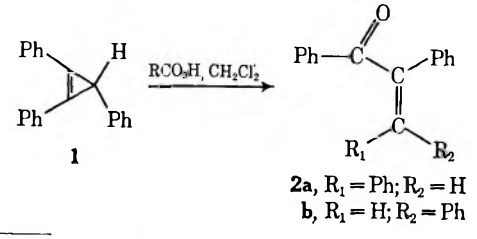
Treatment of triphenylcyclopropene (**1**) with both *p*-nitro- and *m*-chloroperbenzoic acid gave the two isomeric *cis*- and *trans*-α-phenylchalcones (**2a** and **2b**) in the approximate ratio of 82:18. No intermediates were detected when the progress of the reaction was monitored by nmr under buffered conditions. The possibility and significance of oxabicyclobutane intermediates is briefly discussed.

Oxabicyclobutanes have been postulated several times as intermediates in various thermal[2a,b] and photochemical[2c–h] reactions. In none of these cases, however, have oxabicyclobutanes been detected.

The report of Prinzbach and Fischer[2b] provides the most compelling choice for an oxabicyclobutane intermediate in chemical reactions. Peracetic acid oxidation of 1,2-dimethylcyclopropenecarboxylic acid methyl ester gave a 30% isolated yield of the two isomeric *cis*- and *trans*-β-acetylcrotonic acid methyl esters in a ratio of 1:4. If the expected oxabicyclobutanes were intermediates, thermal fragmentation of the bicyclo[1.1.0] ring system[3] would yield the observed products.

As part of a larger effort to synthesize oxabicyclobutanes and determine the chemistry of their ring-opening processes, we have studied the oxidation of triphenylcyclopropene with peracids.

Room-temperature treatment of a methylene chloride solution of triphenylcyclopropene (**1**) with 1.2 equiv of *p*-nitroperbenzoic acid in a flask wrapped with aluminum foil gave only the two isomeric *cis*- and *trans*-



1

2a, R_1 = Ph; R_2 = H
b, R_1 = H; R_2 = Ph

(1) (a) This work was supported by National Science Foundation Grant GP-8878. (b) NOTE ADDED IN PROOF.—A communication recently appeared in which the epoxidation of several alkyl-substituted cyclopropenes was reported: J. Ciabattoni and P. J. Kocienski, *J. Amer. Chem. Soc.*, **91**, 6534 (1969). (c) To whom inquiries should be addressed.

(2) (a) S. Marmor and M. M. Thomas, *J. Org. Chem.*, **32**, 252 (1967); (b) H. Prinzbach and U. Fischer, *Helv. Chim. Acta*, **50**, 1669 (1967); (c) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); (d) E. J. Corey, M. Tada, R. LaMahieu, and L. Libit, *ibid.*, **87**, 2051 (1965); (e) H. E. Zimmerman, R. G. Lewis, J. J. McCullough, A. Padwa, S. W. Staley, and M. Semmelhack, *ibid.*, **88**, 1965 (1966); (f) O. L. Chapman and W. R. Adams, *ibid.*, **90**, 2333 (1968); (g) H. E. Zimmerman and W. R. Elser, *ibid.*, **91**, 887 (1969); (h) N. Furutachi, Y. Nakadaira, and K. Nakanishi, *ibid.*, **91**, 1028 (1969).

(3) Substituted bicyclobutanes fragment into butadienes in an analogous fashion; see G. Closs and P. Pfeffer, *J. Amer. Chem. Soc.*, **90**, 2452 (1968).

TABLE I

PRODUCT RATIOS FROM OXIDATION OF TRIPHENYLCYCLOPROPENE[a]

Peracid	Buffer	Ratio of 2a/2b[b]	Unreacted cyclopropene, %
p-NO_2	None	80:20 ± 4	16
p-NO_2	None	82:18 ± 5	4
m-Cl	None	84:16 ± 3	5
m-Cl	$NaHCO_3$	80:20 ± 4	10
m-Cl	$NaHCO_3$	84:16 ± 5	10
p-NO_2	$NaHCO_3$	78:22 ± 5	6
p-NO_2	$NaHCO_3$	81:19 ± 5	8
m-Cl[c]	Na_2CO_3	83:17 ± 9	37

[a] In methylene chloride solution at room temperature using *ca.* 20% excess peracid. [b] All reported errors are standard deviations. [c] In ethanol-free chloroform solution.

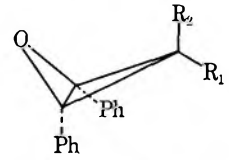
α-phenylchalcones (**2a** and **2b**). The identities of the α-phenylchalcones were established by comparison with authentic samples which were synthesized by two reported procedures.[4] No other products were observed by ir, nmr, uv, and thin layer analysis after *ca.* 90% reaction. Similar experiments with commercially available 85% m-chloroperbenzoic acid gave identical results.

Several runs were also performed with added bases to see whether the liberated p-nitro- or m-chlorobenzoic acids were decomposing isolable intermediates. Unfortunately, control experiments established that the added bases were not effective at rapidly removing p-nitrobenzoic acid from chloroform (see Experimental Section).

Control experiments showed that the *cis*- and *trans*-α-phenylchalcones were individually stable to the reactions conditions and isolation procedure if the products were protected from light and if a large excess of peracid and very long reaction times were avoided. Similarly, triphenylcyclopropene was stable to p-nitrobenzoic acid and the isolation procedure. In the presence of light, dilute solutions of the chalcones underwent slow *cis–trans* isomerization. Large excesses of peracid in the epoxidation reaction led to additional unknown products. Control experiments established that these unknown materials were formed by subsequent oxidation of the chalcones and were not investigated further.

Quantitative ultraviolet analyses of the crude product mixtures obtained under various reaction conditions were performed by an unweighted least-squares regression analysis on the total optical density of the three component mixtures at ten different wavelengths. Subjection of known mixtures of the two chalcones and triphenylcyclopropene to the isolation procedure and ultraviolet analysis revealed that no analytical bias was present. The results are listed in Table I.

The most attractive, although completely unproven, route for formation of the two observed products is *via* oxabicyclobutane(s) **3a** and/or **3b**. In an effort to detect these or any other intermediates, the progress of the oxidation was followed by nmr spectroscopy in ethanol-free chloroform solution. Methylene chloride could not be conveniently used as a solvent because its proton absorption obscures the important region of the spectrum. m-Chloroperbenzoic acid was used both with and without the presence of sodium carbonate. In no

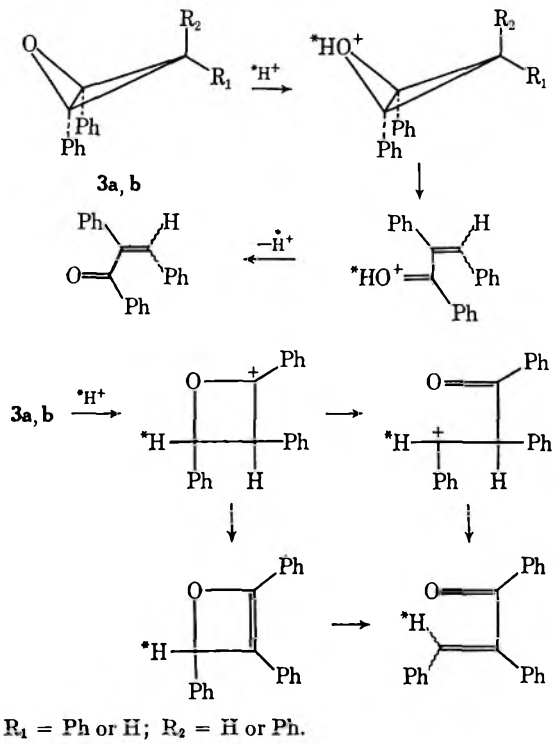


3a, R_1 = Ph; R_2 = H
b, R_1 = H; R_2 = Ph

instance was any evidence for **3a**, **3b**, or any other intermediate found; only the simultaneous disappearance of reactants and appearance of the two chalcone products **2a** and **2b** were observed under conditions where a minimum of 3 mol % of a product such as **3a** or **3b** (with an expected singlet for the tertiary benzylic proton) could be observed. The 3% minimum was established by the internal addition of a known amount of p-dioxane after the reaction was completed.

Since the inorganic buffers were inefficient at removing the liberated phenyl-substituted carboxylic acids, the possibility exists that the suspected oxabicyclobutane(s) **3** decompose by acid-catalyzed processes such as those shown in Scheme I. The second set of

SCHEME I[a]



[a] R_1 = Ph or H; R_2 = H or Ph.

equations in this scheme predicts a shuffling of the atoms in the products. This possibility was tested through the use of m-chloroperbenzoic acid-O-d_1, which should introduce deuterium at the β carbon of the α,β-unsaturated ketone products. Mass spectral analysis of both products showed only undeuterated material, which invalidates the second acid-catalyzed fragmentation. The first mechanism in Scheme I, which involves protonation on oxygen, cannot be eliminated.

If oxabicyclobutanes **3a** and/or **3b** are the immediate precursors of the two chalcones, it is reasonable but not necessary to expect that a stereoselective fragmentation would occur that is controlled by the orbital symmetry characteristics of oxabicyclobutane.[5] The qualitative

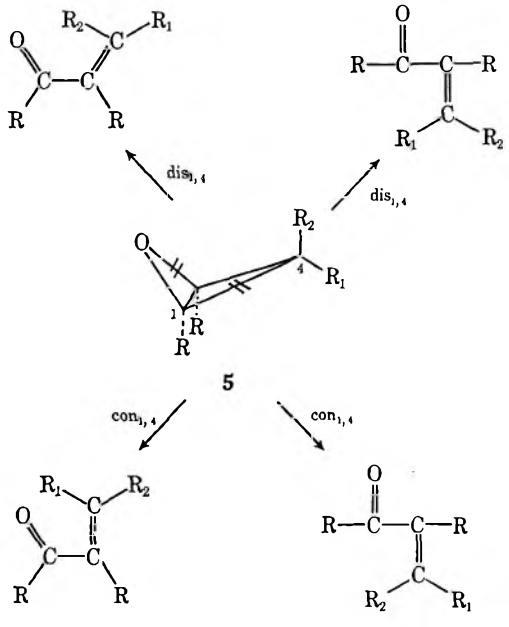
(4) (a) J. Parrick, *Can. J. Chem.*, **42**, 190 (1964); (b) W. Black and R. Lutz, *J. Amer. Chem. Soc.*, **75**, 5990 (1953).

(5) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

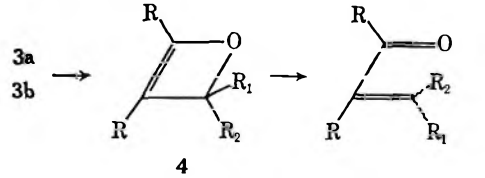
prediction of fragmentation preferences for oxabicyclobutanes, however, is complicated by the lack of symmetry elements which are preserved throughout the reaction. Furthermore, since there is no stereochemistry associated with the oxygen atom, only two theoretical concerted fragmentation modes are possible for oxabicyclobutanes. This situation is contrasted with that for bicyclobutanes, where the extra two hydrogen atoms or other substituents on the additional bridged carbon atom lead to four distinguishable fragmentation pathways.[3]

As is the case with bicyclobutanes,[6] oxabicyclobutanes in theory may fragment to form initially either cisoid or transoid α,β-unsaturated carbonyl products. In order to form the same *cis* or *trans* isomer, opposite rotational modes must prevail in forming cisoid or transoid product (Scheme II).

SCHEME II



Another possibility is that oxabicyclobutanes may prefer to rearrange first to oxetenes[7] of general structure **4**. If so, the product chalcones could be formed by a



cyclobutene–butadiene-type fragmentation. In such a case, only the developing nonbonded interactions of R_1 with R and R_2 with the oxygen atom would direct the ring-opening process to the cisoid α,β-unsaturated carbonyl product; as mentioned before, the presence of the oxygen atom destroys the disrotatory and conrotatory distinctions for fragmentation.

We have performed extended Hückel calculations on the four fragmentation modes of oxabicyclobutane to acrolein (Scheme II). These calculations, subject to their theoretical and practical limitations, fortunately enable distinct predictions to be made. The transoid-$dis_{1,4}$ mode is clearly favored over the transoid-$con_{1,4}$ mode, on the basis of total energy as well as symmetry arguments; in the transoid-$con_{1,4}$ mode the highest occupied orbital of oxabicyclobutane correlates with the lowest unoccupied π orbital of acrolein. A similar result was found for the two cisoid modes. The cisoid-$dis_{1,4}$ mode was clearly favored over the cisoid-$con_{1,4}$ mode for the same two reasons. The use of these predictions must await firm knowledge of whether oxadicyclobutane **3** is indeed an intermediate and, if so, knowledge of the ratio of **3a**/**3b**.

In both our work on triphenylcyclopropene and Prinzbach's work on 1,2-dimethylcyclopropenecarboxylic acid methyl ester, a kinetically controlled epoxidation of the double bonds should give a predominance of oxabicyclobutane **5**, where R_2 is hydrogen and R_1 is phenyl or carbomethoxy. In both cases, a disrotatory opening of the cyclopropane ring (Scheme II) to form a transoid α,β-unsaturated ketone or a conrotatory opening to form a cisoid ketone (energetically unfavorable) would produce the observed major reaction product. It appears fortuitous that both Prinzbach and we observed a 4:1 ratio of the two possible *cis* and *trans* products.

One final set of experiments was performed, even though the results cannot yet be applied to an overall understanding of the oxidation of cyclopropenes. Piperidine-catalyzed equilibration of the α-phenylchalcones was effected in both ethanol and methylene chloride solution until the composition of the mixture no longer changed. Even though the solutions turned yellow, nmr analyses revealed no detectable decomposition of the chalcones, nor did the previously employed least-squares regression analysis reveal any noticeable presence of decomposition products, which should have led to large residuals and standard deviations. The equilibration results are shown in Table II. As is indicated, the thermodynamically favored α-phenylchalcone is the same chalcone that was formed in major amounts in the irreversible, kinetically controlled oxidation of triphenylcyclopropene.

TABLE II

EQUILIBRATION[a] STUDIES ON CHALCONES **2a** AND **2b**

Solvent	Temp, °C	Starting chalcone	Equilibrium ratio of 2a/2b[b]
EtOH	80	**2a**	68:32 ± 3
EtOH	80	**2b**	69:31 ± 3
CH_2Cl_2[c]	120–130	**2a**	64:36 ± 3
CH_2Cl_2[c]	120–130	**2b**	66:34 ± 2

[a] All equilibrations employed a 10-mol excess of piperidine. [b] All reported errors are standard deviations. [c] Undegassed solutions employing undistilled piperidine gave a **2a** to **2b** ratio of 66:34 ± 3 from **2a** and a 64:36 ± 2 ratio from **2b**.

Experimental Section

General.—Nmr spectra were obtained with a Varian Model A-60 spectrometer using tetramethylsilane as internal standard. A Cary Model 11 MS spectrophotometer was used to obtain uv spectra. Ir spectra were recorded with a Perkin-Elmer Model 137 spectrometer. Melting points were obtained on a calibrated Fisher-Johns melting point apparatus. Mass spectra were obtained at both 20 and 75 eV on a Perkin-Elmer Hitachi RMU6E spectrometer. A direct inlet probe was used.

(6) K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968); K. B. Wiberg and G. Szeimies, *Tetrahedron Lett.*, 1235 (1968).

(7) (a) This reaction pathway is most likely "allowed" because of the results from the CNDO[7b] calculations performed by Wiberg[6] on the analogous reaction of bicyclobutane to cyclobutene. The results of Closs,[3] however, effectively rule out this process for the dimethylbicyclobutanes. (b) Complete neglect of differential overlap molecular orbital.

1,2,3-Triphenylcyclopropene (1).—The cyclopropene was prepared from triphenylcyclopropenyl bromide[8] according to the procedure of Breslow and Dowd[9] and recrystallized to constant uv in 95% EtOH: mp 114.0–115.5°; uv max (95% EtOH) 330 mμ (ε 24,200), 313 (29,000), and 228 (30,600); uv max ($CHCl_3$) 334 mμ (ε 23,700) and 317 (29,000); ir (CCl_4) 1820 cm^{-1} (cyclopropene double bond); nmr ($CDCl_3$) δ 7.77–7.20 (m, 15 H, aromatic) and 3.26 (s, 1 H, allylic H) [lit.[8] mp 112–113°; uv max (95% EtOH) 334 mμ (ε 22,800), 318 (28,800), and 218 (27,800); ir 1818 cm^{-1}; nmr δ 7.1 (m, 15 H) and 3.2 (s, 1 H)].

***p*-Nitroperbenzoic Acid.**—The peracid was prepared by either N_2O_2[10] or sodium peroxide[11] oxidation of *p*-nitrobenzoic acid or *p*-nitrobenzoyl chloride, respectively. The peracid analyzed to 99+% purity by iodometric analysis with standardized $Na_2S_2O_3$ in $CHCl_3$–HOAc solution: mp 138–139° dec (sealed tube) [lit.[9] mp 138° dec (sealed tube); lit.[10] mp 136–137° dec (sealed tube)]; ir[12] (Nujol) 3200 (OH), 1750 (C=O), and 870 cm^{-1} (O–O).

***m*-Chloroperbenzoic Acid.**—The peracid was 85% assay and was used as obtained from Research Organic/Inorganic Chemical Co.

***cis*- and *trans*-α-Phenylchalcones (2a and 2b).**—The chalcones were synthesized according to the procedures of Parrick and of Black and Lutz.[4] Mixtures of isomers were separated by a Woelm neutral alumina chromatography (activity II) using benzene–hexane as the eluent. The individual isomers were recrystallized from 95% EtOH to constant uv. Data for *cis*-α-phenylchalcone (2a) follow: mp 89–90° (lit.[4] mp 89–90°); uv max (95% EtOH) 260 mμ (ε 26,200) and 281 (24,400) [lit.[4b] uv max (95% EtOH) 260 mμ (ε 24,600) and 280 (22,900)]; uv max ($CHCl_3$) 260 mμ (ε 21,800) and 284 (20,800); ir (CCl_4) 1666 (C=O) and 1224 cm^{-1} (lit.[4a] ir 1666 cm^{-1}); nmr ($CDCl_3$) δ 8.09–7.92 (m, 2 H, benzoyl *ortho* protons) and 7.55–6.98 (m, 14 H, remaining protons). Data for *trans*-α-phenylchalcone (2b) follow: mp 103–104° (lit.[4] mp 98–99°, 103–103.5°); uv max (95% EtOH) 255 mμ (ε 16,500) and 300 (14,500) [lit.[4b] uv max (95% EtOH) 255 mμ (ε 15,100) and 300–302.5 (13,700)]; uv max ($CHCl_3$) 253 mμ (ε 14,300) and 303 (12,700); ir (CCl_4) 1650 (C=O), and 1250 cm^{-1} (lit.[4a] ir 1649 cm^{-1}); nmr ($CDCl_3$) δ 7.97–7.82 (m, 2 H, benzoyl *ortho* protons) and 7.49–7.15 (m, 14 H, remaining protons).

General Procedure for Peracid Oxidation of Triphenylcyclopropene (1).—A solution of 3.60 mmol of peracid in 45 ml of CH_2Cl_2 (*m*-chloroperbenzoic acid was dissolved in 10 ml of CH_2Cl_2) was added rapidly with stirring in a nitrogen atmosphere to 3.00 mmol of 1 in 5 ml of CH_2Cl_2 at room temperature. All reaction flasks were wrapped with aluminum foil to exclude light. Stirring was continued for *ca.* 6 hr and the unreacted peracid was destroyed with 10% aqueous Na_2SO_3 to give a negative starch–iodide test. The resulting mixture was washed with three 25-ml portions of 5% aqueous $NaHCO_3$ and one 25-ml portion of water. The organic layer was dried over anhydrous Na_2SO_3 and the solvent was evaporated without heating on a rotary evaporator to give a pale yellow oil which solidified. Thin layer chromatography on Merck silica gel G with 5% ether in hexane showed only two spots, corresponding first to the R_f value of a mixture of **2a** and **2b** and second to an R_f value identical with that of unreacted olefin 1. Uv, ir, and nmr spectroscopy showed only the presence of the two chalcones and unreacted 1.

Control experiments performed in the same manner showed that in the absence of large excesses of peracid or long reaction times, the product chalcones were stable to the reaction conditions and work-up. Similarly, triphenylcyclopropene (1) was stable to a CH_2Cl_2 solution of *p*-nitrobenzoic acid and the work-up conditions.

When the oxidations were performed with a >20% excess of peracid, at least one additional component was detected in small amounts, nmr ($CDCl_3$) δ 4.1 (s). This or some other additional component absorbed strongly in the 250–270-mμ region of the uv spectrum. This minor product(s) was not further investigated.

Several reactions were performed with added solid $NaHCO_3$ or Na_2Co_3. No additional products were observed. Only when the reaction was buffered as a two-phase mixture with aqueous $NaHCO_3$ was an additional product found which exhibited in the crude reaction mixture a weak, 1770-cm^{-1} absorption in the ir. No further investigations were performed with aqueous buffers.

Several experiments were performed in which the course of the oxidation of 1 was followed in an nmr tube. *m*-Chloroperbenzoic acid and ethanol-free $CHCl_3$[13] were employed. The spectrum was repeatedly scanned in the region δ 1.0–7.0. Only the disappearance of 1 at δ 3.26 and the appearance of chalcone products were observed. Addition of *p*-dioxane to the nmr tube after the reaction was complete indicated that a minimum of a 3 mol % yield of an intermediate with a one-proton singlet could have been detected in the region scanned. Similar oxidations with *m*-chloroperbenzoic acid in ethanol-free $CHCl_3$ with an added 15-mol ratio of solid Na_2CO_3 also failed to produce any detectable intermediates.

Analytical Method for Product Composition.—Quantitative uv analyses of the various crude multicomponent reaction mixtures were performed by a linear unweighted least-squares regression analysis[14] on the total optical density of the product at ten different wavelengths (eq 1). The determined extinction

$$OD^{\lambda i}_{total} = \epsilon^{\lambda i}_{2a} c_{2a} l + \epsilon^{\lambda i}_{2b} c_{2b} l + \epsilon^{\lambda i}_{1} c_{1} l \qquad (1)$$

coefficients of **2a**, **2b**, and **1** which were used in this analysis are given in Table III. Solutions for analyses were prepared by dissolving a small sample of the product in *ca.* 50 ml of $CHCl_3$ (Mallinckrodt AR grade) and the concentration was adjusted to give approximately unit optical density at 260 mμ. The spectra of all solutions were run immediately because control experiments established that *ca.* 10^{-5} *M* solutions of the chalcones underwent significant *cis–trans* isomerization when not protected from light. No isomerization occurred in the dark. A control experiment in which a 73:17:10 mole ratio of **2a**, **2b**, and **1** was subjected to the work-up and uv analysis gave an analyzed ratio of 73:18:9. The analytical results of several peracid oxidations of **1** are summarized in Table I.

TABLE III

EXTINCTION COEFFICIENTS[a] OF α-PHENYLCHALCONES 2a AND 2b AND TRIPHENYLCYCLOPROPENE (1)

λ, mμ	$10^{-3}\epsilon$ (2a)	$10^{-3}\epsilon$ (2b)	$10^{-3}\epsilon$ (1)
250	17.9	14.0	3.1
260	21.8	13.6	2.8
270	19.7	10.4	5.1
280	20.4	10.1	8.8
290	20.4	11.4	14.0
300	16.9	12.6	19.9
310	11.7	12.3	23.3
320	6.8	9.6	27.2
330	3.3	6.1	21.1
340	1.8	3.6	12.3

[a] Measured in $CHCl_3$ solution. The extinction coefficients were invariant within the measured concentration ranges of 2×10^{-5} to 12×10^{-5} *M*.

Neutralization Rates of *p*-Nitrobenzoic and *p*-Nitroperbenzoic Acid with Inorganic Bases. A. Sodium Bicarbonate.—Solid, anhydrous $NaHCO_3$ was added to a saturated $CHCl_3$ solution of *p*-nitrobenzoic acid and the mixture was stirred at room temperature. The acid concentration was monitored by uv analysis. After 1 hr, 1 equiv of $NaHCO_3$ had only reduced the concentration of *p*-nitrobenzoic acid by 18%.

B. Sodium Carbonate.—A similar experiment as above employing a 25-mol excess of anhydrous Na_2CO_3 reduced the acid concentration by 50% after 15 min. When a saturated $CHCl_3$ solution of *p*-nitroperbenzoic acid was treated with a 100-mol excess of Na_2CO_3, the peracid concentration was reduced by 28% after 1 hr.

C. Disodium Hydrogen Phosphate.—A 50-mol excess of solid, anhydrous Na_2HPO_4 reduced the acid concentration by 13% after 1 hr.

(8) R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **83**, 2367 (1961).
(9) R. Breslow and P. Dowd, *ibid.*, **85**, 2729 (1963).
(10) L. S. Silbert, E. Siegel, and D. Swern, *J. Org. Chem.*, **27**, 1336 (1962).
(11) M. Vilkas, *Bull. Soc. Chim. Fr.*, **26**, 1401 (1959).
(12) Absorptions characteristic of aliphatic peracids are found at 3200, 1745, and 880 cm^{-1}; see L. T. Man, *ibid.*, **33**, 652 (1966).
(13) Ethanol-free chloroform was prepared by passing Mallinckrodt AR grade $CHCl_3$ through a column of Merck alumina (100 g of alumina per 200 ml of $CHCl_3$).
(14) J. Mandel, "The Statistical Analysis of Experimental Data," Interscience Publishers, Inc., New York, N. Y., 1964, p 136.

Oxidation with *m*-Chloroperbenzoic Acid-O-d_1.—*m*-Chloroperbenzoic acid of 99+% purity was prepared by extraction of an ethereal solution of the commercially available material with a neutral phosphate buffer prepared from 35.5 g of disodium hydrogen phosphate and 34.0 g of potassium dihydrogen phosphate dissolved in 1 l. of water. A solution of 3.4 g (0.020 mol) of 99+% *m*-chloroperbenzoic acid in 50 ml of dry, ethanol-free chloroform was stirred with 4.0 g (0.20 mol) of deuterium oxide at room temperature. After 1 hr the organic layer was separated and dried over anhydrous sodium sulfate. The dried chloroform solution was treated with a second 4.0-g (0.20 mol) portion of deuterium oxide for 1 hr. Work-up as before and removal of the solvent on a rotary evaporator without heating gave 2.7 g (80%) of deuterated peracid: ir (Nujol) 2375 (OD), 1715 (C=O), and 861 cm^{-1} (O–O); nmr ($CDCl_3$) δ 8.26–7.33 (m, 4 H, aromatic protons).

A 5.0-mmol sample of triphenylcyclopropene was oxidized with an equimolar amount of *m*-chloroperbenzoic acid-d_1 as previously described. Uv analysis of the product showed 94% reaction with a ratio of **2a**/**2b** of 80:20 ± 6. The crude product was chromatographed on 75 g of Woelm neutral alumina (activity II), *d* 2.2 cm. Application with 25% benzene in hexane and elution with benzene–hexane (increasingly greater amounts of benzene) gave 0.10 g (7%) of **1**, 0.66 g (49%) of **2a** (99:1 ± 4 ratio of **2a**/**2b**), and 0.13 g (10%) of **2b** (88:12 ± 3 ratio of **2a**/**2b**). Infrared analysis of the materials established their identity. The impure *trans* isomer (**2b**) was rechromatographed to yield 63 mg (5%) of a mixture of **2a** and **2b**, and 43 mg (3%) of **2b** (91:9 ± 2 ratio of **2b**/**2a**). No further attempt was made to purify this sample.

Mass spectral analysis at 20- and 75-eV ionizing voltage of these samples showed the absence of deuterium incorporation. The peak intensities in the molecular ion region were virtually identical with those of standard undeuterated samples. The mass spectrum of a control sample of **2b** which had been passed through Woelm neutral alumina (activity II, deactivated with deuterium oxide) was also identical with that of a standard sample of **2b**. The alumina had previously been treated with deuterium oxide and dried at 200–205° (1.0 mm) for 15 hr before deactivation.

Molecular Orbital Calculations.—A probable geometry of oxabicyclobutane was deduced from the known geometries of cyclopropane, oxirane, and bicyclobutane.[15,16] The reaction coordinate was chosen to lie along a pathway defined by a linear variation of the bond angles and bond lengths of oxabicyclobutane to those of acrolein.[16] The exponents of the atoms were chosen as 1.625, 2.275, and 1.000 for carbon, oxygen, and hydrogen, respectively. The respective Coulomb integrals in eV were as follows: C_{2s}, 21.43; O_{2s}, 35.30; C_{2p}, 11.42; O_{2p} 17.76. Resonance integrals were calculated by the Wolfsberg–Helmholz equation using $K = 1.75$. Eigen vectors and eigen values were calculated for eight intermediate geometries by the usual extended Hückel program.[17] The matrix diagonalization was performed in double precision.[18]

Catalytic Equilibration of α-Phenylchalcones (2a and 2b). A. Piperidine in Ethanol.—A 284-mg (1.0 mmol) portion of **2a** was added with stirring to a solution of 850 mg (10.0 mmol) of piperidine (Eastman Practical) in 25 ml of absolute EtOH. The resulting solution, excluded from light, was heated to 80° internal temperature (reflux) in an oil bath. A 1-ml aliquot was removed at selected times and added to a mixture of 400 ml of water and 10 ml of $CHCl_3$. After thorough mixing, the $CHCl_3$ solution was separated and diluted with additional $CHCl_3$ to give a unit optical density at 260 mμ. The diluted solutions were analyzed for the per cent of *cis*- and *trans*-chalcones **2a** and **2b** by uv analysis as described previously. After 24 hr the ratio of **2a** to **2b** was constant (Table III). At the end of the equilibration a portion of the remaining ethanolic solution was added to a mixture of water and $CHCl_3$ as described above and the $CHCl_3$ layer was analyzed by ir and nmr spectroscopy. No absorptions other than those of the *cis*- and *trans*-α-phenylchalcones were observed.

The *trans*-α-phenylchalcone was allowed to equilibrate under the same reaction conditions as above (Table III). Only the two chalcone absorptions were observed in the ir and nmr spectra of the crude reaction product.

When the 24-hr aliquots from both equilibrations were added to water and $CHCl_3$ and the $CHCl_3$ solution was successively washed with 5% aqueous HCl, 5% aqueous $NaHCO_3$, and water, the uv analyses gave slightly different equilibrium mixtures. *cis*-α-Phenylchalcone (**2a**) led to a 71:29 ± 3 ratio and the *trans*-chalcone **2b** gave a 73:27 ± 3 ratio of **2a**/**2b**, respectively.

B. Piperidine in Methylene Chloride.—A solution of 142 mg (0.500 mmol) of **2a** and 425 mg (5.00 mmol) of piperidine in 4 ml of CH_2Cl_2 was heated in a stainless steel sealed tube at 120–130°. At selected times the tube was cooled in ice and a 0.5-ml sample of the orange solution was added to a mixture of 400 ml of water and 15 ml of $CHCl_3$ and shaken well. The colorless $CHCl_3$ layer was filtered through anhydrous Na_2SO_4 and the solvent was removed on a rotary evaporator. The colorless, oily residue was analyzed by uv, ir, and nmr spectroscopy. Only the two chalcones were observed. After 24 hr the composition of the equilibration mixture was constant at 66:34 ± 3 for **2a** and **2b**, respectively.

Similar treatment of **2b** gave a 64:36 ± 2 equilibrium mixture of **2a** and **2b**.

When the two equilibrations were performed with freshly distilled piperidine and when nitrogen gas was bubbled through the reactants for 0.5 hr prior to reaction, **2a** led to a 64:36 ± 3 ratio and **2b** gave a 66:34 ± 2 ratio of **2a** and **2b**, respectively. See Table II for a summary of the results.

C. Other Conditions.—Several equilibrations were attempted with aqueous perchloric acid catalysis as well as with anhydrous *p*-toluenesulfonic acid catalysis in benzene. In the case of aqueous perchloric acid,[19] no isomerization was observed after 48 hr at room temperature using *ca.* 35% aqueous $HClO_4$ and 5×10^{-6} *M* **2a**. With *p*-toluenesulfonic acid in benzene, decomposition of **2a** occurred. Thermal, iodine-catalyzed equilibration[20] also led to decomposition of **2a** and was not investigated further.

Registry No.—**1**, 16510-49-9; **2a**, 7512-67-6; **2b**, 7474-65-9.

(15) P. R. Certain, V. S. Watts, and J. H. Goldstein, *Theor. Chim. Acta*, **2**, 324 (1964); J. F. Chiang, C. F. Wilcox, Jr., and S. H. Bauer, *Tetrahedron*, **25**, 369 (1969); K. B. Wiberg, *ibid.*, **24**, 1083 (1968); M. D. Harmony and K. Cox, *J. Amer. Chem. Soc.*, **88**, 5049 (1966).

(16) L. E. Sutton, Ed., "Tables of Interatomic Distances and Configurations in Molecules and Ions," The Chemical Society, London, 1958, Supplement, 1965. All angles were chosen as 120° and the $C_{1,2}$ distance as 1.43 Å. All C–H bond lengths were 1.08 Å.

(17) Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, Bloomington, Indiana 47001.

(18) Acknowledgment is made to the Computer Center at the University of Rochester for machine time on their IBM 360/65 computer.

(19) D. S. Noyce, W. A. Pryor, and P. A. King, *J. Amer. Chem. Soc.*, **81**, 5432 (1959); D. S. Noyce and M. J. Jorgenson, *ibid.*, **83**, 2525 (1961)

(20) S. Yamashita, *Bull. Chem. Soc. Jap.*, **34**, 487 (1961).

Synthesis of an Isomer of Pteroic Acid, 4-[(2-Amino-4-hydroxypyrimido[5,4-*d*]pyrimidin-6-ylmethyl)amino]benzoic Acid[1]

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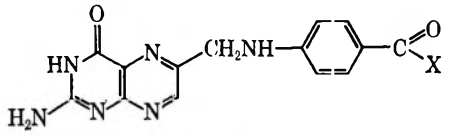
Received June 19, 1969

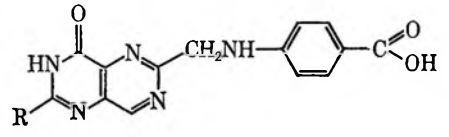
4-[(2-Amino-4-hydroxypyrimido[5,4-*d*]pyrimidin-6-ylmethyl)amino]benzoic acid (**3**) and its 2-hydroxy analog (**4**), in which C_7 and N_8 of the pteridine nucleus are interchanged, were synthesized in seven steps from 5-bromo-2-hydroxymethyl-4-pyrimidinecarboxylic acid. Efforts to condense *p*-carbethoxyanilinoacetamidine hydrochloride (**6**) with mucobromic acid did not succeed.

Many chemically modified analogs of pteroylglutamic acid (**2**) and pteroic acid (**1**) are known to antagonize the growth-promoting activity of the vitamin **2** which is known to function in its tetrahydro form.[3]



1, X = OH
2, X = HNCHCO$_2$H
CH$_2$CH$_2$CO$_2$H

Recent interest in this field has been centered on the preparation and biochemical study of deazapteridine analogs in efforts to determine the structural requirements for the biological activity.[4] No attempt has heretofore been made, however, to investigate the effect on the activity of changing the relative positions of the nitrogen atoms in the pteridine nucleus.

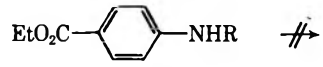


3, R = NH$_2$
4, R = OH

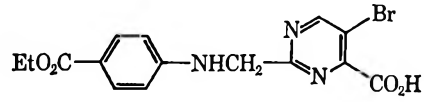
We have been particularly interested in an isomer in which C_7 and N_8 of the pteridine ring of pteroic acid are interchanged. This paper describes the synthesis of **3**, in which this interchange has been accomplished.

An initial approach to this synthesis involved the preparation of 2-amino-6-methylpyrimido[5,4-*d*]pyrimidin-4-ol and unsuccessful efforts to attach *p*-aminobenzoic acid at the 6-methyl site.[5] It seemed more promising, therefore, to prepare first a pyrimidine ring with the desired side chain followed by construction of the second pyrimidine ring. Accordingly, condensation of *p*-carbethoxyanilinoacetamidine hydrochloride (**6**) with mucobromic acid was attempted. Then the expected bromopyrimidinecarboxylic acid **8** might lead to the desired **3** by an approach previously developed in this laboratory.[5] Preparation of the required intermediate is depicted in Scheme I. *p*-Carbethoxyanilino-

SCHEME I



5, R = CH$_2$CN
6, R = CH$_2$C(NH$_2$)=NH·HCl
7, R = CH$_2$CONH$_2$



8

acetonitrile (**5**) was obtained in excellent yield from ethyl *p*-aminobenzoate by the method of Takeda.[6] An attempt to displace the chlorine of chloroacetonitrile with ethyl *p*-aminobenzoate was not successful. The conversion of **5** into **6** was carried out according to the method of Schafer and Peters,[7] which consists of treatment of the nitrile with dry methanol in the presence of sodium methoxide followed by addition of an equivalent amount of ammonium chloride. The structure of the resultant amidine was supported by elemental analysis, infrared spectrum, and its conversion into *p*-carbethoxyanilinoacetamide (**7**) by alkaline hydrolysis. Our efforts to condense **6** with mucobromic acid, however, did not succeed under the various conditions applied. This lack of success might be attributable, at least in part, to the nucleophilic character of the anilino nitrogen, which interferes in the reaction of the amidine with mucobromic acid.

At this stage, our attention turned to a preparation of a 5-bromo-4-pyrimidinecarboxylic acid whose 2 substituent could be converted into a *p*-carboxyanilinomethyl group. After an unsuccessful effort to obtain 5-bromo-2-chloromethyl-4-pyrimidinecarboxylic acid from chloroacetamidine and mucobromic acid, 2-(*p*-tolylsulfonyloxymethyl)-5-bromo-4-pyrimidinecarboxylic acid (**11**) was prepared as shown in Scheme II from the corresponding 2-hydroxymethylpyrimidine **10a**, itself obtained from hydroxyacetamidine (**9**)[8] and mucobromic acid by a modified Budesinsky procedure.[9] An incorporation of the *p*-carboxyanilinomethyl group into the pyrimidine was thereupon achieved by allowing

(1) (a) This investigation was supported by Public Health Service Research Grant CA-05781 from the National Cancer Institute, for which a grateful acknowledgment is expressed. (b) Abstracted in part from a thesis submitted by D. H. K. to the University of North Carolina in partial fulfillment of requirements for the Ph.D. degree, 1965.

(2) To whom all correspondence should be addressed: Research Division, Wyeth Laboratories, Inc., Box 8299, Philadelphia, Pa. 19101.

(3) (a) L. Delmonte and T. H. Jukes, *Pharm. Rev.*, **14**, 91 (1962); (b) R. P. Rao, *J. Sci. Ind. Res.*, **26**, 333 (1967).

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(5) C. E. Cook, Ph.D. Thesis, University of North Carolina, 1960.

(6) A. Takeda, *J. Org. Chem.*, **22**, 1096 (1957).

(7) F. E. Schaefer and G. A. Peters, *ibid.*, **26**, 412 (1961).

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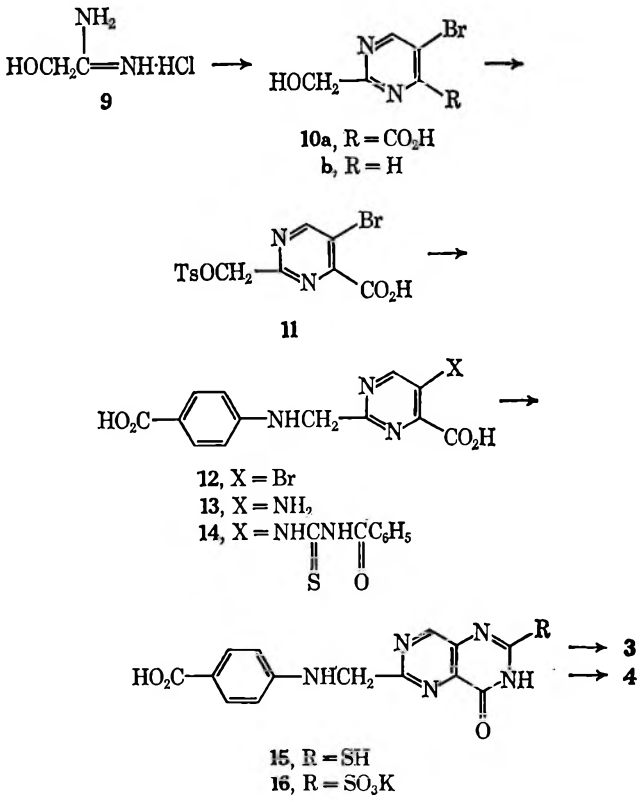
SCHEME II



11 to react with *p*-aminobenzoic acid in dimethylformamide to give 5-bromo-2-(*p*-carboxyanilino)methyl-4-pyrimidinecarboxylic acid (**12**). Treatment of **12** with aqueous ammonia in a sealed tube afforded the corresponding 5-aminopyrimidinecarboxylic acid **13**.

Construction of the second pyrimidine ring was achieved in excellent yield by refluxing a basic solution of the reactive intermediate **14**,[10] which was obtained by treatment of **13** with 1 molar equiv of benzoyl isothiocyanate.

Displacement of the 2-mercapto group of **15** by ammonia had to be accomplished indirectly,[5,11] first converting the mercapto group into the labile sulfonate. Thus, oxidation of **15** with the stoichiometric amount of potassium permanganate[13] afforded the reactive sulfonate **16**. The infrared spectrum of **16** exhibited bands at 1049 and 1238 cm^{-1} which are ascribed to the sulfonate group. The introduction of the amino group was brought about by heating a solution of **16** in aqueous ammonia at 100° in a closed vessel. Since no suitable recrystallization solvent could be found for the product, purification was achieved by dissolution in dilute base followed by precipitation with an acid, giving a pale yellow powder whose analysis[14] indicated it to be the hemihydrate of **3**. The uv spectrum of **3** was similar to that of pteroic acid,[17] exhibiting its absorption maxima at 258 mμ (ε 16,900), 280 (24,400), and 349 (4000) in 0.1% aqueous sodium hydroxide solution, and the nmr spectrum run in basic deuterium oxide solution exhibited its C_8 proton signal at τ 1.88 (s), its *para*-disubstituted phenyl ring protons at τ 2.58 and 3.73 as an AA′XX′ pattern, and its C_6 methylene protons at τ 6.03 (s).

Warming a slightly acidic aqueous solution of the sulfonate **16** on a steam bath caused the loss of sulfur dioxide and afforded N-[(2,4-dihydroxypyrimido[5,4-*d*]-6-pyrimidyl)methyl]-4-aminobenzoic acid (**4**).[18]

Experimental Section

Elemental analyses were performed by Triangle Chemical Laboratories, Inc., Chapel Hill, N. C., and Micro-Tech Laboratories, Skokie, Ill. Melting points were uncorrected. Ir spectra were obtained in KBr pellets using a Perkin-Elmer Infracord Model 137 spectrophotometer, uv spectra were recorded on a Perkin-Elmer Model 202 spectrophotometer, and nmr spectra were obtained on a Varian Model A-60 spectrometer using Me_4Si as internal standard.

***p*-Carbethoxyanilinoacetonitrile (5).**—An aqueous solution of KCN (21.5 g in 60 ml) was added to a hot solution obtained by dissolving 84.4 g of sodium *p*-carbethoxyanilinomethanesulfonate in 150 ml of water, and the resulting mixture was refluxed for 80 min. **Sodium *p*-carbethoxyanilinomethanesulfonate** was prepared from ethyl *p*-aminobenzoate and sodium hydroxymethanesulfonate according to a literature method.[6] Chilling of the reaction mixture caused separation of a precipitate, which was collected on a filter and washed with water. The crude product was recrystallization from 50% EtOH with charcoal treatment to give 61.2 g of needlelike crystals: mp 92–93.5°; nmr ($CDCl_3$) δ 1.33 (t, 3, CH_3CH_2), 4.28 (m, 4, CH_3CH_2, CH_2), and 4.70 ppm (s, 1, NH).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.49; H, 5.92; N, 13.72. Found: C, 64.70; H, 5.89; N, 13.95.

Hydrolysis of **5** with aqueous NaOH solution afforded *p*-carbethoxyanilinoacetamide (**7**): mp 145–146°; ir 3455 (NH), 1686 (ester C=O), and 1662 cm^{-1} (amide C=O).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.61. Found: C, 59.87; H, 6.43; N, 12.60.

***p*-Carbethoxyanilinoacetamidine Hydrochloride (6).**—The procedure of Schaefer and Peters[7] was employed with the following modifications. The reaction period of the base-catalyzed imino ether formation from **5** was extended to 7 hr, and subsequent conversion of the imino ether into the amidine hydrochloride by NH_4Cl was carried out at 57 ± 1° for 48 hr. The crude product was recrystallized from absolute EtOH and 2-butanone to give a crystalline product, yield 71%, mp 189–190°.

Anal. Calcd for $C_{11}H_{16}ClN_3O_2$: C, 51.27; H, 6.26; N, 16.31. Found: C, 51.82; H, 6.49; N, 16.17.

When **6** was hydrolyzed in aqueous KOH solution, the amide **7** was obtained in 60% yield, mp 143–145°. A mixture melting point with the authentic sample obtained from **5** was not depressed.

Hydroxyacetonitrile was obtained according to the procedure of McCasland and Tarbell.[8] A continuous ether extraction of the product from the reaction mixture increased the reported yield more than twofold, bp 79–81° (7.5 mm) [lit.[8] bp 102° (14 mm)].

5-Bromo-2-hydroxymethyl-4-pyrimidinecarboxylic Acid (10a).—Mucobromic acid (25.8 g, 0.1 mol) was dissolved in dry MeOH and diluted with MeOH to 40 ml. Compound **9**[8] (19 g, 0.172 mol) was dissolved in 140 ml of dry MeOH in a 500-ml three-neck flask equipped with a mechanical stirrer and a thermometer. The reaction flask was immersed in an oil bath at 50–55°. Under

(10) No attempt was made to fully characterize this seemingly unstable intermediate, although it was isolated from the reaction mixture.

(11) Although it has been amply demonstrated by Taylor and Cain[12] that the 2-mercapto group of pteridine derivatives can be replaced by amines, rather strenuous reaction conditions coupled with low yields induced us to search for an alternative route which circumvents the limitations of the direct replacement method.

(12) E. C. Taylor and C. K. Cain, *J. Amer. Chem. Soc.*, **73**, 4384 (1951); **74**, 1644, 1788 (1952).

(13) The presence of excess oxidizing agent appears to yield an undesirable, further oxidized compound, whose identification was not attempted.

(14) As was the case in analyses of pteridines,[15] **4** showed a lower value than the calculated value for nitrogen by as much as 1.6% by a convention micro Dumas method. Satisfactory results were obtained by adding a small amount of silver oxide to the combustion tube when a sample was charged.[16]

(15) A. Albert, *Quart. Rev.* (London), **6**, 197 (1952).

(16) L. M. Brancone and W. Fulmor, *Anal. Chem.*, **21**, 1147 (1949).

(17) C. W. Waller, B. L. Hutchings, J. H. Mowat, E. L. R. Stokstad, J. H. Boothe, R. B. Angier, J. Semb, Y. Suffarow, D. B. Cosulich, M. J. Fahrenback, M. E. Hultquist, E. Kuh, E. H. Northey D. R. Seeger, and J. P. Sickels, *J. Amer. Chem. Soc.*, **70**, 19 (1948).

(18) Pyrimidinesulfonic acids are known to transform into hydroxy derivatives in an acidic medium; see D. J. Brown, "The Pyrimidines," Interscience Publishers, Inc., New York, N. Y., 1962, pp 17, 297.

vigorous stirring, 72 ml of methanolic NaOMe solution which was obtained by dissolving 6.9 g of Na in absolute MeOH to give a total volume of 120 ml was added rapidly to the amidine solution followed by an immediate addition of 24 ml of the mucobromic acid solution over a period of 5 min. A mild exothermic reaction took place. When the temperature of the reaction mixture decreased to the original state, the rest of the NaOMe solution was added followed by an addition of the remaining mucrobromic acid solution. The stirring was continued for 2 hr. The inorganic salts were removed by filtration and washed with absolute EtOH. The filtrate and washings were combined and evaporated under reduced pressure to dryness. The black residue was dissolved in 50 ml of 2 *N* HCl and extracted continuously with Et_2O for 24 hr. Evaporation of the Et_2O extract afforded crystalline product, which was collected on a filter and washed with Me_2CO–Et_2O (2:1) and then with dry Et_2O to give 8.23 g (35%) of **10a**: mp 152–153.5° dec; ir 3600 (OH) and 1720 cm^{-1} (C=O).

Anal. Calcd for $C_6H_5BrN_2O_3$: C, 30.93; H, 2.17; N, 12.02. Found: C, 31.28; H, 2.73; N, 12.41.

Addition of a large excess of Me_2CO to a solution obtained by dissolving **10a** in an equimolar aqueous KOH solution caused precipitation of the K salt of **10a**. Recrystallization from Me_2CO–H_2O (4:1) afforded needlelike crystals: mp 251–252° dec; ir 1612 and 1390 cm^{-1} (CO_2^-).

Anal. Calcd for $C_6H_4BrN_2O_3K$: C, 26.58; H, 1.49; N, 10.33. Found: C, 26.53; H, 1.45; N, 10.41.

Heating of **10a** in boiling Me_2CO for 0.5 hr resulted in decarboxylation to give 5-bromo-2-hydroxymethylpyrimidine (**10b**). Purification by sublimation *in vacuo* at 66 ± 0.5° (oil-bath temperature) afforded white crystals, mp 93–94°, no carbonyl absorption band in the ir.

Anal. Calcd for $C_5H_5BrN_2O$: C, 31.77; H, 2.67; N, 14.82. Found: C, 31.78; H, 2.89; N, 14.73.

2-(*p*-Toluenesulfonyloxymethyl)-5-bromo-4-pyrimidinecarboxylic Acid (11).—*p*-Toluenesulfonyl chloride (8.5 g) dissolved in 30 ml of Et_2O was added slowly to a solution obtained by dissolving **10a** in 70 ml of 1 *N* aqueous NaOH solution under vigorous stirring. The stirring was continued for 3 hr, during which 15 ml of additional Et_2O was added. The Et_2O layer was removed, and the aqueous layer was washed with Et_2O. Careful acidification of the aqueous solution with 2 *N* HCl under cooling caused separation of the product, which was collected on a filter and washed with water several times: yield 2.28 g (30%); mp 150 151°; ir 1723 (C=O), 1357, and 1166 cm^{-1} (SO_2).

Anal. Calcd for $C_{13}H_{11}BrN_2O_5S$: C, 40.32; H, 2.86; N, 7.24. Found: C, 40.19; H, 2.84; N, 7.30.

5-Bromo-2-(*p*-carboxyanilino)-methyl-4-pyrimidinecarboxylic Acid (12).—A solution obtained by dissolving 9.33 g of **11** and 17 g of *p*-aminobenzoic acid in 47 ml of dry DMF was stirred at 50–60° (oil-bath temperature) for 48 hr. After most of the DMF was removed *in vacuo*, the residual oil was added dropwise to 140 ml of cold water, whereby precipitation occurred. The precipitate was collected on a filter and washed with water and then with Et_2O repeatedly to give 13.4 g of crude product, mp 240–250°. This was used directly in the following debromoamination reaction.

5-Amino-2-(*p*-carboxyanilino)methyl-4-pyrimidinecarboxylic Acid (13).—A mixture of 13.4 g of crude **12**, 0.5 g of $CuSO_4 \cdot 5H_2O$, and 100 ml of NH_4OH was charged in a steel bomb, and the latter was kept in boiling water for 2.5 hr. After the mixture had cooled to room temperature, the excess ammonia was evaporated under a mild stream of air. Insoluble material was removed by filtration and the filtrate was acidified with 2 *N* HCl to pH *ca.* 1 under cooling. The crystals so obtained were collected on a filter and washed with water. Recrystallization of the crude product from a large excess of water with treatment of charcoal afforded 1.6 g of needlelike crystals, mp 235–236° dec.

Anal. Calcd for $C_{13}H_{12}N_4O_4$: C, 54.18; H, 4.20; N, 19.44. Found: C, 53.89; H, 4.33; N, 19.63.

5-(3-Benzoyl-2-thioureido)-2-(4-carboxyanilinomethyl)-4-pyrimidinecarboxylic Acid (14).[10]—To a solution obtained by dissolving 1.4 g of **13** in 9 ml of dry DMF at 50–60° (oil-bath temperature) was added freshly distilled benzoyl isothiocyanate[19] over a period of 5 min under vigorous stirring. The stirring and warming was continued for 3.5 hr. The reaction mixture was added dropwise to 200 ml of cold water, and the resulting mixture was stirred at 0° for 0.5 hr. The precipitate was collected on a filter and washed with water to give 2.1 g of product, mp 215–218° dec. This was used directly in the following ring-closure reaction.

4-[(4-Hydroxy-2-mercaptopyrimido[5,4-*d*]pyrimidin-6-ylmethyl-amino]benzoic Acid (15).—A solution obtained by dissolving 2.1 g of **14** in 6.8 ml of hot aqueous 3 *N* KOH solution was refluxed for 7 min. Acidification of the reaction mixture with 2 *N* HCl to pH *ca.* 2 under vigorous stirring caused separation of a fine powder, which was collected on a filter and washed with 0.1% aqueous NaCl, 0.05% aqueous NaCl, and water, successively. The filter residue was triturated with Et_2O repeatedly after being dried *in vacuo*, giving 1.6 g (98%) of product which did not melt below 360° but charred at *ca.* 300°. For purification the crude product was dissolved in warm aqueous $NaHCO_3$ solution, treated with charcoal, and filtered. Acidification of the filtrate with HOAc caused separation of hardly filterable fine particles. The resulting mixture was digested for 20 min on a steam bath and cooled slowly to room temperature. After the supernatant liquid was removed by careful decantation, the product was collected on a filter and washed with water: ir 3508, 3225, 2942, 1720, and 1700 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}N_5O_3S \cdot H_2O$: C, 48.42; H, 3.77; N, 20.17. Found: C, 49.04; H, 3.40; N, 19.71.

4-[(2-Amino-4-hydroxypyrimido[5,4-*d*]pyrimidin-6-ylmethyl)-amino]benzoic Acid (3).—To a solution obtained by dissolving 0.5 g of **15** in 5 ml of 1 *N* aqueous KOH was added dropwise 43 ml of aqueous $KMnO_4$ solution (10 mg/ml) with vigorous stirring and chilling (1 ± 1°) over a period of 1 hr. The MnO_2 was removed by filtration and washed with water. A small amount of $Na_2S_2O_5$ was added to the filtrate. The filtrate was then heated to boiling, treated with charcoal, and filtered. Neutralization and subsequent slow cooling of the filtrate caused separation of precipitate, which was collected on a filter and washed with water, giving 0.63 g (80%) of **potassium 6-(4-carboxyanilinomethyl)-4-hydroxypyrimido[5,4-*d*]pyrimidin-2-sulfonate (16)**: mp >360°; ir 3400, 3182, 1708, 1604, 1238, 1170, and 1049 cm^{-1}.

A mixture of 34 ml of concentrated NH_4OH and 0.43 g of **16** was charged in a steel bomb and heated at 100° for 2.5 hr. After being cooled to room temperature, the bomb was opened and the excess NH_3 was evaporated. Neutralization of the remaining solution with 2 *N* HCl caused separation of fine particles, which were collected on a filter to give 0.22 g (68%) of product, mp >360°. For purification, the product was dissolved in 40 ml of hot 0.03 *N* aqueous NaOH solution, treated with charcoal, and filtered. Careful acidification of the hot filtrate with 1 *N* HCl to pH *ca.* 3 caused separation of the product in a colloidal state. After digestion for 30 min on a steam bath, the product was filtered and washed with 0.1 *N* aqueous NaCl solution and then with water twice. Repeated purification by the above manner afforded an analytical sample, which did not melt below 360° but turned to brown from *ca.* 300°: ir 3400, 3310, 3100 (br), 1670 (br), and 1600 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_6O_3 \cdot {}^1/_2H_2O$: C, 52.33; H, 4.09; N, 26.22. Found: C, 52.62; H, 4.22; N, 26.05.

4-[(2,4-Dihydroxypyrimido[5,4-*d*]pyrimidin-6-ylmethyl)amino]-benzoic Acid (4).—Digestion of **16** in slightly acidic medium at *ca.* 95° for 20 min (an odor of SO_2 was noticed during the digestion) resulted in formation of **4**. Repeated purification of the product by a similar manner used for **3** afforded a pale yellow powder which did not melt below 360°: ir 3400, 2100 (br,) 1700 (br), and 1600 cm^{-1}; uv max (0.1 *N* NaOH) 282 mμ (ε 32,400) and 344 (4500).

Anal. Calcd for $C_{14}H_{11}N_5O_4 \cdot {}^1/_2H_2O$: C, 52.17; H, 3.77; N, 21.78. Found: C, 51.85; H, 3.93; N, 21.49.

Registry No.—**3**, 22433-07-4; **4**, 22487-49-6; **5**, 22433-08-5; **6**, 22433-09-6; **7**, 22487-50-9; **10a**, 22433-10-9; **10a** (potassium salt), 22433-11-0; **10b**, 22433-12-1; **11**, 22433-13-2; **12**, 22433-14-3; **13**, 22433-15-4; **14**, 22433-16-5; **15**, 22433-17-6; **16**, 22433-18-7.

(19) J. C. Ambelang and T. B. Johnson, *J. Amer. Chem. Soc.*, **61**, 6321 (1939).

Synthesis of an Isomer of Antheridiol

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Received April 8, 1969

The syntheses are described of 3β-acetoxy-22,25-dihydroxy-$\Delta^{5,24(28)}$-stigmastadien-29-oic acid γ-lactone (III) and of its 7-keto analog (II) which is isomeric with the fungal sex hormone antheridiol. The key reaction was a Reformatsky condensation of a C_{22} aldehyde with a C_7 bromo butenolide.

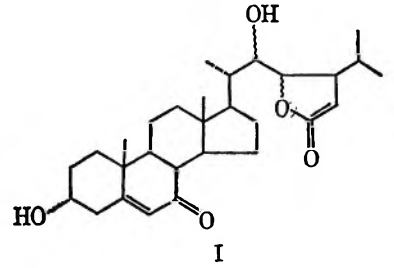
The role hormones play in sexual reproduction in fungi is well established.[1] In the case of the aquatic fungus *Achlya bisexualis*, the mechanism of hormonal control of the sexual process was postulated by Raper several years ago.[2] The substance which initiates the process and which is secreted by the female mycelium was called hormone A. It was isolated in crystalline form in 1965 and renamed antheridiol.[3] The hormone has been shown to be a steroid with the structure I[4] and this structure has now been confirmed by a synthesis carried out by Fried and coworkers of the Syntex Corp.[5]

During the structural investigation, before a satisfactory nuclear magnetic resonance (nmr) spectrum had been obtained,[6] the isomeric structure II for antheridiol was favored and a synthesis of this structure was first undertaken. This paper describes the synthesis of the model steriod III, and the isomer of antheridiol II. The synthetic work provided important evidence for the structure of antheridiol itself.

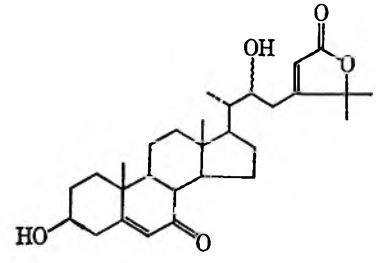
The starting material for the synthesis of III was 3β-acetoxy-22,23-bisnorcholenic acid, which was reduced to the aldehyde IV by a modification of the method of Staab.[7] Treatment with an excess of N-N′-carbonyldiimidazole in boiling tetrahydrofuran gave the imidazolid, which was reduced with lithium tri-*t*-butoxyaluminium hydride in tetrahydrofuran at room temperature to give 3β-acetoxy-22,23-bisnor-Δ^5-cholenaldehyde (IV), mp 113–116°,[8] in high yield.

cis-4-Hydroxy-3,4-dimethyl-2-pentenoic acid lactone was prepared essentially by the method of Stewart and Woolley.[9] It gave, on treatment with N-bromosuccinimide in refluxing carbon tetrachloride under illumination, a mixture of products separated by chromatography into unchanged lactone, the bromo lactone V (R_1 = Br; R_2 = H), mp 41°, and the dibromo lactone V (R_1 = R_2 = Br), mp 120°.

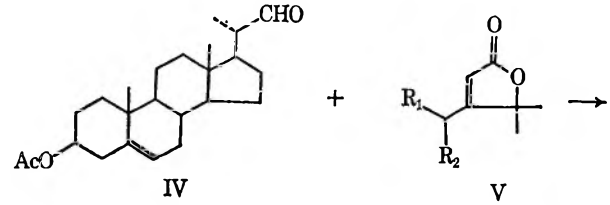
Reformatsky reaction of the aldehyde IV and the bromo lactone V (R_1 = Br; R_2 = H) with activated zinc dust in benzene followed by chromatography of the product afforded 3β-acetoxy-22,25-dihydroxy-



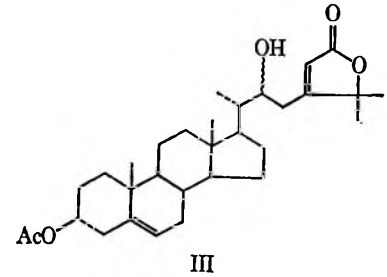
I



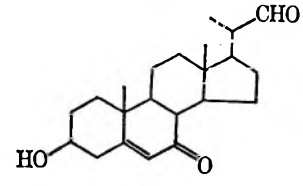
II



IV V



III



VI

$\Delta^{5,24(28)}$-stigmastadien-29-oic acid γ-lactone (III), mp 224–227°, in a yield of 15% (from IV). The substance gave one spot on thin layer chromatography (tlc) as did its product of acetylation, mp 205–207°, and product of deacetylation, mp 240–244°. This indicated that the product III was a single epimer.

It is worth noting that the lactone ring of III was unchanged after treatment with alkali and subsequent acidification. In contrast, when an alcoholic solution

(1) See, *inter alia*, (a) L. Machlis in "The Fungi," Vol. II, G. C. Ainsworth and A. S. Sussman, Ed., Academic Press Inc., New York, N. Y., 1966, p 415; (b) W. H. Nutting, H. Rapoport, and L. Machlis, *J. Amer. Chem. Soc.*, **90**, 6434 (1968); (c) H. van den Ende, *J. Bacteriol.*, **96**, 1298 (1968).

(2) J. R. Raper, *Amer. J. Bot.*, **26**, 639 (1939).

(3) T. C. McMorris and A. W. Barksdale, *Nature*, **215**, 320 (1967).

(4) G. P. Arsenault, K. Biemann, A. W. Barksdale, and T. C. McMorris, *J. Amer. Chem. Soc.*, **90**, 5635 (1968).

(5) J. A. Edwards, J. S. Mills, J. Sundeen, and J. H. Fried, *ibid.*, **91**, 1248 (1969).

(6) This was in part due to the poor solubility of antheridiol in suitable organic solvents. Eventually, a mixed solvent, 4:1 $CDCl_3$–CD_3OD, proved to be best.

(7) H. A. Staab and H. Braunling, *Justus Liebigs Ann. Chem.*, **654**, 119 (1962).

(8) A. P. Centolella, F. W. Heyl, and M. E. Herr, *J. Amer. Chem. Soc.*, **70**, 2953 (1948).

(9) J. M. Stewart and D. W. Woolley, *ibid.*, **81**, 4951 (1959).

of antheridiol was treated with a trace of sodium hydroxide solution, the ultraviolet spectrum changed in 3 hr from a single maximum at 220 mμ to maxima at 237 and 278 mμ. This change was not fully investigated because of lack of material, but it probably involved rearrangement of the α,β-butenolide to the β,γ isomer[10] as well as partial elimination of the 3β-hydroxyl group. The loss of the α,β-unsaturated lactone chromophore exposed the peak at 237 mμ owing to the Δ⁵-7 ketone present in antheridiol.

For the synthesis of II, stigmasteryl acetate was oxidized with anhydrous sodium chromate in acetic acid–acetic anhydride at 35–40° to give 7-ketostigmasteryl acetate, mp 181–183°.[11] Treatment with dilute potassium carbonate solution then gave the keto alcohol. Controlled ozonolysis of this compound in a solution of methylene chloride containing 1% pyridine at −78°, followed by reductive work-up (Zn–CH_3COOH),[12] gave a 40% yield of 3β-hydroxy-Δ⁵-7-ketocholen-22,23-bisnoraldehyde (VI), mp 226–229°.

The mass spectrum of the aldehyde VI (mol wt 344) was very similar to that of antheridiol, thus providing further evidence for the steroid nucleus of the latter compound. Antheridiol (mol wt 470) readily loses a large fragment, *m/e* 126, giving the base peak *m/e* 344 which corresponds to the molecular ion of VI. The only significant difference in the spectra was in the few additional peaks, *viz.*, at *m/e* 470, 452, 434 (all very low intensity), 126, and 111, in the spectrum of antheridiol.

The aldehyde was converted to its tetrahydropyranyl ether (dihydropyran–*p*-toluenesulfonic acid) and then condensed with the bromo lactone V (R_1 = Br; R_2 = H) to give the tetrahydropyranyl ether of II in 15% yield from VI. This product, mp 220–225°, α_D −74°, appeared to be homogeneous by tlc. Removal of the tetrahydropyranyl group by gentle acid treatment afforded 3β,22,25-trihydroxy-$\Delta^{5,24(28)}$-stigmastadien-7-on-29-oic acid γ-lactone (II), mp 241–244°.

The mass spectra of II and antheridiol proved to be almost identical. However, the fragment ion from the side chain of the latter compound gave a much stronger peak at *m/e* 126 than the corresponding fragment from II. Both spectra showed intense peaks at *m/e* 111 [$(C_7H_{10}O_2 - CH_3)^+$]. Like antheridiol, compound II was easily converted into a Δ³,⁵-7 ketone (λ_{max} 278 mμ) on treatment with acid.

The isomer of antheridiol (II) was inactive in the biological assay for hormone A.

Experimental Section[13]

3β-Acetoxy-22,23-bisnorcholenaldehyde (IV).—3β-Acetoxybisnorcholenic acid (20 g)[13b] was added to dry tetrahydrofuran (200 ml) followed by N,N′-carbonyl diimidazole (25 g). The mixture was heated to boiling, when complete solution occurred, and refluxed for 45 min. It was then cooled and poured into water, giving a white precipitate which was separated by filtration, washed thoroughly with water, and dried over P_2O_5, yield 22 g, mp 220–223°. This imidazolid (22 g) was suspended in dry tetrahydrofuran (300 ml) and a solution of lithium tri-*t*-butoxyaluminum hydride (20 g) in tetrahydrofuran (200 ml) was added dropwise during a 1-hr period at room temperature. The resulting solution was concentrated *in vacuo* at room temperature to about 100 ml and poured into dilute 1 *N* hydrochloric acid (400 ml) with vigorous stirring. The precipitate was separated by filtration, washed with water, and air dried, yield 23 g, mp 114–118°. Tlc showed it to be mainly one compound, the aldehyde, with small amounts of alcohol formed by reduction of the aldehyde and unchanged imidazolid. The product was, therefore, purified by chromatography on silica gel (0.05–0.20 mm) with chloroform, giving 14 g of aldehyde, mp 113–116°. This aldehyde has been prepared by ozonolysis of stigmasteryl acetate dibromide by Centolella, *et al.*,[8] who give a melting point of 113–116°. The latter method was tried but was found not to be so convenient as the one described above. Spectral data for compound IV follow: ir 2725 and 1733 cm^{-1}; nmr δ 0.70 (H-18), 1.03 (H-19), 1.13 (d, *J* = 7 Hz, H-21), 5.40 (broad peak, H-6), and 9.61 (d, *J* = 3.5 Hz, H-24).

***cis*-4-Hydroxy-3,4-dimethyl-2-pentenoic Acid Lactone (V, R_1 = R_2 = H).**—The preparation was similar to the one described in the literature,[9] except for the following differences. 2-Hydroxy-2-methylbutan-3-one was acetylated by refluxing with excess acetic anhydride and a little zinc dust for 3 hr. The liquid was cooled and poured into ice–water, causing separation of the fragrant, oily acetate. Sodium bicarbonate was added to neutralize the acetic acid and the acetate was then extracted into ether. The extract was dried (Na_2SO_4) and distilled, and the fraction with a boiling point of 77° (21 mm) was collected and used in the Reformatsky reaction with ethyl bromoacetate. The product of this reaction after treatment with sodium hydroxide solution was acidified and then extracted with ether. The extract was dried (Na_2SO_4), the ether was removed, and the residual brown, viscous liquid was chromatographed on alumina with 5:1 benzene–ether. The lactone was nicely crystalline: mp 42–44°; uv max 208 mμ (ε 13,000); ir 1760 cm^{-1}; nmr δ 1.45 (2 CH_3), 2.03 (d, *J* = 2 Hz, 1 CH_3), and 5.70 (q, *J* = 2 Hz, 1 H).

Reaction of V (R_1 = R_2 = H) with N-Bromosuccinimide.—The lactone (1 g) was dissolved in dry carbon tetrachloride (60 ml), and N-bromosuccinimide (1.4 g) was added. The mixture was refluxed under illumination from a 250-W lamp for 30 min and cooled, and the liquid was filtered away from the succinimide. Removal of the solvent gave an oil (2 g) which was chromatographed on silica gel with 1:3 ethyl acetate–petroleum ether (bp 60–90°) to give, first, the dibromo lactone V (R_1 = R_2 = Br): mp 120°; ir 1748 cm^{-1}; nmr δ 1.63 (s, 2 CH_3), 6.23 (br s, 1 H), and 6.48 (br s, 1 H); mass spectrum *m/e* 282 (M^+), 284, and 286. The bromo lactone V (R_1 = H; R_2 = Br) was eluted next: mp 41°; ir 1760 cm^{-1}; nmr δ 1.58 (s, 2 CH_3), 4.21 (d, *J* = 1.5 Hz, 2 H), and 6.20 (t, *J* = 1.5 Hz, 1 H); mass spectrum *m/e* 204 (M^+), 206, 235, and 250. The last two peaks were presumably formed by loss of bromine from the molecular ion followed by dimerization of the resulting radical ion ($C_{14}H_{18}O_4$ = 250) and loss of a methyl ($C_{13}H_{15}O_4$ = 235).

Anal. Calcd for $C_7H_9O_2Br$ (mol wt, 205.05): C, 41.00; H, 4.39; O, 15.61; Br, 39.00. Found: C, 40.90; H, 4.25; O, 15.73; Br, 39.74.

Late fractions from the chromatography gave unchanged lactone V (R_1 = R_2 = H).

3β-Acetoxy-22,25-dihydroxy-$\Delta^{5,24(28)}$-stigmastadien-29-oic Acid γ-Lactone (III).—A solution of 3β-acetoxy-22,23-bisnorcholenaldehyde (500 mg) and the bromo lactone V (R_1 = H; R_2 = Br) (275 mg) in dry benzene (8 ml) was refluxed together with activated zinc dust for 2 hr. (The zinc dust was activated by treating it with dilute 6 *N* hydrochloric acid for 5 min, washing it several times with water and then with acetone, and drying it at 100° *in vacuo*.) The mixture was diluted with benzene shaken with dilute 2 *N* hydrochloric acid for several minutes and then with water and dried (Na_2SO_4), and the solvent was removed. The residue (700 mg) was chromatographed on silica gel with 1:1 ethyl acetate–petroleum ether to give III: yield 93 mg; mp 224–227°; ir 1757, 1742 (sh), and 1718 cm^{-1} (acetate and lactone); nmr δ 0.70 (H-18), 1.00 (H-19) (the H-21 signal appeared as two inflections on the side of the H-19 singlet), 1.43

(10) The isomerization of α,β-butenolides with alkali is well known in the cardenolide field. See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 739.

(11) L. F. Feiser, M. Fieser, and R. N. Chakravarti, *J. Amer. Chem. Soc.*, **71**, 2226 (1949).

(12) This method was first used for ozonolysis of stigmastadienone by G. Slomp, Jr., and J. L. Johnson, *ibid.*, **80**, 915 (1958).

(13) (a) Melting points were taken on a Kofler hot stage and are uncorrected. Infrared spectra were determined in KBr disks with a Perkin-Elmer Model 21 spectrophotometer and ultraviolet spectra were determined in ethanol with a Perkin-Elmer Model 450 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 A spectrometer, using tetramethylsilane as internal reference. Microanalyses were carried out by Dr. F. Pascher, Bonn, Germany. (b) Purchased from Mann Research Laboratories, Inc., New York, N. Y. 10006.

(H-26 and -27), 1.98 (acetate), 3.99 (broad peak, H-22), 4.52 (very broad peak, H-3), 5.32 (br s, H-6), and 5.80 (s, H-28); mass spectrum m/e 438 (M − 60), 312 (M − 60 − 126), and 111.

Anal. Calcd for $C_{31}H_{46}O_6$: C, 74.66; H, 9.30; O, 16.04; mol wt, 498.68. Found: C, 74.50; H, 9.51; O, 16.01; mol wt, 500 (cryoscopic).

This substance gave a single spot on tlc with different solvent systems. Acetylation with acetic anhydride and pyridine gave a product, mp 205–207°, which was also homogeneous by tlc. Likewise, hydrolysis of the acetate group by treatment of the alcoholic solution with 10% K_2CO_3 solution gave a crystalline product, mp 240–244°, ir 1745 cm^{-1}, which was homogeneous.

7-Ketostigmasterol.—The following method gave better yields than that described in the literature.[11] Stigmasteryl acetate (5 g) was dissolved in acetic acid (500 ml) and acetic anhydride (50 ml). The solution was stirred at 35–40° with sodium chromate (5 g) for 48 hr, concentrated under reduced pressure to a small volume, and poured into water with vigorous stirring. The precipitate was removed by filtration, washed with water, air dried, and crystallized from ethyl acetate–petroleum ether, yielding *ca.* 2 g, mp 176–179°. Recrystallization from methanol raised the melting point to 181–183°.

The keto acetate in methanol (200 ml) was stirred overnight with 10% K_2CO_3 solution (20 ml). Most of the solvent was removed *in vacuo* and water was added to the residue. The insoluble product was collected and dried: it melted partially at 122–124° and completely at 143–145°; uv max 237 mμ (ε 12,200); ir 1675 and 1634 cm^{-1}.

3β-Hydroxy-Δ⁵-7-keto-22,23-bisnorcholenaldehyde (VI).—7-Ketostigmasterol (1 g), dissolved in methylene chloride (100 ml) and pyridine (1 ml), was ozonized at −78° for 45 min. (This reaction time was found to be most suitable for the conditions used. Shorter reaction times gave mixtures of unchanged 7-ketostigmasterol and aldehyde which were not readily separated, while longer reaction times led to attack of the nuclear double bond.) A white suspension formed. This was stirred with zinc dust (2 g) and acetic acid (2 ml) for 2 hr, during which time it warmed to room temperature. It was then washed several times with water and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a crystalline residue which was shaken with a little ethyl acetate and separated by filtration: yield 330 mg; mp 226–229° (recrystallization from chloroform–ethyl acetate did not change the melting point); α_D −124° (*c* 0.5, MeOH); uv max 238 mμ (ε 12,800); ir 3484, 2710, 1727, 1664, and 1626 cm^{-1}; nmr δ 0.73 (H-18), 1.13 (d, J = 7 Hz, H-21), 1.20 (H-19), 5.73 (broad peak, H-6), and 9.63 (d, J = 3 Hz, H-24); mass spectrum m/e 344 (base peak, M^+).

Anal. Calcd for $C_{22}H_{32}O_3$ (mol wt, 344.48): C, 76.70; H, 9.36; O, 13.93. Found: C, 75.74; H, 9.41; O, 14.73. A satisfactory analysis has not been obtained, possibly because the crystals still contained solvent after being heated to constant weight *in vacuo* at 100°.

3β,22,25-Trihydroxy-Δ⁵,²⁴⁽²⁸⁾-stigmastadien-7-on-29-oic Acid γ-Lactone (II).—The keto aldehyde VI (300 mg) was stirred for 30 min with dihydropyran (6 ml) and a small crystal of *p*-toluenesulfonic acid. The resulting solution was concentrated *in vacuo* and chromatographed on silica gel with 1:3 ethyl acetate–petroleum ether. The crystalline fractions of the tetrahydropyranyl ether were combined. The nmr spectrum of this material was similar to that of the starting aldehyde VI, except for increased resonances in the region of δ 1.6 and 3.6 and a broad peak at δ 4.73, all due to the protons of the tetrahydropyran ring. The aldehyde VI could be recovered unchanged by treating the tetrahydropyranyl ether with a solution of dilute HCl in methanol (0.1 ml of concentrated HCl in 100 ml of methanol) for 3 hr at room temperature. Thus no epimerization occurred at C-20 in the formation of the tetrahydropyranyl ether.

The tetrahydropyranyl ether and the bromo lactone V (R_1 = Br, R_2 = H) (180 mg) were dissolved in dry benzene (3 ml), activated zinc dust (60 mg) was added, and the mixture was refluxed for 1.5 hr. It was then cooled, diluted with benzene, washed with dilute hydrochloric acid and water, and dried (Na_2SO_4). The solvent was removed and the residue was chromatographed on silica gel with 1:1 ethyl acetate–petroleum ether, giving the tetrahydropyranyl ether of II: yield 66 mg; mp 220–225°; α_D −74° (*c* 0.2, MeOH); uv max 215 mμ (ε 19,000) and 233 (inflection, 16,000); ir 3472, 1739, 1675, and 1634 cm^{-1}; nmr δ 0.70 (H-18), 0.97 (broad peak, H-21[14]), 1.20 (H-19), 1.45 (H-26 and -27), 5.70 (broad s, H-6), and 5.87 (s, H-28).

Anal. Calcd for $C_{34}H_{50}O_6$: C, 73.61; H, 9.09; O, 17.31; mol wt, 554.75. Found: C, 73.38; H, 9.02; O, 17.74; mol wt, 510 (tensimetric).

This substance appeared to be homogeneous by tlc. The tetrahydropyranyl group was removed by adding 4 ml of a solution of dilute HCl in methanol (0.08 ml of 6 *N* HCl in 100 ml of methanol) to 18 mg of III. It dissolved on shaking, the solution was kept for 2 hr at room temperature, a few drops of sodium bicarbonate solution were added, and the methanol was evaporated in a stream of N_2. Water was added to the residue and the insoluble material was separated, washed with water, dried, and recrystallized from ethyl acetate to give II: mp 241–244°; uv max 214 mμ (ε 18,600) and 232 (inflection, 15,000); ir 3425, 1727, and 1656 cm^{-1}; nmr δ 0.71 (H-18), 1.00 (broad peak, H-21[14]), 1.21 (H-19), 1.47 (H-26 and -27), 5.71 (br s, H-6), and 5.90 (s, H-28).

Anal. Calcd for $C_{29}H_{42}O_5$ (mol wt, 470.63): C, 74.01; H, 9.00; O, 17.00. Found: C, 74.28; H, 9.01; O, 17.14.

When the tetrahydropyranyl ether of II was allowed to stand with the dilute hydrochloric acid and methanol overnight, extensive elimination of the 3β substituent occurred and the Δ³,⁵-7 ketone was isolated: mp 237–240°; uv max 210 mμ (ε 14,900) and 278 (22,200); ir 3410, 1754, 1645, and 1623 cm^{-1}.

Registry No.—II, 22336-99-8; tetrahydropyranyl ether of II, 22287-16-7; III, 22287-17-8; IV, 10211-88-3; V (R_1 = R_2 = H), 4182-41-6; V (R_1 = R_2 = Br), 22319-54-6; V (R_1 = H; R_2 = Br), 22287-47-4; VI, 22287-19-0.

Acknowledgment.—The author is grateful to Dr. Alma Barksdale for the biological assay, to Helen McMorris for technical assistance, and to Dr. G. P. Arsenault and Dr. K. Biemann (Massachusetts Institute of Technology) for the mass spectra. This work was supported by the National Institutes of Health (Grant GM 12150).

(14) This broad peak is probably a result of virtual coupling. For an explanation of this effect, see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 36.

Conversion of Acyclic Carbohydrates into Tetrahydrofuran Derivatives. Acid-Catalyzed Dehydration of Hexitols[1]

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Received July 16, 1969

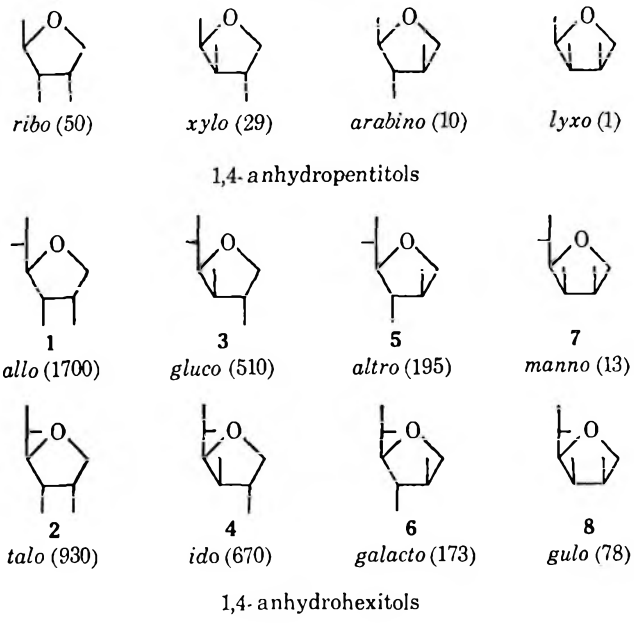
The acid-catalyzed dehydration of hexitols leads primarily to the formation of tetrahydrofuran derivatives. In those cases in which the reaction proceeds readily, ring closure involves displacement of water from the primary alcohol groups in the 1 (or 6) position. Where this reaction is retarded by steric effects, the formation of varying amounts of anhydrides involving ring closure with inversion at the 2 (or 5) position occurs. The rate of the ring-closure reaction involving the primary hydroxyl groups is influenced by changes in the configuration of hydroxyl groups not directly involved in the reaction, by inductive effects, and by an interaction between the hydroxyl group adjacent to the leaving group and the leaving group itself in the transition state.[2] The ease of 1,4-anhydride formation decreases through the series allitol, talitol, iditol, glucitol, altritol, galactitol, gulitol, and mannitol. The formation of 1,4:3,6 anhydrides from the 1,4 anhydrides of iditol and gulitol is approximately 40 times faster than from those of glucitol and mannitol, in which the hydroxyl substituent in the newly formed ring is *endo*.

The acid-catalyzed anhydrization of tetritols and pentitols produces tetrahydrofuran derivatives having the configuration of the starting alditol.[2] The rate of the reaction decreases through the series ribitol, xylitol, arabinitol, and lyxitol and appears to depend on interactions present in the transition states for ring closure. A similar effect of configuration on the rate of 1,4-anhydride ring formation should be observable in the hexitol series if the interactions in the transition state determine the reaction rate.

1,4-Anhydrohexitols.[3]—The hexitols have four asymmetric carbons but have primary hydroxyl groups at both ends. Because of this, there are only six different configurations possible rather than the eight possible for the hexoses. Four of the six hexitols can have enantiomers and two are *meso* compounds; *i.e.*, a total of ten hexitols is known. Tetrahydrofuran rings can be formed at either end of the hexitol chain and could be designated as 1,4 anhydrides and 3,6 anhydrides to emphasize this point. However, in this paper the major concern is with the effects of configurational differences within the tetrahydrofuran ring and these can be compared most readily if all compounds are discussed as 1,4 anhydrides. For example, D-glucitol and L-gulitol are names for the same compound; two different tetrahydrofuran rings can be formed by reaction at the primary hydroxyl groups. Both anhydrides could be named as derivatives of D-glucitol, *i.e.*, 1,4-anhydro-D-glucitol and 3,6-anhydro-D-glucitol. However, it is preferable to name them both as 1,4 anhydrides in which case the latter is named 1,4-anhydro-L-gulitol. A similar situation exists with D-talitol and D-altritol. With the other four configurations, allitol and galactitol are *meso* compounds from which racemic mixtures of 1,4 anhydrides are produced by reaction at either end; either enantiomer of mannitol or iditol reacts to give the same 1,4 anhydride. Thus, D-mannitol can form only 1,4-anhydro-D-mannitol.

The relevance of this discussion is apparent when the effects of configuration on reactions of the hexitols is compared with that observed for the pentitols. Each 1,4-anhydropentitol can give rise to two 1,4-anhydrohexitols if the carbon chain is extended at C-5 (Chart I). One of the hexitols belongs to the D series and the other to the L series. However, the rate of the dehydration reaction is not influenced by the enantiomeric form of the hexitol, and the configurational relationships between the pentitols and the hexitols are most easily seen in this representation. The relative rates of formation from the corresponding alditol in 2 *N* hydrochloric acid at 100° are given in parentheses beside each structure; those of the pentitols were obtained from ref 2, and those of the hexitols from the data in Table I. The expectation that the hexitol series would have the same dependence of rate on configuration as the pentitol series is fully borne out, although the hexitols anhydrize more rapidly than the corresponding pentitols.

CHART I



The effect of configuration of the hexitols on the rate of 1,4 anhydride formation can be rationalized on the following basis. Only those transition states in which the hydroxyl group at C-2 occupies an axial position are allowed, since, when this group is equatorial, it interacts with the leaving group to prevent its departure[2,4]

(1) This investigation was supported in part by a Public Health Service Research Grant (GM-11,963) and by a Public Health Service Research Career Program Award (GM-24,808) from the Institute of General Medical Sciences.

(2) B. G. Hudson and R. Barker, *J. Org. Chem.*, **32**, 3650 (1967).

(3) R. Barker, *ibid.*, **29**, 869 (1964).

(4) Axial and equatorial can be used to describe the disposition of groups in a transition state in which the bond being formed is longer than in the product, and the carbon and oxygen atoms of the forming ring are disposed as they would be in a six-membered-ring system.

TABLE I

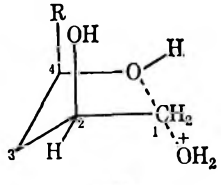
PRODUCTS OF THE ACID-CATALYZED DEHYDRATION OF THE HEXITOLS AND THEIR RATES OF FORMATION[a]

Hexitol	Products[a]	$k_{overall}$ (2 *N*),[b] $sec^{-1} \pm 0.2$	$k_{1,4}$,[c] $sec^{-1} \pm 0.2$	1,4 anhydrides, relative rate of formation[d]	$k_{overall}$ (4 *N*),[e] $sec^{-1} \pm 0.2$
Allitol	1,4-Anhydro-DL-allitol (92)	7.26×10^{-5}	3.3×10^{-5}	133 (1)	2.5×10^{-4}
	One unknown (8)				
D-Talitol	1,4-Anhydro-D-talitol (68)		1.8×10^{-5}	73 (2)	
	1,4-Anhydro-D-altritol (14)	2.66×10^{-5}	3.7×10^{-6}	15 (5)	
	Two unknowns (18)				
L-Iditol	1,4-Anhydro-L-iditol (85)	3.08×10^{-5}	1.3×10^{-5}	53 (4)	1.17×10^{-4}
	2,5-Anhydro-D-glucitol (15)		2.3×10^{-6}		
D-Glucitol	1,4-Anhydro-D-glucitol (85)		9.9×10^{-6}	39 (3)	
	1,4-Anhydro-L-gulitol (13)	1.15×10^{-5}	1.5×10^{-6}	6 (8)	
	2,5-Anhydro-L-iditol (2)		2.3×10^{-7}		
Galactitol	1,4-Anhydro-DL-galactitol (97)	6.67×10^{-6}	3.3×10^{-6}	13 (6)	2.8×10^{-5}
	One unknown (3)				
D-Mannitol	1,4-Anhydro-D-mannitol (41)		2.5×10^{-7}	1 (7)	
	2,5-Anhydro-D-glucitol (45)	1.18×10^{-6}	2.7×10^{-7}		4.2×10^{-6}
	1,5-Anhydro-D-mannitol (14)		8.3×10^{-8}		

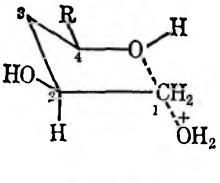
[a] Figures in parentheses are percentages of initial products as determined by gas chromatography. The dianhydrides of glucitol, mannitol, and iditol are formed slowly and are only important at later stages of the reaction. [b] Pseudo-first-order rate constants for the disappearance of hexitol in 2 *N* hydrochloric acid at 100°. [c] Pseudo-first-order rate constants for anhydride formation from hexitol in 2 *N* hydrochloric acid at 100° corrected for symmetry of substrates. [d] Numerals in parentheses refer to structures in Chart I. [e] Pseudo-first-order rate constants for the disappearance of hexitol in 4 *N* hydrochloric acid at 100°.

(Chart II). This requirement fixes the conformation of the carbon chain from carbon 1 to carbon 4. Differences in rate then depend upon the nonbonded interactions between substituents in this conformation. The important nonbonded interactions are those between adjacent *cis*-hydroxyl groups and between a bulky substituent at carbon 4 and a *cis*-hydroxyl group at carbon 3 or at carbon 2.

CHART II

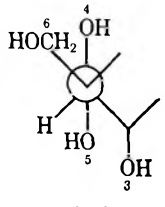


projection along C-2-C-1 bond, 2-OH axial; leaving group can depart

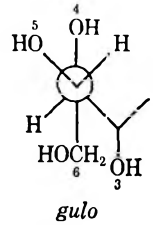


projection along C-2-C-1 bond, 2-OH equatorial; interacts with the leaving group

Differences in rate between isomers differing only in configuration at carbon 5 appear to be due to interactions between the substituents at C-5 and those at C-3. When the hydroxyl groups are *cis* (in the Fischer projection) the rate is always greater than when they are trans. The rate difference is substantial only between the *gulo* and *manno* compounds; the former



manno

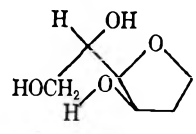


gulo

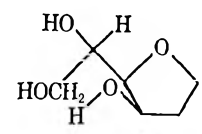
cyclizes six times faster than the latter. If the transition states are similar to that proposed for the parent *lyxo* configuration, then that for the *manno* compound has hydroxyls at C-3 and C-5 eclipsed, while in the *gulo* configuration the hydroxymethyl of C-6 and the hydroxyl at C-3 would be eclipsed. If the important interactions are polar ones, then the conformer having an interaction between hydroxyl groups is less stable.

1,4:3,6-Dianhydrohexitols.—The 1,4 anhydrides of iditol, gulitol, glucitol, and mannitol are converted into the corresponding 1,4:3,6 anhydrides under the conditions of the reaction. The pseudo-first-order rate constants obtained using authentic samples are 5.6×10^{-4}, 5.0×10^{-4}, 1.2×10^{-5}, and 1.3×10^{-5} min^{-1}, respectively. There is a 40-fold difference between rates of formation of 1,4:3,6 anhydrides from 1,4 anhydrides in which the hydroxyl at C-5 is *endo* in the product and those in which this hydroxyl is *exo*. In the former case (the 1,4 anhydrides of mannitol and glucitol) the hydroxyl at C-5 must approach an eclipsed orientation with respect to the oxygen of the 1,4-anhydride ring, whereas in the latter (the 1,4 anhydrides of iditol and gulitol) the C–O dipoles are oriented so as to minimize their interactions (Chart III).

CHART III



gluco and *manno*



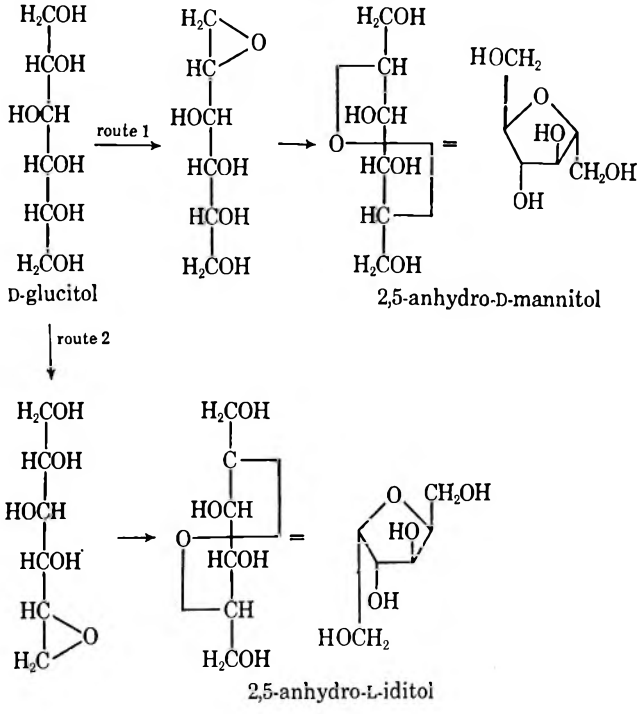
gulo and *ido*

2,5-Anhydrohexitols.—The anhydrization of all of the hexitols except mannitol leads primarily to the formation of 1,4 anhydrides. However, in all cases compounds having the chromatographic characteristics of 2,5 anhydrides are produced. The 2,5 anhydrides of mannitol, glucitol, and iditol were available for comparison with the compounds produced in the anhydrization reaction. In the case of the products from iditol and glucitol, identification is based only on the

gas chromatographic behavior of the products. However, 2,5-anhydro-D-glucitol was isolated from the mannitol reaction mixture and characterized as its 1,3-*O*-isopropylidene-6-*O*-trityl derivative.[5]

The occurrence of 2,5 anhydrides is most readily explained on the basis of the intermediate formation of 1,2 epoxides, which can rearrange to form 2,5 anhydrides with inversion of configuration at C-2. Obviously such epoxide formation can involve either end of the hexitol molecule. In the case of glucitol (Chart IV) only 2,5-anhydro-L-iditol was observed (route 2)

CHART IV



and it would have been formed from the 5,6 epoxide. Since the formation of a 3,6 anhydride (1,4-anhydro-L-gulitol) occurs with greater difficulty than does the formation of 1,4-anhydro-D-glucitol there would be a correspondingly greater opportunity for epoxide formation.

The anhydrization of iditol leads to a significant proportion of 2,5-anhydro-D-glucitol. Apparently the configuration of this alditol allows the formation of both the 1,4-anhydride and the 1,2 (or 5,6) epoxide, since both are formed with significantly greater ease than are most other anhydrides.

D-Mannitol anhydrizes with greater difficulty than any of the other alditols and a large proportion of 2,5-anhydro-D-glucitol is formed. In addition, a significant proportion of 1,5-anhydro-D-mannitol is formed. This material could arise either by direct displacement of a protonated hydroxyl from C-1 by the hydroxyl at C-5 or by opening of a 1,2 epoxide by the hydroxyl at C-5.

The possibility that 1,2 epoxides are important as intermediates in the formation of 1,4 anhydrides has been considered previously[6,7] and shown to be unimportant in this type of reaction. In addition,

(5) G. R. Gray and R. Barker, unpublished results.
(6) F. C. Hartman and R. Barker, *J. Org. Chem.*, **28**, 1004 (1963).
(7) B. A. Applegarth, J. T. Buchanan, and J. Baddiley, *J. Chem. Soc.*, 1213 (1965).

TABLE II
RETENTION TIMES AND MOLAR RESPONSES OF THE ACETATE DERIVATIVES OF HEXITOLS AND THEIR ANHYDRIDES, RELATIVE TO RIBITOL AT 240°

Alditol	Retention time	Molar response
Allitol	2.090	1.168
DL-Talitol	2.412	1.043
L-Iditol	3.043	1.092
D-Glucitol	2.731	0.996
Galactitol	2.725	1.014
D-Mannitol	2.332	1.034
1,4-Anhydro-		
DL-allitol	1.643	0.813
DL-talitol	1.645	0.805
D-altritol	1.151	0.788
D-iditol	1.456	0.894
D-glucitol	1.293	1.024
D-gulitol	1.850	0.856
D-galactitol	1.348	0.902
D-mannitol	1.483	0.935
2,5-Anhydro-		
L-iditol	1.798	0.980
L-glucitol	1.600	0.789
D-mannitol	1.407	0.940
1,5-Anhydro-		
D-glucitol	1.391	0.913
D-galactitol	1.343	1.020
D-mannitol	1.361	0.979
1,4:3,6-Dianhydro-		
L-iditol	0.437	0.586
D-mannitol	0.537	0.554

compounds lacking a hydroxyl group adjacent to the leaving group form 1,4 anhydrides with ease.[2] To further examine the importance of the 2-hydroxyl group on the rate of 1,4-anhydride formation the anhydrization of 2-deoxy-D-glucitol was examined. The pseudo-first-order rate constant for the disappearance of 2-deoxy-D-glucitol in 2.0 *N* hydrochloric acid at 100° is 1.8×10^{-3} min^{-1}. The major product (approximately 85%) appears to be 1,4-anhydro-2-deoxy-D-glucitol, since the reaction mixture after $10 \times t_{1/2}$ releases 1.04 molar equiv of formaldehyde per mole of periodate consumed. The ratio of the rates of formation of 1,4-anhydro-2-deoxy-D-glucitol and 1,4-anhydro-D-glucitol is 2.6:1, in good agreement with the observation that a hydroxyl group adjacent to the leaving group produces a decrease in rate by a factor of 3.[2] 2-Deoxy-D-glucitol (more properly 2-deoxy-D-*arabino*-hexitol) could as well be referred to as 2-deoxy-D-mannitol, and the fact that it undergoes 1,4-anhydride formation 100 times faster than does D-mannitol clearly demonstrates the importance of configuration, in particular of the relative position of the 2-hydroxyl, to the rate of this reaction.

Experimental Section

Hexitols.—D-Glucitol, D-mannitol, and galactitol were obtained from Pfanstiehl Laboratories, Inc. Samples were at least 99% pure as determined by gas–liquid chromatography of their acetate and trimethylsilyl derivatives and were used without further purification. L-Iditol was a gift from Dr. J. W. LeMaistre, Atlas Chemical Industries, Wilmington, Del. Allitol and D-talitol were prepared by reduction of the corresponding lactones with sodium borohydride according to the method of Abdel-Akher, *et al.*[8] These alditols were recrystallized from

(8) M. Abdel-Akher, J. K. Hamilton, and F. Smith, *J. Amer. Chem. Soc.*, **73**, 4691 (1951).

methanol until their physical properties agreed with literature values.

Kinetic Studies.—One milliliter portions of a 4% solution of the hexitol in the appropriate concentration of hydrochloric acid were placed in a series of tubes which were sealed and submerged in a boiling water bath. The variation in temperature observed over a period of several weeks was less than 1°. Samples were withdrawn at intervals and neutralized with sodium hydroxide. They were then concentrated to dryness under a stream of hot, dry air and the acetate derivatives were formed in the presence of the residual salts. It was shown by subjecting known mixtures of hexitols and their anhydrides to this procedure that the salt does not interfere with the derivatization. A suitable aliquot (usually 1 to 5 μl) of the reaction mixture was injected into the gas chromatograph.

All separations were performed on a 5 ft × $^1/_8$ in. column of polyethylene glycol sebacate on Chromosorb Q using helium at 30 ml/min as the carrier gas. The column was maintained at 110–140° for the separation of silyl derivatives and at 200–225° for the separation of acetates. In most cases either derivative could be used to follow the progress of the anhydrization reaction. The detector response to each compound was established when possible using authentic materials and was used with measurements of peak areas to calculate the proportions of the various components present.

In Table II are presented the relative retention times and the molar responses for the hexitols and anhydrohexitols used as standards in this study.

Registry No.—Allitol, 488-44-8; D-talitol, 22576-99-4; L-iditol, 488-45-9; D-glucitol, 50-70-4; galactitol, 608-66-2; D-mannitol, 69-65-8.

Conversion of Acyclic Carbohydrates into Tetrahydrofuran Derivatives. Deamination of 1-Amino-1-deoxypentitols[1a]

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Received July 16, 1969

The 1-amino-1-deoxypentitols were prepared from the corresponding oximes by hydrogenation over platinum. The products of deamination with nitrous acid at 0° were examined by gas chromatography. In each case, the 1,4-anhydropentitol having the configuration of the starting material was the major product. The amounts of pentitol with the parent configuration and anhydropentitol formed by ring closure with inversion at position 2 increased through the series *xylo* < *ribo* = *arabino* ≪ *lyxo*. Bis(1-deoxypentitol)amines are also formed during the reduction of the oximes. The D-*arabino* isomer has been characterized.

Other reports in this series describe the acid-catalyzed formation of the tetrahydrofuran rings of methyl pentofuranosides,[2] 1,4-anhydropentitols,[3] and 1,4-anhydrohexitols.[4] Similar effects of configuration on the rates of these reactions were observed and explained on the basis of interactions between substituents in the transition states. In particular, interactions between groups which were forced to occupy 1,3-diaxial orientations and between a 2-hydroxyl or methoxyl group and the group leaving C-1 appeared to be important.

The 1-amino-1-deoxyalditols have been shown to deaminate readily and to give rise to 1,4-anhydroalditols as major products.[5] The deamination reaction differs from the displacement reactions cited above in that it takes place at lower temperatures, and may therefore be influenced by conformations of the ground states. Further, the reaction is not reversible, and, unlike the dehydration of the alditols, reaction with the solvent produces a stable product. Finally, the transition state for the formation of a tetrahydrofuran derivative in the deamination does not contain a leaving group, or contains one which cannot have the kinds of interaction that a protonated leaving group can have with adjacent hydroxyls. Because of these differences we wished to determine whether the effect of configuration in the acid-catalyzed reactions was observed in this ring-closure reaction.

The deamination of the 1-amino-1-deoxypentitols with nitrous acid is rapid and leads to the formation of various amounts of 1,4-anhydropentitol, pentitol, and anhydrides formed by ring closure between C-5 and C-2, which have inversion at C-2. The proportions of these products are given in Table I.

TABLE I
MOLAR PROPORTIONS OF PRODUCTS FROM DEAMINATION OF 1-AMINO-1-DEOXYPENTITOLS[a]

1-Amino-1-deoxypentitol	1,4 anhydride	2,5 anhydride, inverted	Alditol
ribo	78	15	7
arabino	78	9	14
xylo	89	9	2
lyxo	55	24	20

[a] Values are averages of three separate deamination experiments and duplicate analyses.

The deamination reaction leading to 1,4 anhydrides and alditols having the configuration of the starting amine probably proceeds by one of the routes shown in Scheme I. For convenience, the *ribo* configuration is represented; however, the following discussion is concerned with the general case. It is not possible to distinguish between the two routes, but, to rationalize the differences in proportion of products observed with differences in configuration, it is not necessary to do so.

That the rate of formation of the diazo compound **2** was not influenced by changes in the configuration of the amine **1** was shown by measuring the rates of disappearance of the latter (see Experimental Section). However, the reactant for the formation of 1,4 anhydrides is either the diazo compound **2** or the carbonium ion **3**, and differences in rate of formation of **2** or **3** would not influence the proportion of **7** formed in the

(1) (a) This investigation was supported in part by a Public Health Service Research Grant (GM 11,963) and by a Public Health Service Research Career Program Award (GM 24,808) to R. B. from the Institute of General Medical Sciences; (b) to whom inquiries should be addressed.

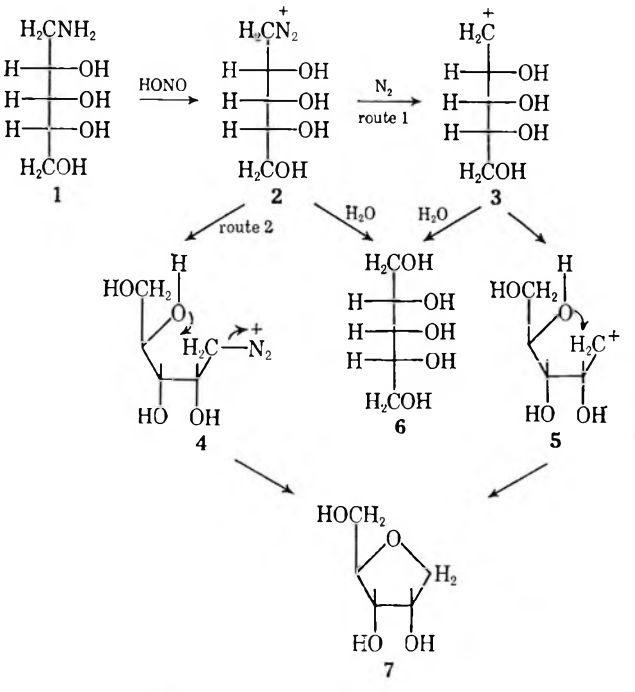
(2) D. Dennis Heard and R. Barker, *J. Org. Chem.*, **33**, 740 (1968).

(3) B. G. Hudson and R. Barker, *ibid.*, **32**, 3650 (1967).

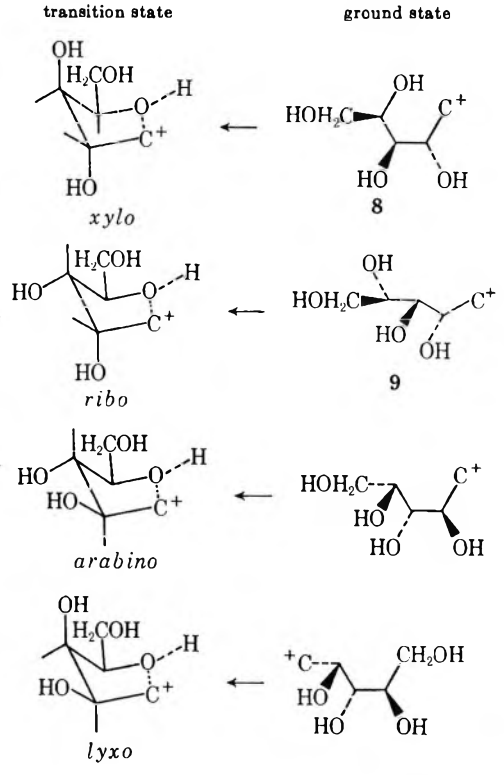
(4) R. Barker, *ibid.*, **35**, 461 (1970).

(5) L. F. Wiggins, *Advan. Carbohyd. Chem.*, **5**, 191 (1950); V. G. Bashford and L. F. Wiggins, *Nature*, **165**, 566 (1950).

SCHEME I



SCHEME II



reaction. This proportion should depend only on the relative rates of the intramolecular reaction (forming **7**) and reaction with solvent (forming **6**).

If the formation of the 1,4 anhydride is a displacement reaction,[6] then the ease of assumption of conformation **4** should affect the rate of the process and the rate would be sensitive to changes in configuration. The same effect would be expected if **5** were the intermediate in the process. On the other hand, neither the rate of conversion of the diazo compound **2** nor of the carbonium ion **3** into the alditol **6** would be expected to be as strongly influenced by configurational changes in the reactant as the ring-closure reaction.

The rates of reaction of the intermediate **2** or **3** cannot be measured. However, the relative rates of cyclization and solvolysis can be estimated from the relative proportions of products at any time in the reaction and, if it is assumed that solvolysis is unaffected by changes in configuration, the effect of configuration on the rate of the cyclization reaction can be estimated from the ratio of pentitol to 1,4 anhydride.

From the data in Table I and on the basis of the assumptions discussed above, it appears that ring formation becomes increasingly more difficult through the series *xylo*, *ribo*, *arabino*, and *lyxo*. However, the differences in rate are small. Probable transition states for the various configurations are shown in Scheme II.

In the acid-catalyzed formation of 1,4-anhydropentitols from the pentitols the rates were found to decrease through the series *ribo* (50), *xylo* (29), *arabino* (10), and *lyxo* (1).[7] In this case, the differences in rates between the pairs of isomers differing in configuration at C-2 were attributed largely to interaction of the hydroxyl group at C-2 with the leaving group in one of them. For example, arabinitol is much slower to cyclize than is ribitol, primarily because of the interference of the C-2 hydroxyl group of the former with the leaving group in the transition state having fewest nonbonded interactions between substituents at C-2, C-3, and C-4. This interaction is proposed to involve hydrogen-bond formation with, or proton transfer to, the 2-OH group. In the deamination reaction, no such interaction can occur and the other effects of configuration (those due to interactions between groups at C-2, C-3, and C-4) should still be apparent. On this basis, the proportion of 1,4 anhydride would be expected to decrease through the series *arabino*, *xylo*, *ribo*, and *lyxo* as was found in an earlier study of the cyclization of benzylated pentitols.[8] This is not the case. It is possible that, in the deamination reaction which is carried out at or below room temperature, the conformations of the ground states are important in determining the ease of cyclization. It has been proposed earlier[8,9] that the ground-state conformations of the pentitols have their hydroxyl groups *gauche*, producing a maximum separation of the C–O dipoles. The ground state for xylitol would then have the conformation **8** and that of ribitol the conformation **9**. The former would be much more likely to give rise to a cyclic product. Alternatively, the ground-state conformers may be extended chains with a zig-zag conformation.[10] In this case the proportion of 1,4 anhydride will reflect the energy difference between the extended chain and the "cyclic" transition state. Such ground-state conformations are less likely to determine the rate of cyclization in the acid-catalyzed dehydration at 100°.

(6) J. Baddiley, J. G. Buchanan, and B. Carss, *J. Chem. Soc.*, 4058 (1957).

(7) Relative rates given in parentheses are corrected for the statistical factor in the case of ribitol and xylitol, and were calculated from the proportion and 1,4 anhydrides of arabinitol and lyxitol formed in the dehydration of arabinitol.[8]

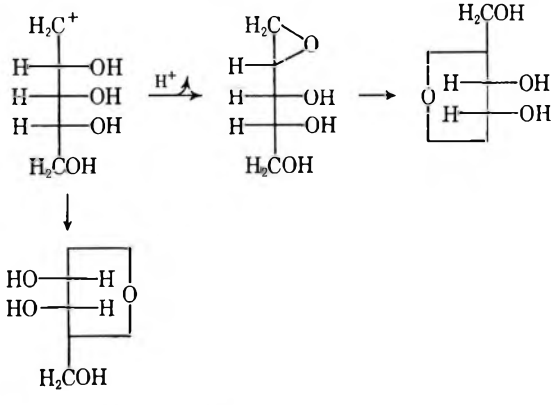
(8) G. R. Gray, F. C. Hartman, and R. Barker, *J. Org. Chem.*, **30**, 2020 (1965).

(9) F. C. Hartman and R. Barker, *Biochemistry*, **4**, 1068 (1965).

(10) H. S. Khadem, D. Horton, and T. F. Page, Jr., *J. Org. Chem.*, **33**, 734 (1968).

In addition to 1,4 anhydrides and alditols, varying proportions of products involving ring closure at C-2 by the hydroxyl at C-5 are found. These products could arise from the intermediate formation of 1,2 epoxides, which would rearrange to form stable tetrahydrofuran derivatives (Scheme III). It is improbable that 1,2

SCHEME III



epoxides are intermediates in the formation of the 1,4 anhydrides, since it has been shown that 1,2-epoxy-4-butanol does not give rise to 3-hydroxyfuran under mildly alkaline conditions.[11] The possibility that these products are formed from a rearranged carbonium ion can be discounted, since only products having inversion at C-2 are found. If a C-2 carbonium ion intermediate was involved, then products should be present having inversion and retention at this center.

A bis(1-deoxy-D-arabinitol)amine was isolated from the reduction of D-arabinose oxime, which was prepared by the neutralization of the acid released during oxime formation with sodium hydroxide. The reduction of the neutral solution followed by the usual work-up gave an amine, which, when treated with nitrous acid, gave an insoluble N-nitroso derivative. The derivative was characterized by molecular weight, elemental analysis, and conversion back into the amine. It gives an atypical Liebermann test and has a strong absorption band at 237 mμ. The occurence of secondary amines in the reduction of oximes has been described previously,[12a] and secondary amines are also formed in the reduction of glycosylamines.[12b]

Experimental Section

Melting points are corrected. Gas chromatography was performed with an Aerograph HY-FI 600-D, equipped with a 5 ft × 1/8 in. column of 10% polyethylene glycol sebacate on Chromosorb Q using helium as the carrier gas. Constant temperature for deamination experiments was maintained using a Haake Ultrathermostat NBS water bath. Absorbancies were measured using a Beckman DU with a Gilford attachment and absorption spectra were obtained using a Cary 15.

Reductions were performed at room temperature at low pressure (50 lb/in.²) using a Parr pressure reaction apparatus. Molecular weights were determined using a Mechrolab vapor phase osmometer. Analyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn.

Preparation of 1-Amino-1-deoxypentitol Hydrochlorides.—The 1-amino-1-deoxypentitols were obtained from the parent pentoses by catalytic reduction of freshly prepared pentose oxime. The amines were purified by preparation and recrystallization of the *N*-salicylidene-1-amino-1-deoxypentitols and the 1-amino-1-deoxypentitol hydrochlorides were generated by acid hydrolysis of the salicylideneamines.

A. 1-Amino-1-deoxy-D-arabinitol Hydrochloride.—To 5.6 g of hydroxylamine sulfate in 40 ml of water at room temperature was added 10 g of D-arabinose. The pH of the solution immediately dropped from 2.6 to 1.8. A solution of 3 *N* ammonium hydroxide was added dropwise to the reaction mixture to maintain a pH of 4.6. The pH reached this constant value in 1.5 hr, indicating the reaction had reached completion.[13]

The reaction mixture was transferred to a 500-ml Parr reduction bottle and 10 ml of glacial acetic acid and 1 g of platinum oxide were added. The mixture was reduced for 18 hr during which time the theoretical amount of hydrogen was taken up. The mixture was filtered through a Celite pad to remove the platinum, and passed over a column containing 150 ml of Dowex 50W × 8 (H^+). The column was washed with water until the eluate was neutral, and these washings were discarded. The column was then eluted with 250 ml of 5 *N* ammonium hydroxide, and the eluate concentrated to dryness at 30°. The residue was taken down to dryness several times from absolute ethanol, leaving the crude amine as a clear syrup (8 g, 80%).

The amine was purified by conversion into the salicylidene derivative. To a solution of 7.5 g of the amine syrup in 7.5 ml of water were added 22.5 ml of absolute ethyl alcohol and 5.25 ml of salicylaldehyde.[14] The mixture was refluxed for 30 min and then concentrated. The resulting crystalline *N*-salicylidene-1-amino-1-deoxy-D-arabinitol (6.0 g, 51%), after recrystallization from absolute ethyl alcohol, had mp 183–185°. Wolfrom, *et al.*, report mp 184–185°. 1-Amino-1-deoxy-D-arabinitol hydrochloride was obtained by acid hydrolysis of the salicylidene derivative and extraction of the salicylaldehyde with methylene chloride. The material obtained by concentration of the aqueous phase was recrystallized from aqueous methanol to a constant melting point of 135–135.5°. Jones, *et al.*, report mp 136.5–137.5°.[15]

Anal. Calcd for $C_5H_{14}NO_4Cl$: C, 32.01; H, 7.52; N, 7.46; mol wt, 187.6. Found: C, 32.24; H, 7.61; N, 7.30; mol wt, 180 ± 5.

1-Amino-1-deoxy-D-ribitol, -D-xylitol, and -D-lyxitol Hydrochlorides.—The crude amine hydrochlorides, the salicylidene derivatives, and the purified hydrochlorides of the 1-deoxypentitols were prepared as described for the *arabino* isomer. They had the properties listed in Table II.

TABLE II

	N-Salicylidene-1-amino-1-deoxypentitol		1-Amino-1-deoxypentitol hydrochloride			
	Mp, °C	Lit.[b] mp, °C	Mp, °C	C, %	H, %	N, %
ribo	124	126	126–128[c]	31.84	7.59	7.45
xylo	128–129	128–129	139–140[e]	32.19	7.42	7.37
lyxo	184–186[a]			28.28	7.85	6.47[d]

[a] *N*-Salicylidene-1-amino-1-deoxy-D-lyxitol: *Anal.* Calcd for $C_{12}H_{17}NO_5$: C, 56.5; H, 6.67; N, 5.48; mol wt, 255. Found: C, 56.4; H, 6.61; N, 5.47. Registry no. 22566-19-4. [b] See ref 14. [c] Lit. value 132.5–134° (ref 15). Registry no. 22566-17-2. [d] 1-Amino-1 deoxy-D-lyxitol hydrochloride could not be crystallized; however, the material was chromatographically pure, and the analysis obtained agrees closely with that expected of a monohydrate $C_5H_{14}NCl \cdot (H_2O)$. [e] Registry no. 22566-18-3.

Deamination Reactions.—Samples of 1-deoxy-1-aminopentitol hydrochlorides (180 mg) were dissolved in water (3 ml). Glacial acetic acid (1 ml) was added and the mixture cooled to 0°. Sodium nitrite (140 mg) was added to the solution in milligram amounts during 1 hr, while the temperature of the reaction mixture was maintained at 0°.

The reaction mixture was then kept at room temperature for 1 hr, degassed by alternately warming and applying a vacuum by means of a water aspirator, and passed over a column (6 ml) of Dowex 50W × 8 (H^+). The eluate was concentrated to dryness, and the residue taken up in water (1 ml) and passed over a column

(11) F. C. Hartman and R. Barker, *J. Org. Chem.*, **28**, 1004 (1963).

(12) (a) R. Paul, *Bull. Soc. Chim. Fr.*, [5] **4**, 1121 (1937); P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press Inc., New York, N. Y., 1967, p 139; (b) F. Kagan, M. A. Rebensdorf, and R. V. Heinzelman, *J. Amer. Chem. Soc.*, **79**, 3541 (1957).

(13) J. W. Haas, Jr., and R. E. Kadunce, *ibid.*, **84**, 4910 (1965).

(14) M. L. Wolfrom, F. Shafizadeh, J. O. Wehrmuller, and R. K. Armstrong, *J. Org. Chem.*, **23**, 571 (1958).

(15) J. K. N. Jones, M. B. Perry, and J. C. Turner, *Can. J. Chem.*, **40**, 503 (1962).

(6 ml) of Rexyn 203 (OH^-). The eluate was concentrated to dryness, to give 100 mg (60–70%) of a mixture of alditol and anhydrides.

The products of the deamination reactions were investigated by paper, thin layer, and gas chromatography. Aqueous solutions of the reaction products were applied to Whatman No. 1 filter paper or to plates of microcrystalline cellulose[16] and were developed in ethyl acetate–pyridine–water (10:4:3) and in methyl ethyl ketone–water (92:8). Carbohydrate components were located by their reaction with periodate/benzidene spray.[17] R_f values were compared with those of authentic alditols and 1,4-anhydroalditols.

Quantitative analysis of the reaction mixtures was performed by gas chromatographic analysis of the acetate and silyl derivatives using 10% polyethylene glycol sebacate on Chromosorb Q. The acetates were formed by treatment of samples (20 mg) with pyridine (0.2 ml) and acetic anhydride (0.1 ml) and separation was achieved at a column temperature of 220°. The silyl ethers were prepared by treatment of samples (50 mg) with pyridine (0.2 ml), trimethylchlorosilane (0.2 ml), and hexamethyldisilazane (0.1 ml), and separation was achieved at a column temperature of 130°. The retention times of the products were compared with those of authentic materials. The molar responses of the alditols and their 1,4 anhydrides were established using authentic materials. The compositions of the deamination mixtures were calculated from the molar responses and are shown in Table I.

To determine the reliability of the procedure, deaminations were performed in the presence of a known proportion of a pentitol which would not be formed in the reaction. (For example, ribitol was added to 1-amino-1-deoxy-D-arabinitol hydrochloride prior to deamination.) The reaction was processed as described and analyzed by gas chromatography. The proportion of ribitol in the products was used as an index of recovery of the alditol and anhydrides. In all cases it was found that at least 80% of the amine had been converted into alditol or anhydrides.

N-Nitrosobis(1-deoxy-D-arabinitol)amine.—In the experiments involving deamination of 1-amino-1-deoxy-D-arabinitol, which had not been purified *via* the salicylidene derivative, the formation of a polyhydroxy compound which strongly absorbed in the uv was observed. This component is fairly insoluble in water, and in one experiment crystallized from the deamination mixture. After several recrystallizations, it had mp 210° and $[\alpha]_D$ +39.2° (*c* 1.84, H_2O).

The compound had E^{M}_{237} 8.75 × 10^2 and E^{M}_{346} 22.6. It gave an atypical Liebermann nitroso test in which the first color obtained was royal blue. The compound consumed 1.0 mmol of periodate/53.0 mg of sample.

Anal. Calcd for $C_{10}H_{22}N_2O_9$: C, 38.2; H, 7.06; N, 8.86; mol wt, 314.3. Found: C, 38.02; H, 7.03; N, 8.94; mol wt, 340 ± 40.

A benzoate, prepared in the usual fashion, had mp 80° and $[\alpha]^{25}_D$ +58.2 (*c* 1.77, $CHCl_3$).

Anal. Calcd for $C_{66}H_{54}N_2O_{17}$: C, 69.2; H, 4.70; N, 2.44; mol wt, 1147. Found: C, 69.8; H, 4.84; N, 2.54; mol wt, 1260 ± 100.

Bis(1-deoxy-D-arabinitol)amine.—Catalytic reduction of the nitroso compound over platinum gave an amine, mp 173.6, $[\alpha]_D$ −10° (*c* 1, H_2O), and pK_a' 7.75, which did not react with salicaldehyde, but which gave a crystalline hydrochloride, mp 199–201 and $[\alpha]_D$ +23° (c 2, H_2O). This amine could be quantitatively converted into the nitroso compound.

Kinetics of Deamination.—Attempts were made to estimate the rates of deamination of the 1-amino-1-deoxypentitol hydrochlorides by measurement of the evolution of nitrogen during reaction; however, reproducible results could not be obtained.

Reproducible results were obtained using a modification of Sorensen's formaldehyde titration as described by Taylor for the measurement of the deamination of aliphatic amino acids.[18]

A solution containing 1 ml of 0.1 *N* 1-amino-1-deoxypentitol hydrochloride and 0.5 ml of 0.2 *N* hydrochloric acid at 25° was mixed with 0.5 ml of 0.4 *N* sodium nitrite. Aliquots (100 μl) were withdrawn at intervals and were immediately mixed with 2 ml of 0.005 *N* sodium hydroxide and 1 ml of water. The pH of the solution was adjusted to 8.5. This solution was mixed with 1 ml of a 20% solution of formaldehyde, which had also been adjusted to pH 8.5. The solution was then purged with argon to prevent absorption of carbon dioxide and was titrated in a 3-min period with 0.001 *N* hydroxide to pH 8.5. All of the 1-amino-1-deoxypentitols were deaminated at approximately the same rate, $k = 0.253 \pm 0.04$ sec^{-1}.[19]

Registry No.—*N*-Nitrosobis(1-deoxy-D-arabinitol)-amine, 22566-20-7; *N*-nitrosobis(1-deoxy-D-arabinitol-amine) benzoate, 22566-21-8; bis(1-deoxy-D-arabinitol)-amine, 22566-22-9; bis(1-deoxy-D-arabinitol)amine hydrochloride, 22566-23-0.

(16) Avicel F. M. C. Corp., Newark, Del.

(17) J. A. Cifonelli and F. Smith, *Anal. Chem.*, **26**, 1132 (1954).

(18) T. W. J. Taylor, *J. Chem. Soc.*, 1897 (1928).

(19) T. W. J. Taylor, *ibid.*, 1099 (1928).

Total Synthesis of Modified Steroids. II. 8β-Methyl-D-homoestranes[1]

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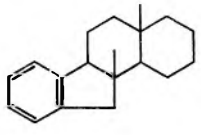
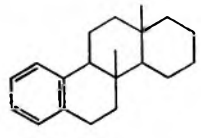
Received June 19, 1969

Synthetic methods have been developed for the preparation of 3-methoxy-8β-methyl-D-homoestra-1,3,5(10),-9(11),14-pentaen-17a-one by two routes. The first of these involved the alkylation of **3** with 2-bromo-3′-methoxyacetophenone, which could be converted into the key intermediate **24**, 3,7,8,8a-tetrahydro-5α-(*m*-methoxyphenethyl)-5β,8aβ-dimethyl-1,6(2H,5H)-naphthalenedione, by a variety of methods. The alternate route proceeded through the allyl derivative **16**, which was transformed into the aldehyde **18** in two steps. Reaction of **18** with *m*-methoxyphenylmagnesium bromide gave **10**, which on reduction and hydrolysis afforded the same intermediate **24**. Acid-catalyzed cyclization of **24** then yielded the D-homo steroid **26**.

The previous paper[1] in this series described the total synthesis of compounds related to 8β-methyl-D-homo-B-norestrane (**1**). Since these compounds are structurally further removed from the natural steroids than the corresponding homolog **2**, a synthesis of the latter system was developed utilizing intermediates already available from the preparation of **1**.



1



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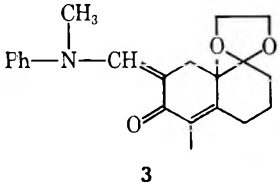
The synthesis of **1** was essentially completed when **3**[3,4] was successfully alkylated with *m*-methoxybenzyl chloride. A similar process for the preparation of **2** would require that **3** be alkylated with *m*-methoxyphenethyl bromide or some equivalent thereof. Although this reagent has been employed for the alkylation of several enolate anions,[5] the pronounced tendency for the bromine to undergo elimination to give the corresponding styrene rather than displacement has severely limited its use. Nevertheless the method, by virtue of its directness, was attractive and alkylation of **3** by *m*-methoxyphenethyl bromide was attempted. No evidence was obtained for the formation



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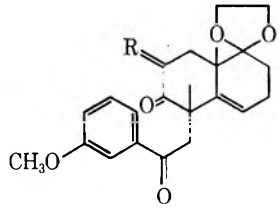


4, R = $CHN(CH_3)Ph$
5, R = H_2

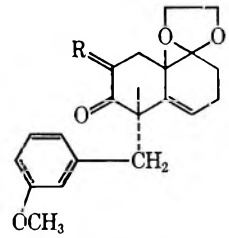
of even small amounts of the desired alkylation product under a wide variety of reaction conditions.

An obvious alternative to *m*-methoxyphenethyl bromide was the commercially available 2-bromo-3′-methoxyacetophenone. It was anticipated that the most serious side reaction in the use of this compound under strongly basic conditions would be that of self-condensation.[6] The anion of **3** prepared by

$$2PhCOCH_2Br \longrightarrow PhCOCH{=}CHCOPh$$

treatment with sodium hydride in dimethoxyethane is stable for extended periods. This fact allowed conditions to be defined under which self-condensation was minimized if not eliminated. Experimentally, it was found that both the temperature and rate of addition of the 2-bromo-3′-methoxyacetophenone were of prime importance. These are the factors which would be expected to effect the rate of self-condensation. By employing low temperatures (0–5°) and a slow rate of addition of the alkylating agent, an 80–90% yield of **4** could be realized. When the reaction was carried out on a large scale, the phenacyl bromide was conveniently added overnight in a cold room by means of an electric pump. It has been established[1] that alkylation of **3** with *m*-methoxybenzyl chloride occurs exclusively from the α side. It is therefore reasonable to assume that the product **4** has the relative stereochemistry shown.

Hydrolysis of **4** by a strong base[3] proved to be more difficult than that of the corresponding benzyl product **6**, which gave **7** in essentially quantitative



6, R = $CHN(CH_3)Ph$
7, R = H_2

yield. Under similar conditions **4** afforded a mixture which was readily separated into neutral and acidic fractions. The neutral product obtained in 60% yield was the desired ketone **5**, whereas the acidic material proved to be the β-keto aldehyde **8**. The nmr spectrum of **8** clearly showed the aldehydic proton at τ 0.62 as well as the enolic hydroxyl proton at τ −0.11. The increased stability of **8** to strong base over the

(1) Part I: D. J. France, J. J. Hand, and M. Los, *Tetrahedron*, **25**, 4011 (1969).

(2) To whom correspondence should be addressed.

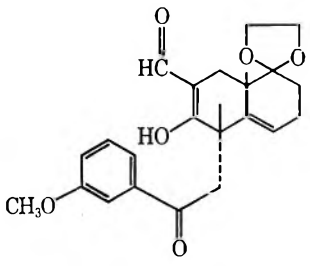
(3) Y. Kitahara, A. Yoshikoshi, and S. Oida, *Tetrahedron Lett.*, 1763 (1964).

(4) Structural formulas containing one or more asymmetric carbon atoms depict one diastereomer but refer to racemic compounds throughout. Each racemate is arbitrarily represented by the diastereomer having the C-13 methyl group (steroid numbering) in the β configuration.

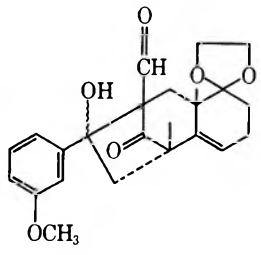
(5) See, *e.g.*, G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. T. McLoughlin, J. Siddall, and H. Smith, *J. Chem. Soc.*, 5072 (1963), and references cited therein.

(6) B. M. Bogoslovskii, *J. Gen. Chem. USSR*, **14**, 993 (1944); *Chem. Abstr.*, **39**, 4600 (1945).

corresponding benzyl analog must be attributed to the presence of the phenacyl carbonyl group. It has been established[7] that under basic conditions **8** is in equilibrium with **9**, with the result that β-diketone cleavage is retarded.

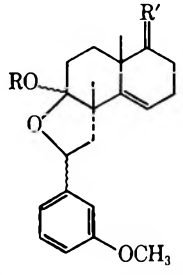


8



9

When **5** was catalytically reduced in methanol at 60°, 1 equiv of hydrogen was absorbed and two products were isolated in varying amounts. These proved to be the hemiketal **10** and the mixed ketal **11**. On one occasion **11** was the sole product. The variation in the ratio of products **10** and **11** is undoubtedly due



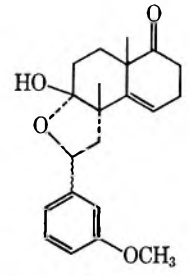
10, R = H; R′ = OCH_2CH_2O
11, R = CH_3; R′ = OCH_2CH_2O
12, R = C_2H_5; R′ = OCH_2CH_2O
13, R = H; R′ = O

to traces of acid in the reaction medium. Similar reduction of **5** in ethanol gave the corresponding ethyl ketal **12**. Treatment of **10** with methanol or ethanol containing a trace of acetic acid resulted in complete conversion into the mixed ketals **11** and **12**, respectively.

That these compounds are mixtures of isomers is indicated by broad melting point range and variable ir and nmr spectra. Thus, two sets of signals are visible at τ 4.0–5.5 for the benzylic and vinyl protons in the nmr spectra. It is noteworthy that this method for the preparation of compounds **10**–**12** is highly stereoselective in that the crude product is predominantly one isomer which can be obtained pure, whereas **10** synthesized by the alternate route described below yields essentially equal amounts of two isomers.

Hydrolysis of **10** or **11** or mixtures of these compounds with aqueous acetic acid yielded the ketone **13**. In this case a complete separation of the two isomers was achieved. It is reasonable to assume that the asymmetric center involving the hemiketal function is the same in both cases, since they were subjected to equilibrating conditions. Further, it would be expected that the hydroxyl group would adopt the β configuration to give a relatively strainless *cis*-fused furan ring. If, then, these compounds differ only in the configuration of the phenyl group, they should be distinguishable by variable-temperature nmr. The isomer in which the phenyl group is β (*cis* to the methyl groups) should cause a shift in the position of the furan ring methyl resonance as the rate of rotation of the phenyl group is decreased. In contrast, a shift would not be expected in the other isomer.

The nmr spectrum of the major isomer of **13** at 40° showed the methyl groups as two cleanly separated peaks. At −30° one of these peaks was shifted so that the methyl groups resonated at essentially the same place. The spectrum of the minor isomer of **13**, on the other hand, showed the methyl groups as a singlet at 40° unchanged by lowering the temperature. Based on this evidence, structure **14** is tentatively assigned to the major isomer.



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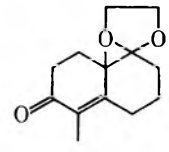
An alternative route to **10** was developed which avoided the use of the blocked ketone **3** and thus eliminated the hydrolysis step. Although direct alkylation of **15** with phenacyl bromide was unsuccessful, good yields of the alkylated product **16** were ob-



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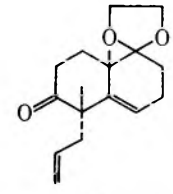
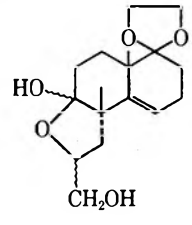


16

tained with allyl bromide.[8] Reaction of **16** with sodium chlorate in the presence of catalytic amounts of osmium tetroxide[9] resulted in complete conversion into a hydroxylated product to which structure **17** was assigned, since its ir spectrum was devoid of



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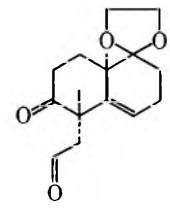

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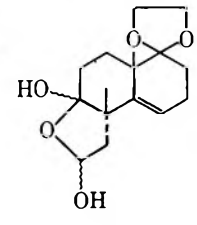


19

carbonyl absorption bands. That **17** was also a mixture was indicated by wide melting point range and variable ir and nmr spectra. Oxidation of this mixture by sodium metaperiodate[9] gave a quantitative yield of the aldehyde **18**. Frequently, **18** was accompanied by a much more polar compound whose ir spectrum showed strong OH but no carbonyl bands. Formulation of this material as the hydrate **19** is

(7) J. J. Hand and M. Los, *Chem. Commun.*, 673 (1969).

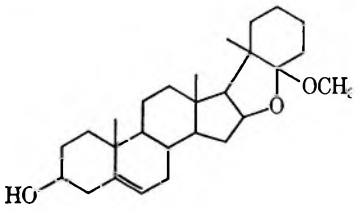
(8) Similarly, the compounds described in part I can be prepared by the direct alkylation of **15** with benzyl chloride.

(9) K. Wiesner, K. K. Chan, and C. Demerson, *Tetrahedron Lett.*, 2893 (1965).

further supported by analytical data as well as the fact that it is quantitatively converted into the aldehyde **18** when passed through a short column of alumina in methylene chloride.

A study of the reaction between the aldehyde **18** and *m*-methoxyphenylmagnesium bromide was necessary to obtain satisfactory yields of the hemiketal **10**. This was somewhat surprising.[10] Titration of aldehyde **18** with the Grignard reagent at room temperature showed that 3 equiv were consumed before a positive Gilman test was obtained. These data are difficult to rationalize, since enolization of both carbonyl groups would require only 2 equiv and acceptable yields of **10** could be isolated from the reaction. It was found experimentally that, when a 20% excess of Grignard reagent was added all at once to **18** at −20°, a 76% yield of **10** could be isolated.

Uhle[11] recently reported the conversion of the ketal **20** into the keto acetate **21** by heating **20** with a mixture of acetic acid and acetic anhydride. When **13**



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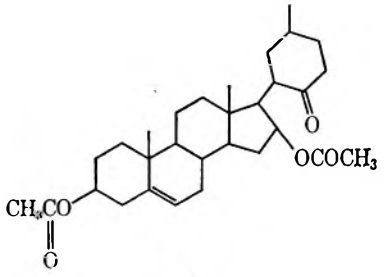
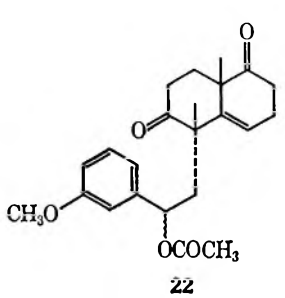


21

was subjected to these conditions, an oily product was formed whose ir spectrum indicated that a similar reaction had occurred to give **22**. An attempt to cyclodehydrate **22** to a tetracyclic compound by treatment with *p*-toluenesulfonic acid in benzene resulted instead in the elimination of the acetoxy group to form in moderate yield the styrene **23**. The nmr spectrum of **23** showed the styrene vinyl protons as a quartet with J = 16 Hz, indicating a *trans* configuration about this double bond. Reduction of this double bond then gave **24**.



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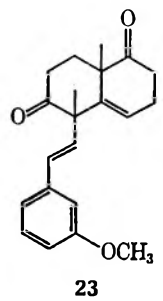

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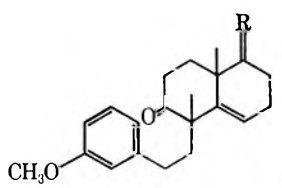
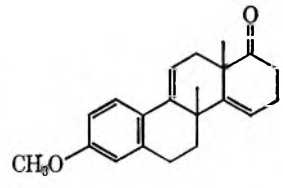


24, R = O
25, R = OCH_2CH_2O



26

Although all the compounds **10**–**12** could be efficiently converted into **24** through **25** by further catalytic reduction in acetic acid at 70° and 3 atm, the most direct route to **24** was that of direct reduction of **5** under the same conditions. Partial hydrolysis of the ketal group invariably occurred during the isolation of **25**, so that the crude product was acid hydrolyzed immediately to the dione **24**.

When the dione **24** was treated with concentrated hydrochloric acid in acetic acid overnight, the 8β-methyl-D-homoestrane **26** was obtained in essentially quantitative yield. The more commonly used reagents for effecting this type of cyclodehydration (polyphosphoric acid, hydrofluoric acid, hydrochloric acid in ethanol, and *p*-toluenesulfonic acid in benzene[5]) gave greatly reduced yields of **26**.

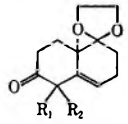
Experimental Section[12]

3′,7′,8′,8′a-Tetrahydro-5′α-(*m*-methoxyphenacyl)-5′β,8′aβ-dimethyl-7′-(N-methylanilinomethylene)spiro[1,3-dioxolane-2,1′-(2′H)-naphthalen]-6′(5′H)-one (4).—To a solution containing 52.95 g (0.15 mol) of **3** in 600 ml of dry dimethoxyethane under nitrogen was added 8.5 g (0.27 mol) of sodium hydride as a 54% suspension in mineral oil. The mixture was heated under reflux with stirring for 2 hr and then cooled in an ice–water bath. A solution of 51.45 g (0.224 mol) of 2-bromo-3′-methoxyacetophenone in 500 ml of dry dimethoxyethane was added at ice-bath temperature during a 4.2-hr period. After the solution had stood overnight, water was added followed by excess 2.5 *M* sodium dihydrogen phosphate solution. The mixture was extracted twice with methylene chloride, and the combined extracts were washed twice with water and dried over sodium sulfate. Removal of the solvent left a crystalline residue which on recrystallization from acetone gave 63.9 g (85%) of **4**, mp 161–164.5°. Two further recrystallizations from acetone afforded an analytical sample: mp 169–170°; ir 1700, 1650, 1580, and 1540 cm^{-1}; nmr τ 4.58 (t, 1, C=CH), 6.20 (s, 3, OCH_3), 6.43 (s, 4 OCH_2CH_2O), 6.61 (s, 3, NCH_3), 8.59 (s, 3, CCH_3), and 8.86 (s, 3, CCH_3).

Anal. Calcd for $C_{31}H_{35}O_5N$: C, 74.23; H, 7.03; N, 2.79. Found: C, 74.39; H, 7.20; N, 2.36.

3′,7′,8′,8′a-Tetrahydro-5′α-(*m*-methoxyphenacyl)-5′β,8′aβ-dimethylspiro[1,3-dioxolane-2,1′(2′H)-naphthalen]-6′(5′H)-one (5) and 3′,7′,8′,8′a-tetrahydro-7′-hydroxymethylene)-5′α-(*m*-methoxyphenacyl)-5′β,8′aβ-dimethylspiro[1,3-dioxolane-2,1′(2′H)-naphthalen]-6′(5′H)-one (8).—To a solution containing 91.8 g of **4** in 610 ml of 2-ethoxyethanol was added 610 ml of water containing 258 g of potassium hydroxide. The solu-

(10) Compounds of type A, where R_1 and R_2 are alkyl groups, have been



A

found to be completely inert to Grignard and alkyllithium reagents (unpublished results from these laboratories).

(11) F. C. Uhle, *J. Org. Chem.*, **31**, 4193 (1966).

(12) Melting points were determined on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined as Nujol mulls or films using a Perkin-Elmer Infracord (Model 137). Proton nmr spectra were determined in deuteriochloroform solution with a Varian A-60A spectrometer with TMS as internal standard. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

tion was heated under reflux in a nitrogen atmosphere for 6 hr. After standing overnight, the solution was diluted with 2 l. of water and extracted twice with ether. The aqueous phase was retained. The extract was washed successively twice with water, once with cold 2 *N* hydrochloric acid, and three times with water. The organic phase was dried over sodium sulfate, the solvent was evaporated, and the residue was triturated with ether to give 43.7 g (62%) of the dione **5**, mp 104–118°. Two recrystallizations of this material from acetone–hexane gave the analytical sample: mp 121–122°; ir 1710, 1690 (C=O), 1650 (C=C), 1610, and 1580 cm^{-1} (phenyl); nmr τ 4.61 (t, 1, C=CH), 6.04 (s, 4, OCH_2-CH_2O), 6.22 (s, 3, OCH_3), and 8.68 (s, 6, 2 CCH_3).

Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.59; H, 7.34.

The aqueous phase from the original extraction was acidified with ice-cold 2 *N* hydrochloric acid and extracted three times with methylene chloride. The combined extract was washed twice with water and brine and dried over sodium sulfate. Evaporation of the solvent and trituration of the residue with ether gave the 13.8 g (18%) of the β-keto aldehyde **8**, mp 165–166°. Recrystallization from methanol gave an analytically pure sample: mp 157–160.5°; ir 1720, 1650, and 1590 cm^{-1}; nmr τ −0.11 (s, 1, enolic OH), 0.62 (s, 1, CHO), 4.26 (t, 1, C=CH), 6.01 (m, 4, OCH_2CH_2O), 6.21 (s, 3, OCH_3), 8.68 (s, 3, CCH_3), and 8.73 (s, 3, CCH_3).

Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.57; H, 6.89.

2′,3′a,4′,5′,5′a,7′,8′,9′b-Octahydro-2′ξ-(*m*-methoxyphenyl)-5′aβ,9′bβ-dimethylspiro[1,3-dioxolane-2,6′(1′H)-naphtho[2,1-*b*]furan]-3′aξ-ol (10) and the Corresponding Methyl Ether 11 and Ethyl Ether 12.—A solution of 10 g of **5** in 180 ml of methanol was reduced with hydrogen at 60° and 3 atm in the presence of 1.5 g of 5% palladium on carbon for 1 hr. The catalyst was removed by filtration and the solvent was evaporated. The residue was crystallized from acetone–hexane to give 5.4 g of the hemiketal **10**. The ir spectrum of this material varies with the sample in the fingerprint region. In all cases, however, no carbonyl band is evident but a strong OH band is present, sometimes as a doublet. Material recrystallized twice from methyl isobutyl ketone gave the following data: mp 153–159°; ir 3400 cm^{-1} (OH); nmr τ 4.61 (t, 1, C=CH), 4.93 (t, 1, PhCH), 6.05 (s, 4, OCH_2CH_2O), 6.22 (s, 3, OCH_3), and 8.65 and 8.67 (d, 6, 2 CCH_3).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.24; H, 7.97.

The mother liquors after removal of **10** were concentrated and the residue was crystallized from hexane to give 2.2 g of methyl ether **11**, mp 80–87°. Two further crystallizations from hexane gave an analytical sample: mp 88–92°; ir shows no OH or C=O bands; nmr τ 4.60 (m, 1, C=CH), 5.18 (t, 1, PhCH), 6.06 (s, 4, OCH_2CH_2O), 6.22 (s, 3, $PhOCH_3$), 6.71 (s, 3, OCH_3), and 8.68 (s, 6, 2CCH_3).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.93; H, 8.09.

A solution of 1 g of **10** in 25 ml of absolute methanol and 2 drops of glacial acetic acid was heated under reflux for 4 hr. The acid was neutralized by the addition of triethylamine and the mixture was poured into water. The solution was extracted with ether and the extract was washed with water and dried over sodium sulfate. Evaporation of the solvent and crystallization of the residue from hexane gave a quantitative yield of the methyl ether **11**.

Reduction of **5** in ethanol afforded the corresponding ethyl ether **12**: mp 93–94° (from hexane); nmr τ 4.68 (t, 1, C=CH) 5.13 (t, 1, PhCH), 6.04 (s, 4, OCH_2CH_2O), 6.21 (s, 3, OCH_3), 6.38 (q, 2, CH_3CH_2), 8.66 (s, 6, 2 CCH_3), and 8.81 (t, 3, CH_3-CH_2).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.23; H, 8.42.

1,2,3a,4,5,5a,9,9b-Octahydro-3aα-hydroxy-2ξ-(*m*-methoxyphenyl)-5aβ,9bβ-dimethylnaphtho[2,1-*b*]furan-6(7H)-one (13).—Hydrolysis of the crude product from the reduction of 10 g of **5** in methanol with 25% aqueous acetic acid at 90° for 1 hr and isolation of the product by ether extraction gave a crude product which on crystallization from acetone–hexane afforded 6.1 g (69%) of one isomer of **13**, mp 131–138°. Three recrystallizations of this material from the same solvents gave an analytical sample: mp 135.5–138.5°; ir 3450 (OH) and 1700 cm^{-1} (C=O); nmr τ 4.41 (m, 1, C=CH), 4.81 (m, 1, PhCH), 6.26 (s, 3, OCH_3), 8.63 (s, 3, CCH_3), and 8.68 (s, 3, CCH_3). When the nmr spectrum was recorded at −30° the methyl signals appeared as a singlet at τ 8.69.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.60; H, 7.59.

Concentration of the mother liquors gave the second crystalline isomer of **13**, mp 129–131°. The analytical sample was obtained from acetone–hexane: mp 132.5–133.5°; ir 3500 (OH) and 1700 cm^{-1} (C=O); nmr τ 3.94 (m, 1, C=CH), 5.22 (m, 1, PhCH), 6.22 (s, 3, OCH_3), and 8.64 (s, 6, 2 CCH_3). The position of the methyl signal was unchanged when the spectrum was run at −30°.

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.82; H, 7.36.

5′α-Allyl-3′,7′,8′,8′a-tetrahydro-5′,β,8′aβ-dimethylspiro[1,3-dioxolane-2,1′(2′H)-naphthalen]-6′(5′H)-one (16).—To a stirred solution of 4.7 g (20 mmol) of the ketone **15** in 100 ml of dry *t*-butyl alcohol under nitrogen was added 5.60 g (50 mmol) of potassium *t*-butoxide. The mixture was heated under reflux for 2 hr and cooled to room temperature, and 2.9 g (22 mmol) of allyl bromide was added. The solution was stirred for 0.5 hr, diluted with water, and extracted twice with ether. The combined extracts were washed twice with water and saturated brine and dried over sodium sulfate. Evaporation of the solvent gave an oil which was crystallized from a small volume of hexane, giving 3.3 g (60%) of the allyl compound **16**, mp 64–65.5°. Two recrystallizations from the same solvent gave an analytical sample: mp 67.5–68.5°; ir 1700 (C=O), 1650, and 1640 cm^{-1} (C=C); nmr τ 3.9–5.3 (m, 4, vinyl H), 6.0 (s, 4, OCH_2CH_2O), 8.78 (s, 3, CCH_3), and 8.92 (s, 3, CCH_3).

2′,3′a,4′,5′,5′a,7′,8′,9′b-Octahydro-3′aξ-hydroxy-5′aβ,9′bβ-dimethylspiro[1,3-dioxolane-2,6′(1′H)-naphtho[2,1-*b*]furan-2′ξ-methanol (17).—To a solution containing 27.6 g (0.1 mol) of **16** in 450 ml of tetrahydrofuran was added a solution of 12.8 g (0.12 mol) of sodium chlorate in 200 ml of water. After 2 ml of a standard solution containing 1 mmol of osmium tetroxide in 5 ml of water was added, the mixture was stored in the dark for 64 hr. Two such reaction mixtures were combined and a solution of 575 g of sodium sulfite in 2.5 l. of water was added. The mixture was shaken thoroughly and extracted twice with methylene chloride. The combined extract was washed with saturated brine and dried over sodium sulfate, and the solvent was evaporated. The residue was crystallized from ether, giving 49.9 g of **17**, mp 122–136°. A second crop of **17** weighed 4.4 g (total yield, 87.5%). A sample was recrystallized twice from acetonitrile: mp 140–160° (with bubbling); ir 3450 cm^{-1} (OH).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.73; H, 8.14.

5′α-Formylmethyl-3′,7′,8′,8′a-tetrahydro-5′β,8′aβ-dimethylspiro[1,3-dioxolane-2,1′(2′H)-naphthalen]-6′(5′H)-one (18) and 2′,3′a,4′,5′,5′a,7′,8′,9′b-Octahydro-5′aβ,9′bβ-dimethylspiro-[1,3-dioxolane-2,1′(2′H)-naphtho[2,1-*b*]furan-2′,3′aξ-diol (19).—To a stirred solution containing 49.9 g (0.18 mol) of **17** in 480 ml of tetrahydrofuran was added slowly 74.1 g (0.346 mol) of sodium periodate in 480 ml of water. An ice–water cooling bath was used to maintain a temperature of 18–20° during the addition. The mixture was stirred overnight and thoroughly shaken with a solution of 230 g of sodium sulfite in 800 ml of water, and the product was extracted into methylene chloride. The extract was washed with saturated brine and dried over sodium sulfate, and the solvent was evaporated. The residue was crystallized from ether–hexane to afford 39.2 g (87.5%) of the aldehyde **18**: mp 61–62.5°; ir 2750 (aldehyde CH), 1710, 1700 (C=O), and 1640 cm^{-1} (C=C); nmr τ 0.43 (t, 1, CHO), 4.48 (t, 1, C=CH), 5.96 (s, 4, OCH_2CH_2O), and 8.62 (s, 6, 2 CCH_3).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.75; H, 7.97.

From many preparations of the aldehyde, varying amounts of a compound less soluble in acetone–hexane than **18** were isolated. This product is formulated as the hydrate **19**. Two recrystallizations from acetone gave an analytical sample: mp 116–130°; ir 3500 and 3600 cm^{-1} (OH), no carbonyl band; nmr showed *ca.* 30% dissociation to the free aldehyde **18** as determined by the intensity of the aldehyde CH band. The methyl groups appeared at τ 3.65 and 8.73.

Anal. Calcd for $C_{16}H_{24}O_5$: C, 64.85; H, 8.16. Found: C, 64.82; H, 8.23.

Preparation of the Hemiketal 10 from the Aldehyde 18.—A stirred solution containing 40.7 g (0.147 mol) of **18** in 500 ml of dry tetrahydrofuran under nitrogen was cooled to −20°. At

this temperature 194 ml of a 0.91 *M* solution of *m*-methoxyphenylmagnesium bromide in tetrahydrofuran was added in one portion. After 5 min, 150 ml of saturated aqueous sodium dihydrogen phosphate was added. Salts were removed by filtration and washed with tetrahydrofuran. The aqueous phase was separated, the organic phase was washed with saturated brine, and the solvent was evaporated. The residue was dissolved in ether, the ether was dried over sodium sulfate, and the solvent was evaporated. The residue was crystallized from ether–hexane to give 43.1 g (77.5%) of the hemiketal **10**, mp 133–143°. This product is a mixture of isomers. The analytical sample was obtained from acetone, mp 132–180°.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.97; H, 8.25.

The analytical sample of the ethyl ether **12** was prepared from the above hemiketal by treatment with ethanol and acetic acid, mp 112–126°.

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.18; H, 8.30.

3,7,8,8a-Tetrahydro-5α-(*m*-methoxystyryl)-5β,8aβ-dimethyl-1,6(2H,5H)-naphthalenedione (23).—A solution of 5.0 g of the hemiketal **13** in 80 ml of acetic acid and 40 ml of acetic anhydride was heated under reflux for 1 hr. The solvents were removed, the residue was dissolved in toluene, and the solvent was again evaporated. The residue was an oil, consisting mainly of the acetate **22**, ir 1740 (acetate C=O) and 1710 cm^{-1} (C=O).

A solution of 2.0 g of *p*-toluenesulfonic acid in 170 ml of benzene was heated under reflux under a Dean–Stark water separator for 20 min. The crude acetate prepared above in 40 ml of benzene was added and heating was continued for 1 hr. The cooled solution was diluted with ether, washed with saturated sodium bicarbonate solution, and dried over sodium sulfate, and the solvent was evaporated. The residue was crystallized from methanol, affording 1.8 g of the styrene **23**. Recrystallization from methanol gave 1.5 g of **23**, mp 89.5–92°. One further recrystallization gave an analytical sample: mp 91–92°; ir 1700 (C=O), 1640 (C=C), and 1600 cm^{-1} (phenyl); nmr τ 3.52 (d, 1, J = 16 Hz, PhCH=CH), 3.90 (d, 1, J = 16 Hz, PhCH=CH), 4.04 (m, 1, C=CH), 6.18 (s, 3, OCH_3), 8.48 (s, 3, CCH_3), and 8.78 (s, 3, CCH_3).

Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.57; H, 7.51.

3,7,8,8a-Tetrahydro-5α-(*m*-methoxyphenethyl)-5β,8aβ-dimethyl-1,6(2H,5H)-naphthalenedione (24). **A.**—A solution containing 324 mg (1 mmol) of **23** in 15 ml of ethanol was reduced with hydrogen at room temperature and atmospheric pressure in the presence of 50 mg of 5% palladium on carbon. Reduction was complete in 4 min. The catalyst was removed and the solvent was evaporated. Crystallization of the residue from ether–hexane gave 283 mg of dione **24**: mp 69–71°; ir 1700 (C=O), 1650 (C=C), 1610, and 1580 cm^{-1} (phenyl); nmr τ 4.11 (m, 1, C=CH), 6.23 (s, 3, OCH_3), 8.65 (s, 3, CCH_3), and 8.76 (s, 3, CCH_3).

Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.39; H, 7.93.

B.—A solution containing 20 g of **5** in 200 ml of acetic acid was reduced with hydrogen at 70° and 3 atm in the presence of 1.0 g of 5% palladium hydroxide on carbon. Reduction was complete in 3.5 hr. The catalyst was removed and the solvent was evaporated. The residue consisted mainly of the ketal **25** together with varying amounts of the dione **24**.

To the residue in 60 ml of tetrahydrofuran was added 48 ml of 2.6 *N* perchloric acid. After 0.5 hr the solution was diluted with water and extracted with ether. The extract was washed twice with water and dried over sodium sulfate. Evaporation of the solvent and crystallization of the residue from ether–hexane gave 16.6 g (96%) of dione **24**, mp 68–70°, identical with that prepared above.

C.—Reduction of the hemiketal **10** under the same conditions described in B followed by hydrolysis gave a similar yield of the dione **24**.

3-Methoxy-8β-methyl-D-homoestra-1,3,5(10),9(11),14-pentaen-17a-one (26).—To 21.5 g of the dione **24** in 170 ml of acetic acid was added 17 ml of concentrated hydrochloric acid. After standing overnight at room temperature, the mixture was poured into water and extracted with ether. The extract was washed twice with water followed by cold 1 *N* sodium hydroxide, water, and saturated brine, and dried over sodium sulfate. The solvent was evaporated to give 19.7 g (97%) of crystalline **26**, mp 89–95.5°. Two recrystallizations from 2-propanol gave an analytical sample: mp 97–97.5°; λ_{max}^{MeOH} 257 mμ (ε 18,300) [3-methoxy-D-homoestra-1,3,5(10),9(11)-tetraen-17a-one is reported[5] to have λ_{max}^{EtOH} 262 mμ (ε 18,700)]; ir 1710 (C=O), 1650, 1640 (C=C), 1610, and 1570 cm^{-1} (phenyl); nmr τ 4.16 (m, 2, 2 C=CH), 6.23 (s, 3, OCH_3), 8.54 (s, C, CCH_3), and 8.78 (s, 3, CCH_3).

Anal. Calcd for $C_{21}H_{24}O_2$: C, 81.78; H, 7.84. Found: C, 81.70; H, 7.90.

Registry No.—**4,** 22430-84-8; **5,** 22430-85-9; **8,** 22430-86-0; **10,** 22430-87-1; **11,** 22430-88-2; **12,** 22487-51-0; **13,** 22430-89-3; **16,** 22430-90-6; **17,** 22430-91-7; **18,** 22430-92-8; **19,** 22430-93-9; **23,** 22430-94-0; **24,** 22430-95-1; **26,** 22430-96-2.

Acknowledgment.—The authors wish to thank Mr. R. S. Wayne for helpful discussion concerning nmr spectra, Professor K. B. Wiberg for stimulating discussion throughout the course of this work, and Dr. M. W. Bullock for his help and encouragement.

Studies on Resin Acids. IV. The Structure, Stereochemistry, and Reactions of Some Dihydroabietic Acids[1]

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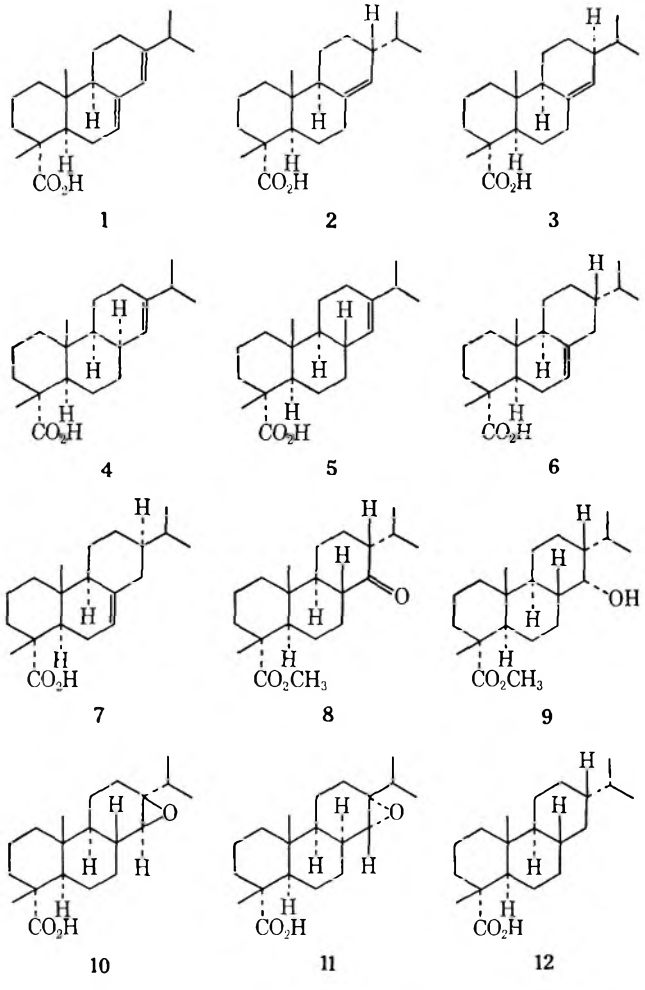
Received June 30, 1969

Unequivocal syntheses of 8α-abiet-13-en-18-oic (**4**), abiet-13-en-18-oic (**5**), and abiet-7-en-18-oic acids (**6**) are described. The stereochemical course of various reactions of these compounds as well as those of the two abiet-8-(14)-en-18-oic acids (**2** and **3**) are discussed.

Direct reduction of abietic acid (**1**) by either chemical or catalytic methods may, in theory, give rise to six different dihydro acids (**2**–**7**). At the time this work was initiated, the structure and stereochemistry of only one of these acids (**2**) was known with certainty,[1,3] although a number of other dihydroabietic acids had been prepared and characterized.[4] Following the initiation of this work, we learned that acids **3**, **5**, and **6** had been obtained and identified in addition to **2** from the lithium–ammonia reduction of abietic acid,[5] and structure **7** had been assigned to one of the acids obtained by Velluz, *et al.*[4b] In earlier work in this laboratory, structure **4** had been assigned to the Δ^{13}-dihydro acid, which is present to the extent of *ca.* 15% in most samples of **2** prepared by reduction of abietic acid;[1] however, Burgstahler, Marx, and Zinkel[5] present rather convincing evidence that this impurity is in fact **5**. The earlier assignment of stereochemistry was based on the course of the rearrangement of an epoxide obtained in low yield from the oxidation of a sample of **2** obtained in the usual manner.[1] In order to reconcile this discrepancy, and also to confirm the structural and stereochemical assignments made by Burgstahler, *et al*,[5] the preparation of acids **4**–**6** by unambiguous routes has been carried out.



The synthesis of **5** was accomplished by first reducing the known[1,5] methyl 14-oxoabietan-18-oate (**8**) with sodium borohydride to give the 14α (axial) alcohol (**9**) contaminated with a small quantity of another alcohol, presumably the 14β-ol. The nmr spectrum of **9** was in accord with that expected for an axial alcohol, with H-14 appearing as a broadened singlet at δ 3.72 and the C-10 methyl peak at relatively high field (δ 0.84) as expected for a compound with a *trans* B,C-ring fusion.[1] Dehydration of this alcohol with phosphorus oxychloride–pyridine and hydrolysis of the esters afforded a mixture of the corresponding acids, from which **5** contaminated with a few per cent of **2** could be obtained. The nmr spectrum of **5** was in agreement with the assigned structure, showing the C-10 methyl signal at δ 0.86. Reaction of **5** with *m*-chloroperbenzoic acid gave epoxide **10**, which was markedly different from that reported earlier and assigned structure **11**.[1] By analogy with the hydrogenation of **5**, which affords almost exclusively abietan-18-oic acid (**12**),[1,5] and hydroboration of the methyl ester of **5**, which gives methyl 14β-hydroxyabietan-18-oate (**13**), it is assumed that **10** is the β oxide.

While this work was in progress, Cross and Myers obtained a glycol from the osmylation of the usual mixture of **2** and **4** or **5**[6] to which they assigned structure **14**; however, when acid **5** was treated with osmium tetroxide, a glycol was obtained which was identical with that prepared by Cross and Myers.[7] The nmr spectrum of this glycol showed H-14 as a doublet with a coupling constant of 9 Hz, indicating a *trans*-diaxial relationship between H-8 and H-14, and on

(1) Part III: J. W. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966). This work was supported in part by Career Development Award GM-5433 from the National Institutes of Health and was presented at the Fifth International Symposium on the Chemistry of Natural Products, London, July 1968.

(2) Abstracted in part from the dissertation presented by J. A. Alford in partial fulfillment of the requirements for the Ph.D. degree, Clemson University, Dec 1968.

(3) A. W. Burgstahler and J. N. Marx, *Tetrahedron Lett.*, 3333 (1964).

(4) (a) R. Lombard and J. Ebelin, *Bull. Soc. Chim. Fr.*, 930 (1953). (b) L. Velluz, G. Muller, A. Petit, and J. Mathieu, *ibid.*, 401 (1954). (c) For a review of work reported prior to 1950, see J. Simonsen and D. H. R. Barton, "The Terpenes," Vol. 3, Cambridge University Press, 1952, pp 374–445.

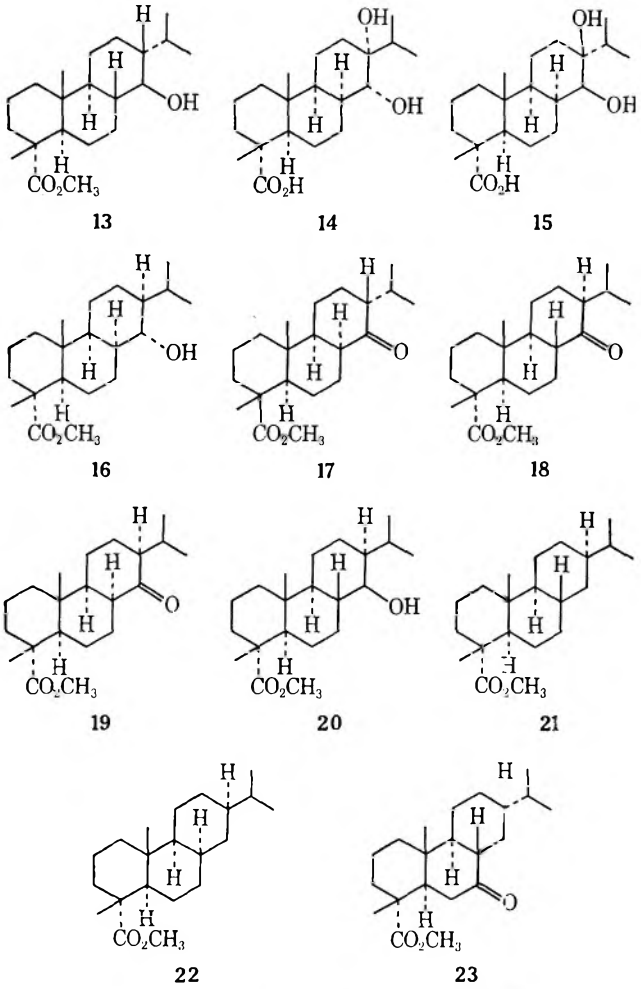
(5) (a) J. N. Marx, Ph.D. Dissertation, University of Kansas, Sept 1965. (b) A. W. Burgstahler, J. N. Marx, and D. F. Zinkel, *J. Org. Chem.*, **34**, 1550 (1969). We would like to thank Professor Burgstahler for sending us a copy of this manuscript prior to its publication.

(6) B. E. Cross and P. L. Myers, *J. Chem. Soc., C*, 471 (1968).

(7) We would like to thank Professor Cross for a sample of this compound.

this basis it must be 13β,14β-dihydroxyabietan-18-oic acid (**15**).[8]

In order to clarify the nature and origin of the epoxide assigned structure **11**, an unambiguous synthesis of **4** and its epoxide was attempted. Hydroboration–oxidation of the methyl ester of **3**[5] gave a mixture of a hydroxy ester and a glycol. This hydroxy ester and its acetate showed C-10 methyl signals in the nmr at δ 1.00 and 1.10, respectively, indicative of a *cis* B,C-ring fusion.[1] Since it is well known that diborane adds to olefins in a *cis* fashion, this compound must be methyl 14α-hydroxyy-8α,13β-abietan-18-oate (**16**), and on this basis of the nmr spectrum the glycol is the 18-ol corresponding to **16**.



In an effort to confirm the stereochemistry of **16** by chemical means, the 14 tosylate was prepared, with the intention of effecting the conversion of **16** into 8α,13β-abietan-18-oic, acid, using the method described earlier.[1] However, lithium aluminum hydride reduction of the tosylate followed by oxidation with Jones reagent afforded **3** as the only isolable product, the result of elimination of tosylate, rather than displacement by hydride. Lithium–ammonia reduction of the tosylate proceeded with cleavage of the sulfur–oxygen bond and reduction of the ester function to give the glycol obtained as a by-product in the hydroboration of **3**. The examination of models of the tosylate of **16** indicates that the 14 position is extremely hindered to the approach of a reagent from the β side, and this may explain the failure of these reactions to afford the desired product.

In a further effort to confirm the structure and stereochemistry of **16**, it was oxidized to a ketone, employing conditions which were assumed to preclude isomerization at either enolizable position (C-8 or C-14).[9] However, the rotatory dispersion curve of this compound showed a negative Cotton effect of moderate amplitude (−31), rather than the positive Cotton effect predicted by the octant rule for a ketone with a *cis* B,C-ring fusion. The nmr spectrum of this ketone showed a C-10 methyl signal at δ 0.87, intermediate between the position of the corresponding signals for methyl 14-oxoabietan-18-oate (**8**, δ 0.96[1]) and methyl 14-oxo-8α-abietan-18-oate (**17**, δ 0.72[1]). On the basis of the rotatory dispersion curve of this ketone, and the fact that it was isomerized to the stable isomer **8** by base, it was tentatively assigned the 8β,13β-14-oxo structure (**18**), resulting from epimerization at C-8 during oxidation.[10] However, compound **18** was subsequently prepared by Herz and coworkers[11] by an unambiguous route and found to be different from the compound described above. Since there are only four possible ketones with a gross structure corresponding to **8**, and since three of these, **8**, **17**, and **18**, are known,[1,11] the oxidation product of **16** is probably methyl 14-oxo-8α,13β-abietan-18-oate (**19**). This assignment of stereochemistry was further confirmed by a comparison of the chemical-shift differences of the C-10 methyl in compounds **8**, **17**, **18**, and **19**, when the spectra were run in benzene-d_6 and chloroform-*d*. From these data, which are summarized in Table I, it can be seen that Δδ for the isomers with a *trans* ring fusion is −0.21 and −0.27 for **8**[11,12] and **18**,[11] respectively, while Δδ for **17** is −0.09.[12] A similar comparison of chemical-shift differences for the compound assigned structure **19** was −0.12, indicating that the B,C-ring fusion is *cis*. The anomalous rotatory dispersion curve of **19** may be caused by any one of several factors, but is most probably due to some form of deformation of ring C, brought about by the severe steric interaction between C-14 and the C-10 angular methyl group.

TABLE I
C-10 CHEMICAL-SHIFT DATA FOR METHYL 14-OXOABIETAN-18-OATES[a]

Ketone	Solvent: Chloroform-*d*	Solvent: Benzene-d_6
8	0.96,[b] 0.97[c]	0.75,[d] 0.77[c]
17	0.72[b]	0.63[d]
18	0.97[c]	0.70[c]
19	0.87	0.75

[a] All values reported as parts per million relative to tetramethylsilane. [b] Reference 1. [c] Reference 11. [d] J. W. Huffman and T. Kamiya, unpublished work.

The sodium borohydride reduction of **19** gave essentially one hydroxy ester, which was different from the known 8α,13β,14α-ol (**16**), and was also neither

(8) B. E. Cross and P. L. Myers [*J. Chem. Soc.*, *C*, 711 (1969)] have independently reached the same conclusions. See also ref 5b.

(9) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956).

(10) Burgstahler, *et al.* (ref 5b), have concluded that this compound is **18**. However, on subsequent reinvestigation this structure has been revised to **19** (A. Burgstahler, personal communication).

(11) W. Herz, personal communication. We would like to thank Professor Herz for carrying out the comparison of these ketones.

(12) Footnote *d*, Table I.

of the epimeric methyl 14-hydroxyabietan-18-oates (**9** and **13**). The nmr spectrum of this alcohol showed a relatively shielded C-10 methyl signal at δ 0.88, indicating a *trans* B,C-ring fusion, and H-14, although at rather low field for an axial proton (δ 3.38), appeared as a very diffuse multiplet ($W_{1/2}$ = 15 Hz), which indicates that this compound has an equatorial hydroxyl group. The only structure consistent with these data is methyl 14β-hydroxy-13β-abietan-18-oate (**20**), and comparison with a sample of this material prepared by Herz and coworkers confirmed this assignment of stereochemistry.[13] An examination of models of **19** indicates that attack by borohydride would be expected to occur from the α side of the molecule to give a 14β-hydroxy ester. However, in this compound there is an extremely severe steric interaction between the angular methyl and hydroxyl group, and under the conditions of the reaction C-8 is isomerized prior to reduction.

With the structure and stereochemistry of **16** clarified, an attempt was made to prepare the still unknown 8α-abiet-13-en-18-oic acid (**4**). Treatment of hydroxy ester **16** with phosphorus oxychloride–pyridine led to a 1:1 mixture of the methyl esters of **3** and a new acid, presumably **4**. Chromatography of this mixture on silver nitrate–silica gel led to the separation of the isomers; however, the methyl ester of the new acid could be obtained only in *ca.* 90% purity. The nmr spectrum of this ester agreed well with that expected for **4**, with H-14 appearing as a multiplet at δ 5.20 and the C-10 methyl protons at δ 0.91.[14] The stereochemistry of the new unsaturated ester was further confirmed when it was found that hydrogenation of the 1:1 mixture of $\Delta^{(8,14)}$ and Δ^{13} esters obtained from the dehydration gave a 1:2 mixture of methyl 13β- (**21**) and 8α,13β-abietan-18-oate (**22**). Since **3** is known to afford a mixture of **21** and **22** (containing 62% **21**[5b]) on hydrogenation, and since **4** would be expected to give nearly exclusively **22**, the hydrogenation data indicate that the new acid is indeed **4**. Reaction of the methyl ester of **4** with *m*-chloroperoxybenzoic acid gave a complex mixture of products; however, a lack of material precluded a detailed study of the course of this reaction. Although it has not been possible to isolate acid **4** from the lithium–ammonia reduction of abietic acid, the reported physical and chemical properties of the compound assigned structure **11** strongly indicate that this compound must indeed be the α oxide derived from **4**, and that acid **4** must be present in the reduction mixture.

During the course of their work on the reduction of abietic acid, Burgstahler and Marx reported the isolation of a 1:1 mixture of abiet-7- and -13-en-18-oic acids (**6** and **5**)[5a] from which the Δ^7 acid was subsequently obtained in pure form by chromatography.[5b] In an effort to effect an alternate separation, we have converted the mixture of acids into the methyl esters and subjected this mixture to hydroboration–oxidation. Chromatography of this mixture gave no effective separation, and it was consequently oxidized to the mixture of **7** and **14** ketones (**23** and **8**). Although this mixture again could not be resolved by chromatography, advantage was taken of the known reluctance of **8** to form carbonyl derivatives[1,5,6] and the mixture was converted into an easily separable mixture of **8** and the oxime of **23**. Hydrolysis of this oxime gave pure **23**, which was identical with a sample prepared by the method of Cross and Myers.[6] The rotatory dispersion curve of **23** showed a negative Cotton effect curve of moderate amplitude, in agreement with the assigned structure.[15] The gross structure of **23** and its stereochemistry at C-13 were confirmed by reduction under Wolff–Kishner conditions to abietan-18-oic acid (**12**). In an effort to convert **23** into the desired abiet-7-enoic acid, it was reduced to a mixture of stereoisomeric 7-ols; however, attempted dehydration with phosphorus oxychloride–pyridine gave an intractable mixture. This conversion was effected *via* the Bamford–Stevens reaction of the tosylhydrazone of **23**, which gave, although in mediocre yield, **6**, the spectral properties of which were in agreement with the indicated structure. Finally, **6** was isolated from its mixture with **5** by recrystallizing their (−)-α-phenethylamine salts.

During the course of this work it became quite clear that the so-called "rule of α attack," which is of considerable utility in the steroid series,[16] is not valid in the dihydroabietic acid series. It has already been noted[1] that additions to the 8,14 double bond in **2** occur almost exclusively from the β side, while this work indicates that in 13β-abiet-8(14)-en-18-oic acid (**3**) additions proceed to a considerable extent from the β side of the molecule.[17] In the Δ^{13} olefins the course of addition reactions is governed by the stereochemistry of C-8, with the 8β isomer (**5**) undergoing virtually exclusive β attack,[6,8] while the 8α isomer (**4**) reacts preferentially (and predictably) from the α face. Insufficient data are available to permit any generalizations concerning the stereochemistry of additions to the Δ^7-abietenes.

Experimental Section[18]

Methyl 14α-Hydroxyabietan-18-oate[19] (**9**).—To a solution of 18.0 g of keto ester **8** in 500 ml of methanol at 0° was added 20.0 g of sodium borohydride in small portions over a period of 10 min. The solution was stirred for an additional 40 min at room temperature. The volume of the methanol was reduced by one-half with the aid of an aspirator, and the mixture was poured into water, extracted with chloroform, and dried. Removal of sol-

(13) W. Herz, personal communication. We would like to thank Professor Herz for a sample of **20**.

(14) The angular methyl group in this compound lies above the plane of the double bond and would be expected to appear at somewhat higher field than if this were not the case. The C-10 methyl signal of methyl 8α-abiet-12-en-18-oate also appears at δ 0.91.[1]

(15) P. Crabbe, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1965, p 44.

(16) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 14, and references cited therein.

(17) W. Herz and R. N. Merrington [*J. Org. Chem.*, **30**, 3198 (1965)] have already noted that additions to methyl pimar-8(14)-en-18-oate acid led to a mixture of 8α and 8β isomers.

(18) Melting points were determined on a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were taken as films or potassium bromide pellets on a Perkin-Elmer Model 137 spectrophotometer. Vapor phase chromatographic analyses were performed on an F & M Model 810 chromatograph, utilizing a 6 ft × 0.125 in. column packed with SE-30 on Chromosorb W. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60 nuclear magnetic resonance spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard. Signals are given in parts per million relative to this standard. Optical rotatory dispersion curves were determined in methanol with a Jasco Model ORD/UV-5 spectropolarimeter. Rotations at the sodium D-line were determined in 95% ethanol using a Rudolph Model 70 polarimeter. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(19) This preparation was originally carried out by Dr. T. Kamiya.

vent *in vacuo* yielded an oil which crystallized on trituration with hexane. Recrystallization from the same solvent afforded 14.3 g (79%) of white needles: mp 104–106°; $[\alpha]D$ +14° (*c* 0.900); nmr 3.72 (br s, H-14), 1.18 (C-4 methyl), 0.92 (d, J = 7 Hz, isopropyl), and 0.84 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.98; H, 10.69.

Abiet-13-en-18-oic Acid (5).—To a solution of 14.0 g of alcohol **9** in 50 ml of pyridine was added 14.0 g of phosphorus oxychloride. The mixture was protected from moisture with a calcium chloride drying tube and heated on a steam bath for 7 hr. The solution was cooled and carefully poured over 150 g of ice–water, and the excess pyridine was neutralized with hydrochloric acid. The mixture was extracted with methylene chloride, washed with water, and dried. Removal of the solvent afforded 13.1 g (98%) of oil, the nmr spectrum of which indicated that it contained about 10% 8(14) isomer. A solution of 16.0 g of this oil and 40.0 g of anhydrous lithium iodide in 150 ml of dry collidine was heated at reflux under nitrogen for 18 hr. The solution was cooled, poured into 250 ml of ice–water, neutralized with concentrated hydrochloric acid, extracted with methylene chloride, washed with water, and dried. Removal of the solvent afforded 10.0 g of white solid. The nmr spectrum indicated that the mixture contained 90% the desired compound plus 10% 8(14) isomer. After three recrystallizations from acetone, the nmr indicated that the solid product was richer in the 8(14) isomer (**2**), and the filtrates were converted into the diamylamine salt, which was recrystallized three times from acetone. Regeneration of the acid with acetic acid and subsequent recrystallization from acetone afforded 2.4 g of abiet-13-en-18-oic acid:[20] mp 162–164°; $[\alpha]D$ −7.2° (*c* 1.092) (lit.[5b] mp 146–147°; $[\alpha]D$ +6°); nmr 5.09 (br s, H-14), 1.18 (C-4 methyl), 0.97 (d, J = 7 Hz, isopropyl), and 0.86 ppm (C-10 methyl).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.12; H, 10.80.

Epoxidation of Abiet-13-en-18-oic Acid.—To a solution of 1.5 g of the acid in 25 ml of methylene chloride at 0° was added slowly and in small portions 1.1 g of *m*-chloroperbenzoic acid. The solution was stirred overnight at room temperature and then heated at reflux for 7 hr. The solution was washed twice with 25 ml of 10% sodium bisulfite solution, three times with saturated sodium bicarbonate, and once with water, and dried over magnesium sulfate. After removal of solvent, there was obtained 1.4 g of oil which crystallized from 2-butanone. Recrystallization from acetone afforded 0.75 g of **10** as white needles: mp 226–228°; $[\alpha]D$ +11.2° (*c* 1.163); nmr 2.82 (s, H-14), 1.16 (C-4 methyl), 0.95 (d, J = 6 Hz, isopropyl), and 0.82 ppm (C-10 methyl).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.73; H, 9.87.

Hydrogenation of Abiet-13-en-18-oic Acid.—A solution of 0.100 g of the acid **5** in 19 ml of acetic acid was hydrogenated with 0.050 g of platinum oxide at 59 psi and room temperature. The reaction mixture was filtered through Celite and the product was precipitated by the addition of water. Recrystallization from aqueous acetone gave 0.075 g of abietan-18-oic acid (**12**), mp and mmp 178–180°.[1]

Hydroboration of Methyl Abiet-13-en-18-oate.—To a solution of 0.450 g of the methyl ester (prepared from the acid and ethereal diazomethane) in 10 ml of dry diglyme was added 0.100 g of sodium borohydride. The reaction was cooled in an ice bath and 0.050 g of freshly distilled boron fluoride etherate in 2 ml of diglyme was added over a period of 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 4 hr. A few drops of water followed by 3 ml of 10% sodium hydroxide and 3 ml of 30% hydrogen peroxide were added slowly. The mixture was stirred overnight and poured into 25 ml of water. The precipitate was collected and recrystallized from hexane to give 0.310 g (70%) of product, mp 134–135°, identified as methyl 14β-hydroxyabietan-18-oate (**13**) by mixture melting point (134–135°) and by comparison of the infrared spectra with that of an authentic sample.[1]

13β,14β-Dihydroxyabietan-18-oic Acid (15).—To a solution of 0.150 g of **5** in 2.5 ml of pyridine was added 0.200 g of osmium tetroxide. The black solution was allowed to stand for 72 hr at room temperature. An additional 15 ml of pyridine, 15 ml of water, and 0.5 g of sodium bisulfite were added, and the solution was vigorously stirred for 2 hr. The pyridine was neutralized with concentrated hydrochloric acid, and the resulting precipitate was collected. Two recrystallizations from ether–hexane afforded 0.095 of glycol: mp and mmp 183–184°; ir spectrum identical with that of the material prepared by Cross and Myers;[6] nmr (pyridine) 3.39 (d, J = 9 Hz, H-14), 1.39 (C-4 methyl), 1.10 (d) and 0.98 (d, J = 7 Hz, isopropyl), and 0.94 ppm (C-10 methyl).

Methyl 14α-Hydroxy-8α,13β-abietan-18-oate (16).—To a solution of 10.0 g of methyl 13β-abiet-8(14)-en-18-oate[5] (**3**) in 150 ml of dry diglyme was added 2.0 g of sodium borohydride. The reaction was cooled in an ice bath and 8.4 g of freshly distilled boron trifluoride etherate was added over a 1-hr period. The gelatinous reaction mixture was allowed to warm to room temperature and stirred for 4 hr. A few drops of water followed by 50 ml of 10% sodium hydroxide and 50 ml of 30% hydrogen peroxide were added cautiously. The mixture was stirred overnight and poured into water. The white precipitate, yield 10.0 g, mp 100–110°, was dried, dissolved in hexane–benzene (1:4), and chromatographed on Merck acid-washed alumina. Elution with hexane–benzene (1:4) gave 0.78 g of starting ester. Elution with methylene chloride–benzene (1:4) gave 7.26 g (69%) of hydroxy ester **16**, which was recrystallized from hexane: mp 136–138°; $[\alpha]D$ −11.7° (*c* 1.109); nmr 3.62 (m, H-14), 1.19 (C-4 methyl), 1.00 (C-10 methyl), and 0.90 (d) and 0.80 (d, J = 7 Hz, isopropyl).

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.87. Found: C, 74.77; H, 10.81.

The 14 acetate, mp 122–123°, $[\alpha]^{23}D$ −47.3° (*c* 1.053), was formed in the usual manner and was recrystallized from methanol: nmr 5.21 (m, H-14), 1.20 (C-4 methyl), 1.11 (C-10 methyl), and 0.90 (d) and 0.80 (d, J = 7 Hz, isopropyl).

Anal. Calcd for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 72.79; H, 10.23.

Elution with methylene chloride–methanol (19:1) gave 1.83 g of diol. Two recrystallizations from methanol gave crystals, mp 155–157° (lit.[5b] mp 155–157°), $[\alpha]D$ +7.5° (*c* 1.594), which held tenaciously to solvent and failed to give satisfactory analytical data.

Anal. Calcd for $C_{20}H_{36}O_2 \cdot CH_3OH$: C, 74.07; H, 11.84. Found: C, 74.59; H, 11.96.

Methyl 14α-Tosyloxy-8α,13β-abietan-18-oate.—To a solution of 5.0 g of hydroxy ester **16** in 15 ml of pyridine was added 3.75 g of *p*-toluenesulfonyl chloride. The solution was stirred overnight at room temperature and poured into water. The precipitate was recrystallized from cold acetone to give 6.80 g (93%) of tosylate, mp 112–113°, $[\alpha]D$ −21.5° (*c* 1.024).

Anal. Calcd for $C_{28}H_{42}O_5S$: C, 68.55; H, 8.63. Found: C, 68.31; H, 8.54.

Attempted Preparations of 8α,13β-Abietan-18-oic Acid (22).

A.—To a solution of 3.0 g of tosylate in 90 ml of absolute ether was added 1.50 g of lithium aluminum hydride. The reaction mixture was heated at reflux for 18 hr and cooled, the excess hydride was decomposed with water, and the mixture was acidified with 10% hydrochloric acid. The ether layer was washed, dried, and evaporated, and the residue was dissolved in hexane and passed through a column of 50 g of Merck acid-washed alumina. Evaporation of the hexane eluant furnished 1.57 g (88%) of material which could not be induced to crystallize. The nmr spectrum exhibited a one-proton singlet at 5.5 ppm, indicating that elimination had taken place. A 0.5-g portion of this material was dissolved in 20 ml of acetone, mixed with 2 ml of Jones reagent, and stirred for 30 min. The mixture was poured into water, extracted with methylene chloride, and dried. After removal of solvent, there was obtained 0.45 g of the colorless oil. Crystallization of the oil from acetone afforded 0.25 g of 13β-abiet-8(14)-en-18-oic acid (**3**), mp 148–149°. The nmr spectrum of the residual oil from the evaporation of the mother liquors was identical with that of 13β-abiet-8(14)-en-18-oic acid.

B.—A solution of 1.0 g of tosylate in 20 ml of ether was added to 75 ml of liquid ammonia. To this solution was added 0.5 g of lithium and the blue reaction mixture was stirred for 1 hr. Sufficient anhydrous ethanol was added to destroy the blue color, the reaction mixture was allowed to stand overnight, and 50 ml of water was added. The mixture was extracted with methylene chloride and dried, and the solvent was removed to give 0.48 g (76%) of product, mp 155–157°. The infrared and nmr spectra of the product were identical with those of the diol obtained from hydroboration of methyl 13β-abiet-8(14)-en-18-oate.

(20) Glpc data indicate that our material contains *ca.* 9% $\Delta^{8(14)}$ isomer; Dr. D. F. Zinkel, personal communication.

Methyl 14-Oxo-8α,13β-abietan-18-oate (19).—To a solution of 1.50 g of chromium trioxide, 1.50 g of sodium dichromate, and 2.4 ml of acetic acid in 12 ml of water was added 1.50 g of hydroxy ester 15 in 45 ml of benzene at 0°. The reaction mixture was stirred at 0° for 2 hr and at room temperature for 18 hr. The organic layer was separated, washed with water, and dried over magnesium sulfate. After removal of the drying agent and the solvent, there was obtained 1.5 g (100%) of white solid. Recrystallization from hexane and then methanol furnished the analytical sample: mp 79–80°; nmr 1.20 (C-4 methyl), 0.92 (d) and 0.82 (d, J = 7 Hz, isopropyl), and 0.87 ppm (C-10 methyl); mmp (with the 8β,13β isomer) 45–56°; ORD $[\phi]_{589}$ −250°, $[\phi]_{311}$ −2400°, $[\phi]_{287}$ 0°, $[\phi]_{274}$ +770°.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.19; H, 10.11.

A 0.5-g sample of this ketone in 10 ml of methanol containing 0.5 g of potassium hydroxide was heated at reflux for 30 min and poured into water, and the precipitate was collected. Recrystallization from methanol afforded 0.4 g (80%) of material, mp 79–80°. A mixture melting point with methyl 14-oxoabietan-18-oate (**8**) was 79–80°. Infrared and nmr spectra were identical with those of an authentic sample of this material.

Methyl 14β-Hydroxy-13β-abietan-18-oate (20).—To a solution of 0.050 g of **19** in 3 ml of 95% ethanol was added 0.050 g of sodium borohydride, and the reaction mixture was heated at reflux 2.5 hr. The clear solution was cooled, diluted with 12 ml of 5% hydrochloric acid, extracted with ether, washed thoroughly with water and saturated sodium chloride, and dried, and the solvent was removed to give 0.050 g of crystalline residue. Tlc (silica gel G, 5% ethyl acetate in benzene) showed the presence of nonpolar material, and 0.043 g of the solid was taken up in benzene and chromatographed on silica gel. Elution with 1% ethyl acetate–benzene gave 0.002 g of nonpolar material, while the later fractions with ethyl acetate–benzene mixtures gave first 0.011 g of impure alcohol and then 0.024 g (48%) of **20**, which was homogeneous to tlc and showed nmr signals at 3.47 (m, $W_{1/2}$ = 15 Hz, H-14), 1.18 (s, C-4 methyl), 1.09 and 0.90 (d, J = 6 Hz, isopropyl), and 0.90 ppm (s, C-10 methyl). The analytical sample, mp 130–131°, was crystallized from hexane. This material was identical (mixture melting point and nmr) with a sample prepared by Herz, *et al.*[13]

Anal. Calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.68; H, 10.84.

8α-Abiet-13-en-18-oic Acid (4).—To a solution of 0.30 g of methyl 14α-hydroxy-8α,13β-abietan-18-oate (**16**) in 3 ml of pyridine was added 0.5 ml of phosphorus oxychloride. The reaction mixture was heated overnight on a steam bath, cooled, and slowly added to 15 ml of ice–water. The excess pyridine was neutralized with concentrated hydrochloric acid and the mixture was extracted with ether, washed, and dried. Removal of the solvent yielded 0.272 g (92%) of semicrystalline material. The nmr spectra of this material indicated that it was a 1:1 mixture of the abiet-8(14)- and -13-en-8-oates. A 0.265-g portion of this material was taken up in hexane and chromatographed on 25 g of silver nitrate impregnated silica gel. Elution with 4:1 hexane–benzene gave 0.091 g of **3**, while later fractions with the same solvent pair gave first 0.020 g of a mixture and then 0.094 g of nearly pure (*ca.* 80% by nmr) **4** as the methyl ester. This material showed nmr signals at 5.21 (m, H-14), 1.20 (s, C-4 methyl), 0.95 (d, J = 6 Hz, isopropyl), and 0.91 ppm (s, C-10 methyl). In view of the small amount of this material available and the fact that it could not be induced to crystallize, a sample was subjected to mass spectrometry in lieu of analysis and gave a parent peak at m/e 318 (calculated mol wt, 318).

Hydrogenation of Methyl 13β-Abiet-8(14)-en-18-oate (3) and 8α-Abiet-13-en-18-oic Acid (4).—A solution of 0.05 g of the mixture of esters from above in 10 ml of acetic acid was hydrogenated in the presence of 0.05 g of Adams catalyst at 35 psi for 6 hr. The solution was filtered, diluted with water, extracted with ether, washed with water and diluted base, and dried. After removal of solvent, analysis by glc indicated the presence of two compounds (**22** and **21**) in a ratio of 2:1. These were identified by a comparison of their retention times with those of authentic samples.

Lithium–Ammonia Reduction of Abietic Acid.—The reduction and isolation of abiet-8(14)-en-18-oic acid was carried out as described previously.[1,5] From 145 g of the diamylamine salt of abietic acid, there was obtained 27.6 g (29%) of the *ca.* 4:1 mixture of abiet-8(14)-en-18-oic acid (**2**) and abiet-13-en-18-oic acid (**5**), mp 190–194°, which was used for those experiments requiring the 8(14)-unsaturated acid. From the mother liquors, employing the method of Marx, could be isolated 10.0 g (9%) of 13β-abiet-8(14)-en-18-oic acid (**3**), mp 148–150° (lit. mp 148–150°), identical with a sample prepared by the hydrogenation of levopimaric acid.[5] Regeneration of the acids from the solid mixture of salts collected prior to the isolation of 13β-abiet-8(14)-en-18-oic acid afforded an additional 40.0 g (36%) of the mixture of abiet-8(14)- and -13-en-18-oic acids, mp 187–195° after five recrystallizations. The material remaining in the mother liquors was purified through the diamylamine salt to give 0.65 g (0.6%) of abiet-13-en-18-oic acid, mp 162–164°, identical with the material mentioned above. In addition to the above compounds, 3.0 g (27%) of the 1:1 mixture of abiet-7-en-18-oic acid (**6**) and abiet-13-en-18-oic acid (**5**) (lit.[5a] mp 161–162°) was obtained.

Methyl 7-Oxoabietan-18-oate (23).—Hydroboration-oxidation of 3.0 g of the mixture of the methyl esters of abiet-7- and -13-en-18-oic acids was carried out as previously described to give 2.80 g of crude product which was dissolved in hexane and chromatographed on 80 g of Merck acid-washed alumina. Elution with hexane and hexane–benzene (1:1) gave 0.29 g of starting esters. The first benzene fraction gave 0.18 g of crystals, which on recrystallization afforded pure methyl 14β-hydroxyabietan-18-oate. Further elution with benzene gave 1.81 g of a mixture of this compound and a 7-hydroxy ester. Attempts to separate the mixture by rechromatography were unsuccessful, and it was converted into the mixture of the corresponding ketones.

To a solution of 8.0 g of the mixture of 7- and 14-hydroxy esters in 600 ml of acetone at 0° was added 40 ml of Jones reagent. The reaction mixture was stirred for 2.5 hr and sufficient methanol was added to destroy the excess chromic acid. The volume was reduced to 200 ml, and the reaction mixture was diluted with 500 ml of water, extracted with ether, and dried over magnesium sulfate. Removal of the drying agent and solvent afforded 7.5 g (93%) of oil which could not be crystallized. Attempts to separate the mixture by column chromatography again failed, and the ketones were separated *via* the 7-oximino compound.[21]

A solution of 8.5 g of the mixture of keto esters, 16.0 g of sodium acetate, and 28.0 g of hydroxylamine hydrochloride in 240 ml of methanol was heated at reflux overnight. The solution was cooled, poured into water, extracted with methylene chloride, washed with water, and dried over magnesium sulfate. Removal of drying agent and solvent gave 8.5 g of oily product. The oil was dissolved in benzene–hexane (1:1) and chromatographed on Merck acid-washed alumina. Elution with benzene gave methyl 14-oxo-abietan-18-oate (**8**), identical with an authentic sample.[1] Elution with benzene–methylene chloride (1:1) gave 4.1 g of the oxime of methyl 7-oxoabietan-10-oate, mp 183–185°. Recrystallization from methanol and then hexane gave the analytical sample: mp 185–186.5°; nmr 1.25 (C-4 methyl), 0.98 (C-10 methyl), and 0.87 (d, J = 6 Hz, isopropyl).

Anal. Calcd for $C_{21}H_{35}NO_3$: C, 72.12; H, 10.09; N, 4.01. Found: C, 72.36; H, 9.98; N, 4.01.

To obtain the required 7-keto compound (**23**), a solution of 0.5 g of the oxime, 20 ml of methanol, 2 ml of water, and 2 ml of concentrated sulfuric acid was heated at reflux for 80 hr. The solution was cooled, poured into water, extracted with ether, and dried. After removal of solvent, an oil was obtained which was dissolved in benzene and filtered through a short column of alumina. Recrystallization of the material eluted with benzene from pentane and then methanol gave 0.3 g (63%) of methyl 7-oxoabietan-18-oate (**23**): mp 86.5–87°; nmr 1.23 (C-4 methyl), 1.09 (C-10 methyl), and 0.88 (d, J = 6 Hz, isopropyl); ORD $[\phi]_{539}$ −260°, $[\phi]_{306}$ −3620°, $[\phi]_{282}$ 0°, $[\phi]_{270}$ +1564°. Cross and Meyers[6] report this compound as an oil; however, a sample prepared by their method was identical with that prepared by this route.

Wolff–Kishner Reduction of Methyl 7-Oxoabietan-18-oate.—A solution of 0.5 g of the keto ester, 2.0 g of potassium hydroxide, and 5 ml of anhydrous hydrazine in 60 ml of ethylene glycol was heated at 150° for 1.5 hr. The condenser was removed and the temperature was allowed to rise to 195° during a 2-hr period. The reaction was held at this temperature for an additional 1 hr. The solution was cooled, acidified with hydrochloric acid, poured into ice–water, extracted with ether, and dried. After removal of solvent, there was obtained 0.40 g of oil which crystallized from acetone to give 0.24 g (51%) of abietan-18-oic acid (**12**), mp and mmp 176–178°.[1] The infrared and nmr spectra were identical with those of an authentic sample.[1]

(21) An attempt to separate this mixture with Girard's T reagent was successful, although the product recovery was not satisfactory.

p-**Toluenesulfonylhydrazone of Methyl 7-Oxoabietan-18-oate.**—A solution of 0.300 g of keto ester, and 0.372 g of *p*-toluenesulfonylhydrazine in 25 ml of 0.2 *M* ethanolic hydrochloric acid was heated at reflux for 2 hr and then boiled for 19 min without the condenser. An equal volume of water was added, and the white precipitate was collected and recrystallized from aqueous methanol, affording 0.365 g (90%) of material, mp 81–82°.

Anal. Calcd for $C_{28}H_{42}N_2O_4S$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.67; H, 8.26; N, 5.31.

Abiet-7-en-18-oic Acid (6). A.—To a solution of 0.1 g of sodium in 5 ml of ethylene glycol was added 0.140 g of the *p*-toluenesulfonylhydrazone. The reaction mixture was poured into water and extracted with ether. The ether solution was extracted with 20% potassium hydroxide solution, acidified, and reextracted with ether. The solvent was removed and the resulting oil was crystallized from acetone to give 0.025 g of product: mp 166–167° (lit.[5b] mp 180–182°); nmr 5.30 (m, H-7), 1.25 (C-4 methyl), 0.87 (d, J = 7 Hz, isopropyl), and 0.82 ppm (C-10 methyl).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.90; H, 10.59. Found: C, 79.04; H, 10.44.

B.—To a boiling solution of 3.0 g of the mixture of abiet-7- and -13-en-18-oic acids obtained from the reduction of abietic acid in 50 ml of acetone was added 1.4 g of (−)-α-phenethylamine; boiling was continued until the amine salt began to precipitate. The solution was cooled and the precipitate was recrystallized once from acetone, five times from ethyl acetate, and five additional times from aqueous acetone. The acid was regenerated from the salt and recrystallized three times from acetone to give 0.80 g of **6**, mp 178–180°. The infrared and nmr spectra were identical with those of abiet-7-en-18-oic acid prepared by the Bamford–Stevens reaction.

Registry No.—**3**, 17611-13-1; **5**, 17611-11-9; **6**, 77611-19-7; **9**, 22565-86-2; **10**, 22565-87-3; **15**, 22565-88-4; **16**, 22565-89-5; **16** 14 acetate, 22565-90-8; **16** 14 tosylate, 22565-91-9; **19**, 22565-92-0; **23**, 22576-93-8; **23** oxime, 22565-93-1; **23** *p*-toluenesulfonylhydrazone, 22576-94-9.

Acknowledgment.—The spectropolarimeter used in this work was obtained through a National Science Foundation Research Instrument Grant. The mass spectral determination was carried out at the Research Triangle Institute.

Studies on Resin Acids. V. Preparation and Reactions of Ring-A Olefins from Dehydroabietic Acid[1]

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Received June 30, 1969

The lead tetraacetate decarboxylation of dehydroabietic acid has been found to give three olefins (**2**, **5**, and **6**) and the acetate of 18-norabieta-8,11,13-trien-4-ol (**7**). Hydroboration–oxidation of this mixture of olefins gives principally 18-norabieta-8,11,13-trien-19-ol (**12**) and 18-norabieta-8,11,13-trien-3α-ol (**13**), plus small quantities of 19-nor-5β-abieta-8,11,13-trien-7-one (**17**). To elucidate the structure of **17**, it was necessary to prepare 18- and 19-norabieta-8,11,13-trien-7-one by oxidation of the corresponding hydrocarbons. It was found that sodium–ammonia reduction of dehydroabietonitrile gives the 19-nor hydrocarbon (**20**), rather than 18-norabieta-8,11,13-triene as suggested originally. The structure of **17** was confirmed by its synthesis in two steps from methyl 7-oxoabieta-5,8,11,13-tetraen-18-oate (**22**).

The readily available diterpenes, dehydroabietic acid (abieta-8,11,13-trien-18-oic acid[2]) and podocarpic acid (12-hydroxypodocarpa-8,11,13-trien-19-oic acid[2]), have received considerable attention as possible precursors for the synthesis of steroids or steroid analogs.[3] The basic goal of these workers was the conversion of dehydroabietic acid (**1**) into abieta-4(18),8,11,13-tetraene,[4] which was accomplished by various methods and with varying degrees of success. The earliest workers in this area investigated the acid-catalyzed dehydration of abieta-8,11,13-trien-18-ol (**3**) and recognized that this led to mixtures of olefins.[3a,b] Later workers prepared what was described as pure **2** by either Hofmann[3c,d] or Cope[3d] eliminations carried out on 4-dimethylamino-18-norabieta-8,11,13-triene (**4**) or, alternatively, by the lead tetraacetate decarboxylation of **1**.[3e]

The single-step decarboxylation of **1** with lead tetraacetate, carried out in these laboratories some years ago and reported to lead to essentially pure **2**, is by far the most convenient of the methods employed to date for this conversion. However, subsequent reinvestigation of this reaction, making use of techniques which were not available during the course of the earlier work, indicates that the material described as **2** is actually a mixture of three olefins.[5] Repetition of the lead tetraacetate decarboxylation of dehydroabietic acid and careful analysis of the nmr spectrum indicated that the material previously described as pure **2** was in fact a mixture of **2**, abieta-3,8,11,13-tetraene (**5**), and abieta-4,8,11,13-tetraene (**6**) in a ratio of 2:2:1. In addition to a 65% yield of the olefin mixture, there was also obtained an oily acetate in 7% yield. The spectral data for this compound indicated that it was probably the same as the 4-acetoxy-18- or -19-norabieta-8,11,13-triene (**7** or **8**) re-

(1) Part IV: J. W. Huffman, J. A. Alford, and R. R. Sobti, *J. Org. Chem.*, **34**, 473 (1969). This work was supported in part by Career Development Award GM-5433 from the National Institutes of Health.

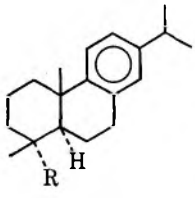
(2) The systematic method of nomenclature employed in this paper is that outlined by J. ApSimon, M. Fetizon, E. Fujita, L. Gough, W. Herz, P. R. Jefries, D. Mangoni, T. Norin, K. Overton, S. W. Pelletier, J. W. Rowe, and E. Wenkert, Abstracts, 6th International Symposium on the Chemistry of Natural Products, Mexico City, April 1969, p 35.

(3) (a) A. Brossi, H. Gutmann, and O. Jeger, *Helv. Chim. Acta*, **38**, 1730 (1950); (b) R. P. Jacobsen, *J. Amer. Chem. Soc.*, **75**, 4709 (1953); (c) H. H. Zeiss and W. B. Martin, *ibid.*, **75**, 5935 (1953); (d) J. W. Huffman and R. F. Stockel, *J. Org. Chem.*, **28**, 506 (1963); (e) J. W. Huffman and P. G. Arapakos, *ibid.*, **30**, 1604 (1965); (f) C. R. Bennet and R. C Cambie, *Tetrahedron*, **23**, 927 (1967); (g) R. N. Seelye and W. B. Watkins, *Tetrahedron Lett.*, 1271 (1968).

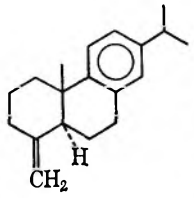
(4) In the case of the workers in ref 3f, the conversion was in the podocarpic acid series.

(5) (a) A. W. Burgstahler, personal communication; A. W. Burgstahler and J. N. Marx, *J. Org. Chem.*, **34**, 1562 (1969). We would like to thank Professor Burgstahler for copies of the nmr spectra of this mixture of olefins, as well as that obtained by the method of Zeiss and Martin.[3c] We would also like to thank Professor Burgstahler for sending us a copy of his manuscript prior to publication. (b) J. F. Biellmann, R. Werrig, P. Daste, and M. Raynaud, *Chem. Commun.*, 168 (1968).

ported by Seelye and Watkins.[3g,6] Hydrolysis of this acetate gave a crystalline alcohol (**9** or **10**), having the same melting point as that reported by Seelye and Watkins.[3g,6] Repetition of the nitrous acid deamination of 4-amino-18-nor-abieta-8,11,13-triene (**11**)



1, R = CO_2H
3, R = CH_2OH
4, R = $N(CH_3)_2$
7, R = $OCOCH_3$
9, R = OH
11, R = NH_2
21, R = CN



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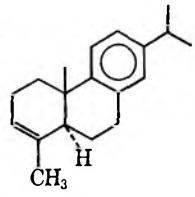

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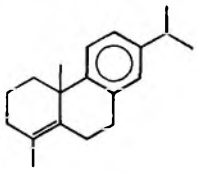
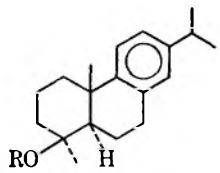
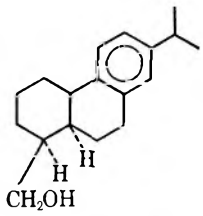


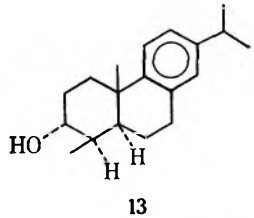
6



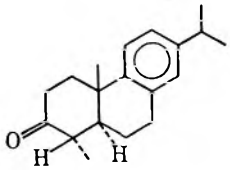
8, R = CH_3CO
10, R = H



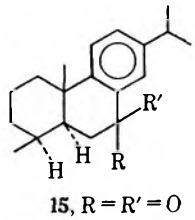
12, R = CH_2OH



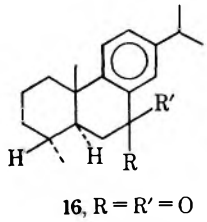
13



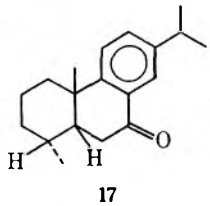
14



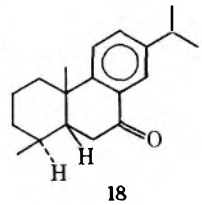
15, R = R′ = O
19, R = R′ = H



16, R = R′ = O
20, R = R′ = H



17



18

gave a mixture of **2**, **5**, and **6** in approximately the same ratio reported earlier,[3g,6,7] plus small amounts of the 4-acetoxy and 4-hydroxy compounds mentioned above. The nmr spectrum of the acetate showed three-proton singlets for the C-4 and C-10 methyl at δ 1.55 and 1.18, while the alcohol had singlets at δ 1.21 and 1.16.[8] By analogy with the chemical-shift differences observed in the steroid series, the conversion of **10** into its acetate should result in the shielding of the angular methyl by *ca.* δ 0.04,[9] with simultaneous strong deshielding of the C-4 methyl owing to the proximity of the acetate group. However, by similar reference to chemical-shift differences in the steroid series, the conversion of **9** into its acetate should somewhat deshield the angular methyl group,[9] with again a rather profound change in the chemical shift of the C-4 methyl. Thus, it is probable that the alcohol is 18-norabieta-8,11,13-trien-4-ol (**9**) and the acetate is **7**.[10] The mechanism of the formation of **7** and **9** during the course of the preparation of the mixture of olefins has been discussed,[3f,6] as has the course of the lead tetraacetate decarboxylation of podocarpic acid.[3f] It is apparent that, since the ratio of olefins obtained by the decarboxylation of **1** is quite different from that observed in the podocarpic acid series,[11] the reaction must not proceed through an "open" carbonium ion, but apparently follows a course similar to that of a nitrous acid deamination.

In order to compare the various methods of preparation of **2** and its isomers, the Hofmann elimination of **4**[3c,d] was repeated and found to give a mixture containing 80% **2** and 10% each of **5** and **6**.[5a]

Although the various olefins obtained from the lead tetraacetate oxidation could be readily identified by nmr spectroscopy, and the 4(18) olefin has been well characterized by chemical means,[3,5] very little was known concerning the chemical behavior of **5** and **6**. Consequently, the mixture of olefins was subjected to hydroboration–oxidation to give a mixture of hydrocarbons and five alcohols. The hydrocarbons were present in small amount (see Experimental Section) and two of the five alcohols constituted the bulk of the reaction product. From this mixture two pure compounds, the known 18-norabieta-8,11,13-trien-19-ol (**12**)[5] and a crystalline alcohol isomeric with **12**, were obtained. The nmr spectrum of this crystalline alcohol showed a doublet (J = 7 Hz) at δ 0.99 and a C-10 methyl singlet at δ 1.18, with a proton adjacent to a secondary alcohol as a multiplet at δ 3.83. Since $W_{1/2}$ for this signal was 7 Hz, it could be assigned as an equatorial proton, and, assuming the normal *cis* addition of diborane, this alcohol is 18-norabieta-8,11,13-trien-3α-ol (**13**).[12] Oxidation of **13** followed by acid-catalyzed isomerization gave 19-norabieta-8,-

(6) These authors did not make a stereochemical assignment for the acetoxy function in their original communication. [While this manuscript was in preparation, these authors assigned the 4α configuration to this alcohol: *Tetrahedron*, **25**, 447 (1969)]. It should also be noted that the deamination of a primary amine similar to **11** (probably 4-amino-8α,13β,18-norabietane) to give a mixture of olefins was reported some years ago by V. N. Belov and S. D. Kustova, *Zh. Obshch. Khim.*, **24**, 1087 (1954).

(7) In their work, the authors in ref 3g and 6 assign an nmr chemical shift of δ 1.34 to the C-4 methyl group of **6**. This is almost certainly the C-10 methyl signal from **6**, which is also present in the mixture[3f] (see Experimental Section). The signal for the vinyl methyl at C-4 should be in the range of δ 1.5–1.8, and is buried in the envelope of ring protons.

(8) In these and all the other dehydroabietic acid derivatives discussed, the isopropyl group appears in the nmr as a doublet (J = 6–7 Hz) centered at *ca.* δ 1.2.

(9) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 14–24.

(10) (a) Similar conclusions have been reached by Seelye and Watkins[6] for these compounds and by Bennet and Cambie[3,6] for a similar alcohol in the podocarpic acid series; however, these authors have assigned the nmr peak at δ 1.21 and 1.55 in **9** and **7**, respectively, to the C-10 methyl group, for reasons which are not immediately obvious. (b) J. W. Rowe (personal communication) has isolated **9** as a naturally occuring substance, and his independent nmr assignments agree with ours.

(11) In the podocarpic acid reactions the ratio of **2**/**5**/**6** is *ca.* 3:1:6.[3f]

(12) This compound has apparently been obtained as one component of an unseparated mixture of alcohols from the hydroboration of **5**[5b] (J. F. Biellmann, personal communication).

11,13-trien-3-one (**14**), the spectral properties of which did not agree with those reported by Brannon, *et al.*[13] These authors find the C-10 methyl signal in the nmr at δ 1.26, with the C-4 methyl doublet (J = 7 Hz) at the same position. The nmr spectrum of our sample of **14** clearly shows the C-10 methyl signal at δ 1.37, with the C-4 methyl doublet at δ 1.12.[14] The rotatory dispersion curve of **14** showed a positive Cotton effect (amplitude +16), in agreement with the assigned structure and stereochemistry. It was subsequently found that it was possible to isolate **14** by the direct oxidation of the crude mixture of alcohols. Although tlc indicated that there were three alcohols in addition to **12** and **13** in the hydroboration mixture, they were present in small quantity and could not be isolated in a pure state.

In one hydroboration–oxidation experiment, in which the total crude reaction mixture was oxidized directly with chromic acid, there was obtained in addition to **14** a second, and crystalline, ketone. This ketone showed a carbonyl band in the infrared at 5.97 μ, indicative of a conjugated ketone. The ultraviolet spectrum confirmed this conclusion, and the nmr showed that H-14 was deshielded relative to its normal position. On the basis of these data and microanalysis, it was apparent that this compound is one of the four stereoisomeric 18- or 19-norabieta-8,11,13-trien-7-ones (**15**–**18**). Although one of these isomers had been prepared previously,[3a] it is of unknown stereochemistry, and, in order to clarify the stereochemistry of the crystalline ketone, the preparation of the two 7 ketones in the natural (5α) series was undertaken. Since it has been shown that catalytic hydrogenation of the mixture of olefins from the decarboxylation of abiet-8(14)-en-18-oic acid proceeds largely by attack from the α face of the molecule to give fichtelite,[15] the similar mixture of olefins from dehydroabietic acid was hydrogenated to give 18-norabieta-8,11,13-triene (**19**). Chromic acid oxidation[16] of **19** gave the desired 7-one (**15**). This compound, although similar to the crystalline ketone mentioned above, was not identical with it.

The preparation of 19-norabieta-8,11,13-triene (**20**) by a multistep sequence from **12** has been described;[5a] however, a much more attractive route appeared to be the direct sodium–ammonia reduction of dehydroabietonitrile (**21**).[17] Although the product of this reduction had tentatively been assigned structure **19**, a comparison of the reported nmr spectrum of the reduction product of **21** with that of **19** indicated that it was probably the 4 epimer **20**. Repetition of the metal–ammonia reduction gave a hydrocarbon which was different from **19** and the spectral properties of which agreed well with those reported for **20**.[5a] However, the melting point of the 12,14-dinitro derivative of this hydrocarbon did not agree with that reported by Burgstahler and Marx,[5a] although the nmr spectrum of the derivative was in accord with theirs.[18] The melting point of our nitro compound agrees well with that reported by Perold and Jeger for the derivative of a hydrocarbon of gross structure **19** or **20**, which was obtained by partial dehydrogenation of fichtelite.[19] The same hydrocarbon could also be obtained by Wolff–Kishner reduction of the aldehyde obtained by oxidation and isomerization of **12**.[20] Chromic acid oxidation of **20** afforded **16**, which again was not identical with the 7 ketone obtained by hydroboration–oxidation.

Although neither **15** nor **16** were identical with the ketone obtained from the hydroboration, a comparison of the nmr chemical shifts of these ketones permitted a tentative assignment of stereochemistry to the original ketone. In the compound with an equatorial methyl groups (**16**), both rings A and B should be in the normal chair and half-chair conformations, respectively; and by comparison with data in the 18,19-bisnorpodocarpa-8,11,13-triene series,[21] this was found to be the case. In compound **16**, the C-10 methyl signal appears at δ 1.16 with a chemical-shift difference of δ 0.07 when compared with the corresponding hydrocarbon (**20**), in excellent accord with those reported by Wenkert, *et al.*[21] In the case of compounds in the 7-ketodehydroabietane series having an axial C-4 methyl, it has been noted that ring B exists in a half-boat conformation, relieving the rather severe 1,3-methyl interaction between the axial C-4 methyl group and the angular methyl.[21] Again, the nmr spectra of **19** and **15** are in agreement with this conclusion, with the C-10 methyl signal in **19** appearing at δ 1.25; however, the difference in chemical shift between **19** and **15** is δ 0.10, somewhat more than that observed by Wenkert, *et al.*[21] The crystalline ketone isolated from the hydroboration must, therefore, be one of the two *cis* isomers (**17** or **18**). If compound **17** were to exist in a steroidlike conformation (**17a**) the C-4 α-methyl group would be axial, while in the nonsteroid conformation (**17b**) it would be equatorial. In the case of **18**, the steroid conformation with C-4 equatorial (**18a**) should be preferred. The angular methyl group in both **17a** and **18a** appears to have the same spatial relationship to the aromatic ring and carbonyl group as it does in **16**, and consequently the chemical shift for these protons should be in the range of δ 1.10–1.25.[21] Since the chemical shift of the C-10 methyl signal in the crystalline ketone appears at δ 1.48, well downfield from that expected for **18a**, it seemed probable that this ketone was 19-norabieta-8,11,13-trien-7-one (**17**).

In an effort to confirm the structure and stereochemistry of the compound assigned structure **17**, methyl

(13) D. R. Brannon, H. Boaz, B. J. Wiley, J. Mabe, and D. R. Horton, *J. Org. Chem.*, **33**, 4462 (1968). In their original communication [*Chem. Commun.*, 681 (1968)] these authors assign, without explanation, different values to the chemical shift of the C-4 methyl protons than they do in the full paper.

(14) The sample of **14** to which the authors in ref 13 assign the 3-keto structure was obtained in very small quantity, and characterized principally by mass spectrometery. It should be noted that, in two other 3-keto abieta-8,11,13-trienes discussed in ref 13, the C-10 methyl signals appear at δ 1.41 and 1.44. Compound **14** has also been prepared by Biellman,[5b,12] but its properties have not been described in detail.

(15) N. P. Jensen and W. S. Johnson *J. Org. Chem.*, **32**, 2045 (1967); see also ref 5a.

(16) (a) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958); (b) E. Wenkert and J. W. Chamberlin, *ibid.*, **81**, 683 (1959).

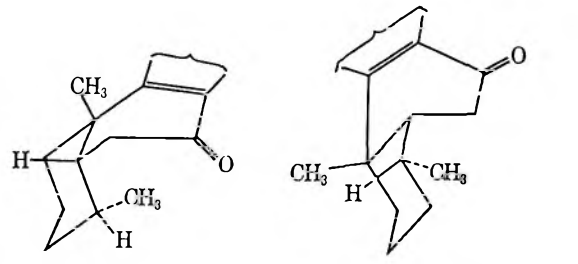
(17) P. G. Arapakos, *ibid.*, **89**, 6794 (1967).

(18) Neither we nor Professor Burgstahler have a satisfactory explanation for this discrepancy in melting points, unless one is dealing with different crystalline modifications of the same compound.

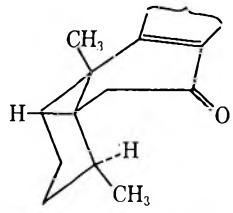
(19) G. W. Perold and O. Jeger, *Helv. Chim. Acta*, **32**, 1085 (1949).

(20) This aldehyde was prepared by Burgstahler and Marx[5a] by chromic acid oxidation of **12**. However, we employed the Moffatt oxidation procedure: K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965).

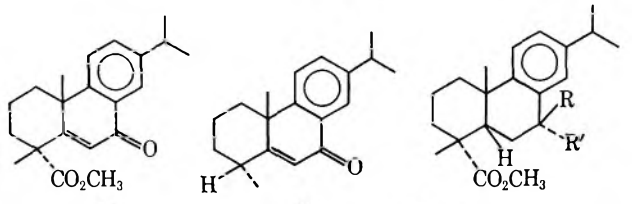
(21) E. Wenkert, A. Alonso, P. Beak, R. W. J. Carney, P. W. Jeffs, and J. D. McChesney, *J. Org. Chem.*, **30**, 713 (1965).



17a 17b



18a



22 23 24, R = H; R′ = OCOCH$_3$ 25, R = OCOCH$_3$; R′ = H

7-oxoabieta-5,8,11,13-tetraen-18-oate (**22**)[22] was subjected to vigorous basic hydrolysis with simultaneous decarboxylation to give 19-norabieta-5,8,11,13-tetraen-7-one (**23**). It is assumed that this sequence gives rise to the stable 19-nor isomer, rather than the 18-nor compound. In addition to **23**, a small quantity of **17** was obtained from this reaction, apparently *via* a 1,4-hydride transfer.[23] Catalytic hydrogenation of **23**, employing a rhodium catalyst to minimize hydrogenolysis, gave **17**, identical with the material obtained from the hydroboration–oxidation sequence.

Although the route by which this ketone is formed during the hydroboration sequence is unclear, it must be derived from the Δ^4 olefin (**6**) by β attack of diborane. Since **17** was not obtained in those reactions in which the mixture of alcohols was separated from the other components of the hydroboration mixture, this ketone is probably formed from the corresponding hydrocarbon through benzylic oxidation.

In the lead tetraacetate decarboxylation of podocarpic acid methyl ether, a considerable quantity of C-7 oxidation products was obtained.[3f] Examination of the more polar fractions from the decarboxylation of **1** gave no indication of any appreciable amount of this type of oxidation in the dehydroabietane series under the reaction conditions used. Repetition of the reported lead tetraacetate oxidation of methyl dehydroabietate[24] gave both isomeric 7 acetates (**24** and **25**), rather than just one isomer as reported earlier.[25]

(22) E. Wenkert, R. W. J. Carney, and C. Kaneko, *J. Amer. Chem. Soc.*, **83**, 4440 (1961).

(23) A compound which was assigned structure **23** had been reported earlier;[3d] however, it is not identical with that prepared in this work. It is possible that the earlier compound is actually the C-4 epimer; however, a lack of material precluded a detailed reinvestigation.

(24) G. Dupont, R. Dulou, G. Ourisson, and C. Thibault, *Bull. Soc. Chim. Fr.*, 708 (1955).

Experimental Section[26]

Decarboxylations of Dehydroabietic Acid. A.—The reaction of dehydroabietic acid with lead tetraacetate was carried out as previously described.[2e] From 27.95 g of acid, there was obtained, after chromatography on alumina, 15.43 g (68%) of a mixture of olefins which consisted of 19-norabieta-3,8,11,13-tetraene (**5**), 19-norabieta-4(18),8,11,13-tetraene (**2**), and 19-norabieta-4,8,-11,13-tetraene (**6**) in a ratio of 2:2:1. The composition of the mixture was determined by the relative areas of vinyl and aromatic peaks in the nmr. The benzene fractions from the chromatography gave 1.95 g (7%) of 4-acetoxy-18-norabieta-8,11,13-triene (**7**) as an oil: nmr 1.96 (s, CH_3CO), 1.55 (s, C-4 methyl), and 1.18 ppm (s, C-10 methyl). This ester was hydrolyzed to the 4-ol (**9**) by the method of Cambie. From 1.06 g of acetate, there was obtained, after chromatography on Merck alumina and elution with hexane, 0.048 g of a mixture of the Δ^3, Δ^4, and $\Delta^{4(18)}$ olefins in a ratio of 1:2:1. Elution with benzene gave 0.177 g of recovered acetate, while the methylene chloride fractions afforded 0.415 g (52%) of 18-norabieta-8,11,13-trien-4-ol (**9**) as a white solid. Recrystallization from hexane gave material of mp 90–91° (lit.[3g,10b] mp 91.5–92.5°); nmr 1.21 (s, C-4 methyl) and 1.16 ppm (s, C-10 methyl). The infrared spectrum of this compound was essentially the same as that reported previously for a noncrystalline substance assigned this structure.[3d]

B.—The potassium carbonate elimination reaction of 4-methylamino-18-norabieta-8,11,12-triene was carried out as previously described.[3c,d] From 3.10 g of base hydrochloride there was obtained 0.77 g of a hydrocarbon mixture which, by integration of the nmr spectrum, consisted of 80% 4(18) olefin **2** and *ca.* 10% each of the endocyclic isomers.

C.—4-Amino-18-norabieta-8,11,13-triene (**11**) was prepared essentially according to the method of Seelye and Watkins.[3g,6] The infrared spectrum of this material was identical with that of a sample prepared by the method of Huffman and Stockel.[27] The nmr assignments were in agreement with those of Seelye and Watkins,[3g,6] and the picrate had a melting point of 218–220° (lit. mp 218–220°,[3g] 222–223° [27]). The deamination was carried out according to the procedure of Seelye and Watkins,[3g,6] and, from 10.0 g of amine, chromatography on alumina and elution with hexane gave 1.70 g (18%) of a mixture of hydrocarbons containing 60% **2**, 33% **5**, and 7% **6**. The benzene fractions gave 0.084 g (0.8%) of the 4-acetate (**7**), identical with that prepared above, while benzene–methylene chloride fractions gave 0.120 g (1.2%) of the 4-ol (**9**) as a white solid which was recrystallized from hexane, mp and mmp 89–90°. In contrast to the experience of the earlier workers, no difficulty in crystallizing this material was encountered.

From an analysis of the nmr spectra of the various mixtures of hydrocarbons obtained in these experiments, correlations with the data of Bennett and Cambie, and examination of the spectrum of a pure sample of Δ^4 olefin (*vide infra*), it is possible to assign the following signals in the nmr spectra of the three olefins: 19-norabieta-3,8,11,13-tetraene (**5**), 5.30 (m, H-3) and 1.05 ppm (s, C-10 methyl); 19-norabieta-4(18),8,11,13-tetraene (**2**), 4.70 (d, J = 15 Hz, H-19) and 0.99 ppm (s, C-10 methyl); 19-norabieta-4,8,11,13-tetraene (**6**), 1.66 (s, C-4 methyl) and 1.38 ppm (s, C-10 methyl).

Hydroboration–Oxidation of Abietatetraene Mixture.—To a solution of 4.00 g of the olefin mixture obtained by the lead tetraacetate decarboxylation and 1.40 g of lithium aluminum hydride

(25) The assignments of stereochemistry made in ref 24 are in fact reversed; however, the original stereochemical assignments of P. F. Ritchie, T. F. Sanderson, and L. F. McBurney [*J. Amer. Chem. Soc.*, **75**, 2610 (1953)] are correct. The nmr spectrum of **24** has been noted by W. Herz and H. J. Wahlborg [*J. Org. Chem.*, **30**, 1881 (1965)], while that of **25** is mentioned in ref 13.

(26) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as films or potassium bromide pellets on a Perkin-Elmer Model 137 spectropolarimeter. Ultraviolet spectra were determined as methanol solutions using a Perkin-Elmer Model 202 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60 spectrometer using deuteriochloroform as solvent and tetramethylsilane as an internal standard. Signals are given in parts per million relative to the standard. Optical rotatory dispersion curves were determined in methanol with a Jasco ORD/UV-5 spectropolarimeter. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(27) J. W. Huffman and R. F. Stockel, unpublished work. See also R. F. Stockel, Ph.D. Dissertation, Clemson University, 1962; *Can. J. Chem.*, **41**, 834 (1963).

in 100 ml of dry ether at 0° was added dropwise over a 30-min period 5.0 ml of redistilled boron trifluoride etherate in 80 ml of dry ether. The reaction mixture was allowed to warm to room temperature and stirred for 2.5 hr. Ice and saturated sodium chloride were added and the ether was decanted. The ethereal solution was dried, the solvent was removed *in vacuo* with gentle warming, and the mixture of alkylboranes was taken up in 150 ml of tetrahydrofuran and 80 ml of 10% sodium hydroxide. To this solution was added 60 ml of 30% hydrogen peroxide and the reaction mixture was stirred for 18 hr at room temperature. The aqueous layer was drawn off and extracted three times with ether, and the ethereal extracts were combined with the original organic phase. The combined extracts were washed with water and dried, and the solvents were removed at reduced pressure to give 4.29 g of colorless oil. Tlc [silica gel G, benzene–ethyl acetate (8:1)] showed a six-component mixture, with one component moving near the solvent front. Two of the remaining five components of the mixture appeared to predominate. The mixture was dissolved in hexane and chromatographed on 80 g of Merck acid-washed alumina. Elution with hexane gave 0.555 g of 19-norabieta-4,8,11,12-tetraene (6), which was identified by its nmr spectrum (*vide supra*).[28] Elution with benzene–methylene chloride mixtures gave, in order, 0.125 g of a mixture of two alcohols with very similar R_f values on tlc and 0.337 g of 18-norabieta-8,11,13-trien-3α-ol (**13**) as a white solid: nmr 3.83 (m, $W_{1/2}$ = 7 Hz, H-3), 1.18 (s, C-10 methyl), and 0.99 ppm (d, J = 7 Hz, C-4 methyl). The analytical sample, mp 119–120°, was crystallized from hexane.

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.51; H, 10.50.

Further elution with benzene–methylene chloride mixtures gave 0.203 g of a mixture of the 3α-ol and two other compounds, while the final benzene–methylene chloride fractions gave 0.645 g of 18-norabieta-8,11,13-trien-19-ol (**12**) as a colorless oil. The nmr spectrum agreed well with that reported by Burgstahler and Marx,[5a] with signals at 3.75 (d, J = 6 Hz, H-19) and 1.03 ppm (s, C-10 methyl).

In another run, 1.166 g of the mixture of alcohols, after the separation of the hydrocarbon fraction, was dissolved in 100 ml of acetone and treated with excess Kiliani reagent. After the crude product was isolated in the usual manner, it was separated into 0.094 g of acidic material and 0.987 g of a neutral fraction. Tlc (silica gel G–benzene) indicated that this neutral fraction consisted of two major components, and it was dissolved in hexane and chromatographed on 25 g of acid-washed alumina. Elution with benzene–hexane (3:2) gave 0.167 g of 19-norabieta-8,11,13-trien-3-one (**14**) as a colorless oil:[29] $\lambda_{C=O}$ 5.86 μ; nmr 1.37 (s, C-10 methyl) and 1.10 (d, J = Hz, C-4 methyl); ORD $[\phi]_{400}$ +324°, $[\phi]_{301}$ +1610°, $[\phi]_{264}$ −810°. For analysis this material was converted into the 2,4-dinitrophenylhydrazone, mp 154–155° from ethanol–ethyl acetate.

Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.42; H, 6.65; N, 12.27.

The acid fraction was dissolved in ether and treated with excess ethereal diazomethane. After removal of the solvents, tlc (silica gel G–benzene) indicated the presence of three compounds and the material was not investigated further.

In one run carried out on 4.0 g of olefins in which the total crude hydroboration mixture was oxidized directly as described above, the first hexane–benzene fractions from the chromatography of the neutral fraction gave 0.045 g of 19-nor-5β-abieta-8,11,13-trien-7-one (**17**): mp 104–105° from hexane; $\lambda_{C=O}$ 5.97 μ; λ_{max} 252 mμ (log ε 4.08) and 303 (3.43); nmr 8.02 (br s, H-14), 1.48 (s, C-10 methyl), and 0.91 ppm (d, J = 7 Hz, C-4 methyl). Owing to the solubility of this material in common solvents, it was converted into the dinitrophenylhydrazone, mp 197–199° from ethanol–ethyl acetate.

Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.51; H, 6.79; N, 12.20.

19-Norabieta-8,11,13-trien-3-one (**14**).—To a solution of 0.110 g of 18-norabieta-8,11,13-trien-3α-ol (**13**) in 15 ml of acetone was added Kiliani reagent dropwise until a permanent orange color persisted. The reaction mixture was allowed to stand at room temperature for 19 min, 2 drops of water and 3 drops of 10% sodium hydroxide were added, and the precipitated solids were removed. The acetone solution was diluted with water and extracted with three portions of ether, the ethereal extracts were combined, washed with water, and dried, and the solvent was removed *in vacuo* to leave 0.081 g of oil. This oil was taken up in 5 ml of diglyme, 0.5 ml of 2 *N* hydrochloric acid was added, and the mixture was heated on the steam bath for 30 min. The reaction mixture was diluted with water and extracted with two portions of hexane. The hexane extracts were combined, washed with water, and dried, and the solvent was removed at reduced pressure to give 0.070 g (64%) of ketone, identical with that described above.

18-Norabieta-8,11,13-triene (**19**).—Catalytic hydrogenation (platinum oxide–ethanol, 30 psi, 25°) of 1.50 g of the mixed olefins from the lead tetraacetate decarboxylation of dehydroabietic acid gave 1.50 g (100%) of hydrocarbon, nmr 1.15 (s, C-10 methyl) and 0.99 ppm (d, J = 7 Hz, C-4 methyl). The 12,14-dinitro derivative had a melting point of 174–176° (lit.[5a] mp 176–177°).

18-Norabieta-8,11,13-trien-7-one (**15**).—To a solution of 0.70 g of **19** in 25 ml of acetic acid was added a solution of 1.10 g of chromium trioxide in a solution of 2 ml of water and 25 ml of acetic acid. The reaction mixture was stirred at room temperature for 18 hr, the solvent was removed at reduced pressure, and the residue was taken up in ether. The ethereal extracts were washed with water and 10% aqueous sodium hydroxide and dried, and the solvent was removed at reduced pressure to leave 0.28 g of yellow oil. Chromatography on acid-washed alumina and elution with hexane gave 0.056 g of recovered hydrocarbon, while elution with hexane–benzene (3:1) gave 0.092 g (14%) of **15** as a colorless oil: $\lambda_{C=O}$ 5.96 μ; μ_{max} 254 mμ (log ε 3.99) and 303 (3.28); nmr 7.82 (br s, H-14), 1.25 (s, C-10 methyl), and 1.05 ppm (d, J = 7 Hz, C-4 methyl). For analysis this compound was converted into the dinitrophenylhydrazone, mp 180–182° from ethanol.

Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.87; H, 6.55; N, 12.64.

19-Norabieta-8,11,13-trien-18-al.—To a solution of 0.538 g of 18-nor-abieta-8,11,13-trien-19-ol (**12**) in 4 ml of DMSO and 8 ml of benzene was added 1.40 g of dicyclohexylcarbodiimide, 0.20 ml of pyridine, and 0.10 ml of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 21 hr, diluted with ether, and washed thoroughly with water and 10% hydrochloric acid. The ethereal solution was dried and the solvent was removed at reduced pressure to give 0.326 g of brown oil. This oil was taken up in 15 ml of diglyme and treated with 1.5 ml of 2 *N* hydrochloric acid as described above to give 0.224 g of oil, which was dissolved in hexane–benzene (3:2) and filtered through a short alumina column to give 0.102 g (19%) of aldehyde, the infrared spectrum of which was identical with that reported earlier.[3d] This compound showed nmr signals at 9.53 (d, J = 4 Hz, H-18) and 1.12 ppm (s, C-10 methyl).

19-Norabieta-8,11,13-triene (**20**). **A.**—To a solution of 3.0 g of sodium in 50 ml of liquid ammonia was added 1.50 g of dehydroabietonitrile. The reaction mixture was stirred at reflux for 2 hr and then the ammonia was allowed to evaporate. The residue was taken up in ether, water was added cautiously, and the aqueous layer was drawn off and washed with ether. The ether layers were combined, washed with water and dilute hydrochloric acid, and dried, and the solvent was removed *in vacuo* to give an off-white oil, the infrared spectrum of which showed the presence of some unreacted nitrile. The oil was taken up in hexane and filtered through alumina to give 0.727 g (53%) of hydrocarbon as a colorless oil with nmr signals at 1.09 (s, C-10 methyl) and 0.93 ppm (d, J = 5 Hz, C-4 methyl). The 12,14-dinitro derivative was prepared and after chromatography and recrystallization from methanol had a melting point of 130–131° (lit. mp 151–153°,[5a] 133–134°[19]).

Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.88; H, 7.56; N, 8.09. Found: C, 65.65; H, 7.39; N, 8.17.

The dinitro derivative had nmr signals at 7.60 (s, H-11), 1.12 (s, C-10 methyl), and 0.95 ppm (d, J = 5 Hz, C-4 methyl).

B.—To a solution of 0.132 g of 19-norabieta-8,11,13-trien-18-al in 15 ml of diethylene glycol was added 1.0 ml of hydrazine and 1.0 g of sodium hydroxide. The reaction mixture was heated at 150° for 2 hr and then at reflux for 4 hr. After cooling, the solution was diluted with water and extracted with two portions of hexane. The hexane extracts were combined, washed with water, and dried, and the solvent was removed. The residue

(28) In subsequent runs, considerably smaller quantities (0.1–0.2 g) of saturated hydrocarbons (abietatrienes) were obtained in this fraction.

(29) The balance of the material was, from the infrared spectrum of the crude neutral fraction, the 18 and/or 19 aldehyde. Subsequent experience indicated that these aldehydes were somewhat unstable to chromatography on alumina.

was redissolved in hexane and filtered through alumina to give 0.051 g (41%) of **20**, identical with that described in part A.

19-Norabieta-8,11,13-trien-7-one (16).—The hydrocarbon was oxidized as described above in the preparation of the 18-norketone. From 0.50 g of starting material there was obtained 0.183 g (33%) of 7-one **16** as a colorless oil: $\lambda_{C=O}$ 5.96 μ; λ_{max} 254 mμ (log ε 4.04) and 302 (3.80); nmr 7.90 (br s, H-14), 1.16 (s, C-10 methyl), and 0.90 ppm (d, J = 5 Hz, C-4 methyl). For analysis, the dinitrophenylhydrazone, mp 204–295° from ethanol–ethyl acetate, was prepared.

Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 5.71; N, 12.44. Found: C, 66.42; H, 6.73; N, 12.29.

19-Norabieta-5,8,11,13-tetraen-7-one (23).—To a solution of 1.68 g of methyl 7-oxoabieta-5,8,11,13-tetraen-18-oate (**22**) in 10 ml of diethylene glycol was added 0.60 g of sodium hydroxide and a few drops of water. The reaction mixture was heated at reflux for 18 hr, cooled, diluted with water, and extracted with four portions of hexane. The hexane extracts were washed with water and diluted hydrochloric acid and dried, and the solvent was removed at reduced pressure to give 0.89 g of brown oil. Tlc (silica gel G–benzene) indicated the presence of two compounds, and the mixture was taken up in hexane–benzene (3:1) and chromatographed on alumina. Elution with hexane–benzene (2:1) gave 0.041 g of 19-nor-5β-abieta-8,11,13-trien-7-one (**17**), mp and mmp 100–102°. The more polar hexane–benzene fractions gave 0.173 g of **23** as off-white crystals: mp 65–67°; $\lambda_{C=O}$ 6.03 μ; λ_{max} 256 mμ (log ε 4.08), 266 (sh, 4.00), and 304 (3.34); nmr 8.03 (br s, H-14), 6.30 (d, J = 1.5 Hz, H-6), 1.48 (s, C-10 methyl), and 1.19 ppm (d, J = 6 Hz, C-4 methyl). This compound was too soluble in common solvents to be satisfactorily recrystallized, and was converted into the dinitrophenylhydrazone, mp 222–223° from ethyl acetate, for analysis. A mixture melting point with the derivative, mp 230–231°, of a ketone assigned this structure previously[3d] was 212–220°.

Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 66.95; H, 6.29; N 12.49. Found: C, 66.68; H, 6.12; N, 12.36.

19-Nor-5β-abieta-8,11,13-trien-7-one (17).—Catalytic hydrogenation (5% rhodium on alumina, methanol, 25 psi) of 0.056 g of **23** gave, after filtration and evaporation of solvent, 0.035 g of brown semisolid. The infrared spectrum of this material indicated that it was a mixture of ketone and alcohol, and tlc (silica gel G–benzene) confirmed this observation. The residue was taken np in hexane–benzene (3:1) and chromatographed on Merck acid-washed alumina. Elution with hexane–benzene (1:1) gave 0.009 g of **17** as white crystals, mp 99–101°, mmp 102–104° with the material obtained previously. Elution with benzene–methylene chloride (1:1) gave 0.024 g of a mixture of alcohols, which was not investigated further.

Lead Tetraacetate Oxidation of Methyl Dehydroabietate.—The reaction with lead tetraacetate was carried out as described by DuPont.[24] From 2.00 g of ester there was obtained 0.172 g of methyl 7α-acetoxyabieta-8,11,13-trien-18-oate (**24**): mp 160–161° (lit. mp 167°); $\lambda_{C=O}$ 5.80 μ; nmr 5.89 (q, $W_{1/2}$ = 7 Hz, H-7), 1.27 (s, C-4 methyl), and 1.18 ppm (s, C-10 methyl). Hydrolysis of this ester afforded the 7α-ol, mp 107–108° (lit.[24] mp 111°). The dark brown, gummy residue, 1.94 g, remaining after removing the crystalline α acetate was taken up in 200 ml of methanol to which was added 8.0 g of potassium hydroxide and 10 ml of water. The reaction mixture was heated at reflux for 2 hr, concentrated to a small volume, and diluted with ether, and the ether extracts were washed with water and dried. After removal of the solvent, there was obtained 0.531 g of a dark brown glass which was taken up in benzene and chromatographed on acid-washed alumina. Elution with benzene gave 0.183 g of colorless oil, which appeared to be a mixture of recovered starting material and elimination products. The methylene chloride fractions afforded 0.176 g of a mixture of 7β (**25**) and 7α-ols (**24**), which by integration of the nmr spectrum contained 63% β isomer. A sample of methyl 7β-hydroxyabieta-8,11,13-trien-18-oate (**25**), prepared by borohydride reduction of the 7 ketone, gave nmr signals at 4.82 (t, J = 8 Hz, H-7) and 1.28 ppm (s, C-10 methyl and C-4 methyl). The corresponding acetate has a similar spectrum with H-7 shifted to 6.08 ppm.

Registry No.—**1**, 1740-19-8; **2**, 22478-62-2; **5**, 22478-63-3; **6**, 22478-64-4; **7**, 22566-05-8; **13**, 22576-98-3; **14**, 22566-06-9; **14** 2,4-dinitrophenylhydrazone, 22566-07-0; **15**, 22566-08-1; **15** 2,4-dinitrophenylhydrazone, 22593-99-3; **16**, 22566-09-2; **16** 2,4-dinitrophenylhydrazone, 22566-10-5; **17**, 22566-11-6; **17** 2,4-dinitrophenylhydrazone, 22566-12-7; **19**, 19407-17-1; **20**, 19407-18-2; **23**, 22566-15-0; **23** 2,4-dinitrophenylhydrazone, 22566-16-1; **24**, 22565-68-0; **25**, 17901-36-9.

Acknowledgments.—The spectropolarimeter used in this work was obtained through a National Science Foundation Research Instruments Grant. We would like to thank T. F. Sanderson of Hercules, Inc., for a generous gift of dehydroabietonitrile.

The Photochemical Lactolization and Deconjugation of *trans*-Steroidal α,β-Unsaturated Acids

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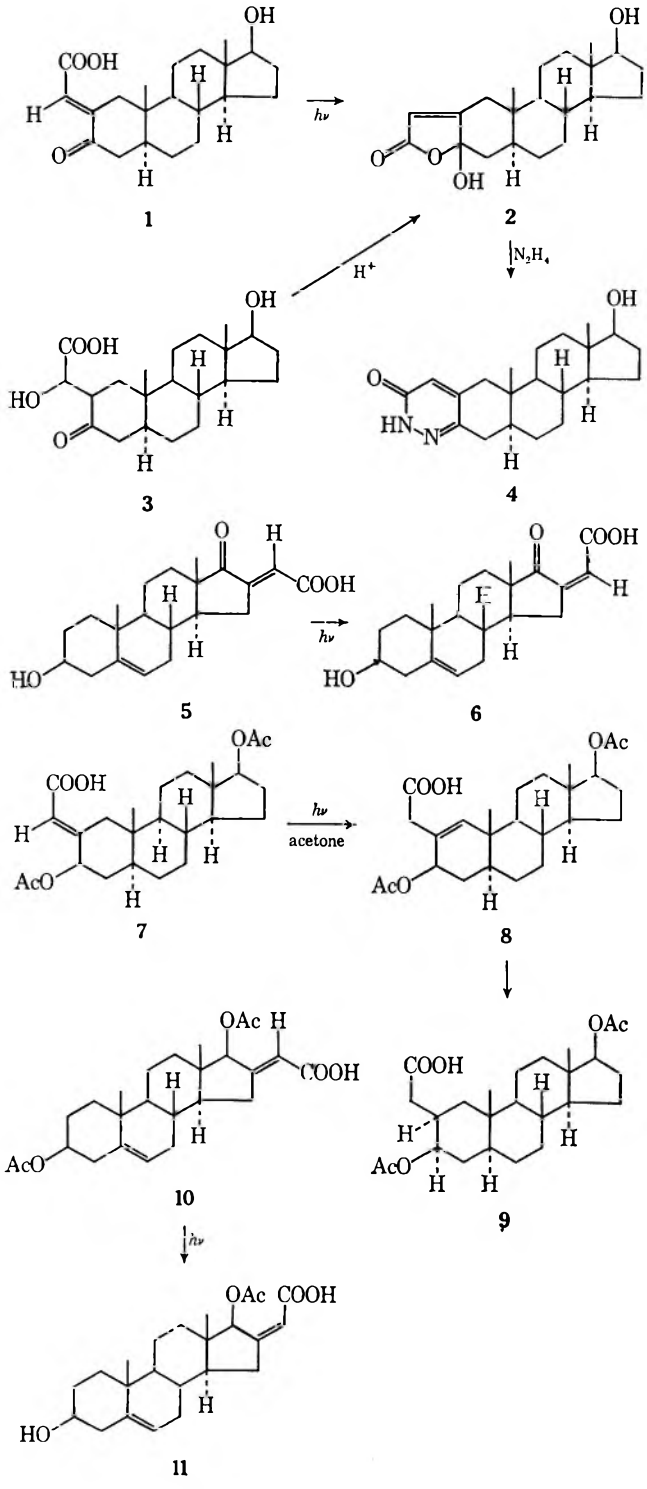
Received June 30, 1969

The photoisomerization of 2-(*trans*-ylideneacetic acid)-17β-hydroxy-5α-androstan-3-one (**1**) was studied and was shown to give 3ξ,17β-dihydroxy-5′(2′H)-oxo-5α-androstano[3,2-*b*]furan (**2**). Irradiation of the corresponding 17-keto-16-(*trans*-ylideneacetic acid)androst-5(6)-en-3β-ol (**5**) gave only *trans–cis* isomerization of the side chain. A shift of the side-chain double bond in 2-(*trans*-ylideneacetic acid)-3β,17β-dihydroxy-5α-androstane diacetate (**7**) to the C-1(2) position was observed when the irradiation was carried out in acetone. This deconjugated acid **8** was characterized by the facile ketonization of its C-3 hydroxyl function in refluxing alkaline solution. Only *trans–cis* isomerization occurred when 16-(*trans*-ylideneacetic acid)-3β,17β-dihydroxyandrost-5(6)-ene diacetate (**10**) was similarly irradiated. Some aspects of the mechanisms of these transformations are discussed.

In the course of the study of general methods for the synthesis of ring-A fused heterocyclic steroids, we became interested in the chemistry of 2-(*trans*-ylideneacetic acid)-17β-hydroxy-5α-androstan-3-one (**1**).[1] The results of our study of the photochemical behavior of this system are reported here.

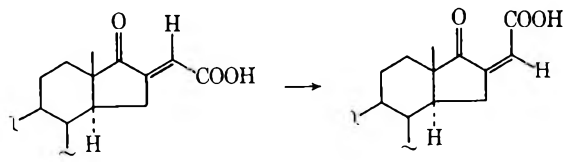
Irradiation of **1** using ultraviolet light (3550 Å) for 3–4 hr in methanol gave a product with infrared, ultraviolet, and nmr spectra characteristic of the α,β-unsaturated lactol **2**. This compound was found to be identical with the lactol obtained from the acid-catalyzed cyclodehydration of **3**. The lactol was further characterized by its quantitative conversion into the pyridazone **4** with ethanolic hydrazine.[1]

(1) M. Debono, R. M. Molloy, and L. Patterson, *J. Org. Chem.*, **34**, 3032 (1969).



Previous study of the photochemistry of γ-keto α,β-unsaturated acids has been limited to a report by Lutz concerning the lactolization of aroyl-α- (and β-) methylacrylic acids.[2] Lutz observed that the parent *trans*-benzoylacrylic acid did not cyclize upon irradiation with sunlight, but was isomerized to the open-chain *cis* isomer. Since **1** has alkyl substitution on the side-chain olefinic bond, it follows from Lutz's observation that the cyclic lactol form could be expected in the isomerization of **2**.

Photolysis of the 16-ylideneacetic acid 17-keto steroid **5** did not result in lactol formation, but a *trans*-*cis* isomerization of the side chain occurred to give a keto acid, **6**, as evidenced by the shift of the nmr signal for the olefinic proton of **6** from δ 6.3 to 6.1 ppm.[2] This shift corresponds to the removal of the side-chain olefinic proton from the deshielding region about the C-17 carbonyl group. The reaction appeared to reach equilibrium rapidly, and the ratio of *cis* to *trans* isomers approached 1:1 within 6 hr. The factors



which determine whether the keto group will interact with the side-chain carboxyl group to form a lactol remain obscure. Undoubtedly a number of steric and electronic factors are operative in this transformation.

Conversion of the C-3 carbonyl group of **1** into a 3β-acetoxyl group by reduction and acetylation gave **7**, which was expectedly inert to the irradiation conditions which isomerized **1**.[3] However, irradiation of **7** in acetone caused disappearance of the uv and ir bands characteristic of α,β-unsaturated acid (217 mμ and 1650 cm^{-1}, respectively).

The product showed an upfield shift of the olefinic proton signal from δ 5.9 to 5.62 (isolated double bond), where it is partially superimposed on the broad multiplet at δ 5.42 (allylic C-3 proton). In addition, the doublet at δ 4.2, which corresponds to the signal for the equatorial C-1 proton, is no longer present.[4] These data are consistent with the structural assignment **8**, which results from the deconjugation of the olefinic bond to the C-1 position. Shift of the double bond in α,β-unsaturated acids to the β,γ position upon photolysis has been observed by Kropp[5,6] with crotonic acid, while others have observed this with acyclic α,β-unsaturated aldehydes and ketones.[7] This structural assignment was confirmed by hydrogenation to **9**, which had also been obtained from the hydrogenation of **7**.[1] The 2β configuration of the side chain of **9** was assigned on the basis of steric hindrance of the β side favoring hydrogenation from the α side.

The acid **8** was further characterized by its novel behavior under basic conditions.

When a methanolic solution of **8** containing excess base was refluxed for 3 hr, a keto acid was formed. Its nmr spectrum showed disappearance of the olefinic proton, the loss of one proton on carbon bearing oxygen, and a shift of the C-19 methyl from δ 0.78 to 1.12,[8] while the carboxylic proton was still evident (δ 10.13, which disappeared with D_2O). Treatment of **12** with methanolic *p*-toluenesulfonic acid at room temperature

(2) R. E. Lutz, P. S. Bailey, C. Dien, and J. W. Rinker, *J. Amer. Chem. Soc.*, **75**, 5039 (1953).

(3) (a) P. Kurath and W. Cole, *J. Org. Chem.*, **26**, 1939 (1961); (b) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *ibid.*, **23**, 1832 (1958).

(4) (a) H. Hauth, D. Stauffacher, P. Niklaus, and A. Melera, *Helv. Chim. Acta*, **48**, 1087 (1965); (b) R. L. Clarke, S. J. Daum, P. E. Shaw, and R. K. Kullnig, *J. Amer. Chem. Soc.*, **88**, 5865 (1966).

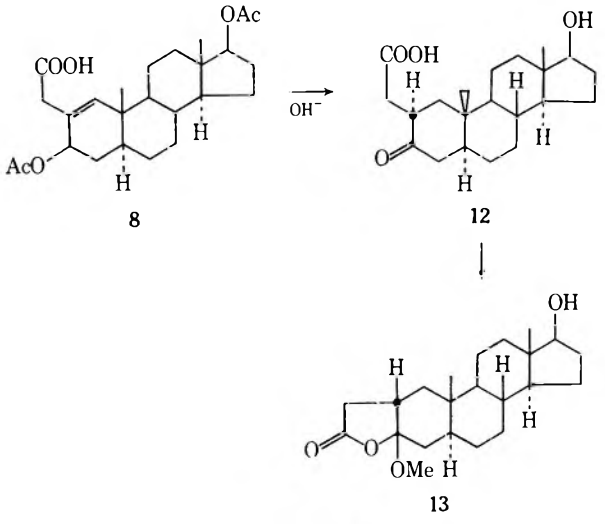
(5) P. J. Kropp and H. J. Krauss, *J. Org. Chem.*, **32**, 3222 (1967).

(6) For a recent study on the photoisomerization of ethyl crotonate, see R. R. Rando and W. von E. Doering, *ibid.*, **33**, 1671 (1968).

(7) For a representative summary of examples, see R. O. Kan, "Organic Photochemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1966, p 29.

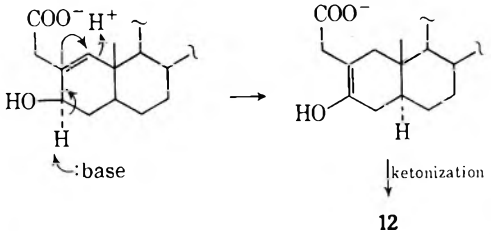
(8) This chemical-shift position for the C-19 methyl group could be estimated from Zurcher's rules, which are summarized in N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day Inc., San Francisco, Calif., 1964, p 19.

for 0.5 hr gave methoxylactol **13**. Its infrared spectrum showed a carbonyl band at 1770 cm^{-1}, and its nmr had a signal at δ 3.32 (s, 3 H, CH_3O–). The isolation of **13** indicates that the base treatment of **8** resulted in ketonization of the C-3 oxygen function.



The general features of this transformation are analogous to the work of Elderfield on the transformation of the $\Delta^{\alpha,\beta}$-lactol ring of strophanthidin into the lactolic side chain in isostrophantidin.[9] When the steroidal acid **7** was subjected to base treatment under conditions which isomerized **8**, no ketonization occurred, indicating that β,γ unsaturation, rather than α,β unsaturation, was necessary and that it was unlikely that isomerization of **8** to **7** occurred prior to formation of **12**.

The reaction can be formally represented as a base-catalyzed isomerization of a Δ^1 to a Δ^2 double bond, as shown in the following scheme.



Irradiation of the corresponding 16-*trans*-ylideneacetic acid 3β,17β-dihydroxyandrost-5-ene-3,17-diacetate (**10**) in acetone did not result in deconjugation but resulted solely in the *trans–cis* isomerization of C-16 side chain to give **11**. The product of this transformation retained the ultraviolet chromophore at 217 mμ and the nmr signal for the olefinic proton at δ 5.92, which corresponds to a downfield shift of δ 0.22 from the corresponding signal for the *trans* isomer at δ 5.7.

The difference between the photolyses of **7** and **10** in acetone deserves further comment. Reports concerning the conversion of α,β-unsaturated to β,γ-unsaturated carbonyl compounds propose that γ-hydrogen abstraction occurs through a six-membered transition state, a variation of the Norrish type II reaction.[10,11] Without speculating about the triplet or singlet character of the excited states involved, it seems reasonable that factors which assist the formation of a six-membered transition state will favor the deconjugation.[12] Models of **7** show that the C-2 side chain and the C-1 equatorial proton can achieve coplanarity, and close approach of the carboxyl carbonyl to the C-1 equatorial proton is possible without much conformational deformation of ring A. These factors would tend to facilitate γ-hydrogen abstraction and isomerization by the mechanism described above. Analogous discussion of the steric factors in **10** leads to the conclusion that the C-15 protons and the C-16 ylideneacetic acid side chain can not achieve coplanarity; therefore, an increased carboxyl–C-15 proton distance results, making abstraction of C-15 protons difficult.

Experimental Section

Melting points are uncorrected. Uv spectra were recorded on a Cary 15 spectrophotometer. Ir spectra were determined on a Perkin-Elmer 21. Nmr spectra were obtained on a Varian HR-60 with TMS as an internal standard. Irradiations were carried out in a Rayonet–Srinivasan–Griffin photochemical reactor under purified nitrogen at 35–40°, using quartz vessels.

Irradiation of 17β-Hydroxy-3-oxo-5α-androstane-$\Delta^{2,\alpha}$-acetic Acid (1).—Irradiation of 1.0 g of **1** in 450 ml of methanol was carried out in a Rayonet Chamber reactor equipped with 3550-Å ultraviolet sources under a stream of nitrogen for 3–4 hr.[1] The reaction mixture was evaporated to dryness under reduced pressure. The residue **2** was recrystallized from EtOH: yield 0.5 g; mp 256–260°; uv max (EtOH) 214 mμ (ε 30,000); ir ($CHCl_3$) 1760 and 1640 cm^{-1}; nmr δ 5.86 (br s, 1 H).

The compound was identical in all respects with the compound prepared from **3** by acid dehydration.[1]

Conversion of 3ξ,17β-Dihydroxy-5′(2′H)-oxo-5α-androstano-[3,2-*b*]furan (2) into the Pyridazone 4.—The lactol **2** (0.30 g) in 10 ml of EtOH was treated with 0.25 ml of hydrazine hydrate and refluxed for 6 hr.[1] Evaporation of solvent and recrystallization of the product from EtOH gave 200 mg, mp 268–270°.

Anal. Calcd for $C_{21}H_{30}N_2O_3 \cdot {}^1/_2C_2H_5OH$: C, 72.29; H, 9.10; N, 7.67. Found: C, 72.54; H, 8.84; N, 8.11.

Irradiation of 3β-Hydroxy-17-oxo-androst-5-en-16-ylideneacetic Acid (5).—A solution of 1.00 g of **5** in 500 ml of MeOH was irradiated by the above procedure for 3 hr.[3a] The solvent was removed under reduced pressure, and the product was collected, yield 501 mg. The nmr spectrum showed a 1:1 mixture of *cis* and *trans* keto acids. The *cis* acid could be fractionally crystallized from MeOH: yield 55 mg; mp 180–185°; nmr ($CDCl_3$ and 0.3 ml of DMSO) δ 6.20 (m, 1 H, >C=CHCOOH) and 1.07 and 1.01 (s, 3 H each, 2 angular CH_3).

Anal. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 73.10; H, 8.00.

Photoisomerization of 3β,17β-Diacetoxy-5α-androstan-2-ylideneacetic Acid (7).—The irradiation of **7** (2.5 g) was performed in 500 ml of Me_2CO, using the method described above, for 18 hr.[1] The solvent was removed under reduced pressure, and the residue was recrystallized from Et_2O–Me_2CO mixtures to give **8**: yield 1.35 g (54%); mp 211–213°; nmr ($CDCl_3$) δ 0.8 (s, 3 H, angular CH_3), 2.03 (s, 6 H, acetate), 4.6 (br t, 1 H, C-17 H), 5.5 (m, 1 H, C-3 H), 5.6 (s, 1 H, C-1 H), and 10.1 (m, 1 H, COOH).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.20; H, 8.42.

When this irradiation was carried out in MeOH, no significant amount of deconjugation occurred, and only starting material was isolated.

Photoisomerization of 3β,17β-Diacetoxyandrost-5-en-16-ylideneacetic Acid (10).—A solution of 2.0 g of **10** in 500 ml of Me_2CO was irradiated with 3550-Å ultraviolet light for 6 hr[3a] using the procedures outlined above. Evaporation of solvent gave a mixture which showed two components on tlc (silica gel,

(9) (a) W. D. Paist, E. R. Blout, F. C. Uhle, and R. C. Elderfield, *J. Org. Chem.*, **6**, 273 (1941). (b) For a review of the examples of this phenomenon in the strophanthidin series, see L. F. Fieser and M. Feiser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p 736.

(10) See ref 7, p 73.

(11) J. A. Barltrop and J. Wills, *Tetrahedron Lett.*, 4987 (1968).

(12) M. J. Jorgenson and L. Gundel, *ibid.*, 4991 (1968).

EtOAc). The less polar component was identified as starting material on the basis of nmr evidence (side-chain olefinic proton δ 5.7, 17-acetate at δ 2.19) and tlc. Fractional crystallization from MeOH gave the more polar component **11**: yield 990 mg; mp 208–211°; uv max (EtOH) 216 mμ (ϵ 9150); ir ($CHCl_3$) 1650 cm^{-1}; nmr ($CDCl_3$) 2.02 (s, 3 H, acetate, C-3 H), 4.45 (m, 1 H, C-3 H), 5.40 (m, 1 H, C-5 olefinic H), 5.60 (m, 1 H, C-17 H), and 5.94 (m, 1 H, side-chain olefinic H, *cis*). (The preceding values are for the D_2O run, since the carboxyl proton overlapped the last three signals at δ 5.40.)

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.95; H, 7.96.

Hydrogenation of 3β,17β-Diacetoxy-5α-androst-1-en-2-ylacetic Acid (8).—A solution containing 503 mg of **8** and 50 mg of platinum oxide in 250 ml of EtOH was hydrogenated at 1 atm pressure until hydrogen uptake diminished. The solvent was evaporated under reduced pressure, and the residue was recrystallized from ether to give 92 mg of recovered starting material. The mother liquors were concentrated, and the residue was recrystallized from ether to give 21 mg of a crystalline solid, mp 214–215°. The nmr spectrum of this compound showed angular methyl signals at 46 and 53 cps and two acetate singlets at δ 1.92 and 2.02. The C-3 and C-17 protons appeared at δ 4.92 and 4.10 (m), respectively.

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.32; H, 8.85.

Base-Catalyzed Isomerization of 8.—A solution containing 787 mg of **8** and 787 mg of NaOH in 100 ml of MeOH and 100 ml of H_2O was refluxed for 3 hr and then allowed to cool to room temperature. The solvent was evaporated to half its volume, 200 ml of H_2O was added, and the mixture was acidified with dilute HCl. The precipitate was collected and recrystallized from MeOH–Et_2O to give **12**: yield 483 mg; mp 217–219°; nmr ($CDCl_3$ –DMSO) δ 1.12 (s, 3 H, C-19 CH_3) and 3.63 (m, 1 H, C-17 H).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.12; H, 9.54.

17β-Hydroxy-5α-androstan-2α-ylacetic Acid 3-ξ-Methoxylactol (13).—A solution containing 400 mg of **12** and 30 mg of TsOH in 60 ml of MeOH was allowed to stand at room temperature. Tlc indicated that most of the starting material had been converted into a less polar product. The reaction mixture was poured into 300 ml of H_2O, extracted twice with 500 ml of Et_2O, and dried ($MgSO_4$). Evaporation of solvent and recrystallization from ether gave the crystalline solid **13**: yield 245 mg; mp 205–206°; ir ($CDCl_3$) 1770 cm^{-1}; nmr ($CDCl_3$) δ 0.72 (s, 3 H, C-18 CH_3), 0.84 (s, 3 H, C-19 CH_3), 3.32 (s, 3 H, OCH_3), and 3.6 (m, 1 H, C-17 H).

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.71; H, 9.36.

Registry No.—**2**, 20712-22-5; **4**, 22287-21-4; **6**, 22287-22-5; **8**, 22287-23-6; **9**, 20708-74-1; **11**, 22287-06-5; **12**, 22287-07-6; **13**, 22287-08-7.

Acknowledgments.—The authors wish to acknowledge the fine technical assistance of Mr. Lawrence E. Patterson, Dr. William Hargrove and associates (physico-chemical data), Mr. George Maciak and associates (microanalyses), and Mrs. Nancy Cone for their help in preparation of this article.

The Structure of Damsinic Acid, a New Sesquiterpene from *Ambrosia ambrosioides* (Cav.) Payne[1]

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Received July 14, 1969

The structure of a new sesquiterpene, damsinic acid, from *Ambrosia ambrosioides* (Cav.) Payne has been shown to be **2**. Pyrazoline derivatives of damsin (**1**) and damsinic acid were assigned structures based on CD and nmr studies.

We recently reported the isolation and identification of the pseudoguaianolide damsin (**1**)[3] as the cytotoxic principle of *Ambrosia ambrosioides* (Cav.) Payne. There was obtained in addition an inactive substance, mp 112–113°, which analyzed for $C_{15}H_{22}O_3$ and contained a carboxyl and carbonyl function, a secondary and tertiary methyl group, and an exocyclic methylene, as established by physical methods (uv, ir, nmr, and mass spectrum).[3] The structure of the compound, damsinic acid, has been determined as **2** from the following evidence. The nmr peaks for compounds reported in this paper are given in Table I.

The nmr spectrum of damsinic acid indicated an α-substituted acrylic acid side chain which was confirmed by (a) the spectral changes observed on hydrogenation to the dihydro acid **3**, (b) the formation of the methyl ester **4** with 1 mol of diazomethane and two isomeric pyrazoline esters **5a** and **5b** with excess reagent,[4] and (c) the liberation of acid **6** and formaldehyde on ozonolysis. The nature of the bicyclic system was established by dehydration followed by dehydrogenation of the diol **7** to chamazulene (**8**). The azulene product was not consonant with the requirement of one tertiary methyl group in the starting materials. Apparently a 1,2-methyl shift had occurred during aromatization, a migration already reported for other pseudoguaianolides.[5,6]

The location of the ketone group in the five-membered ring was suggested by the ir band at 1735 cm^{-1}. The C-4 position was preferred, in keeping with the previously isolated pseudoguaianolides from *Ambrosia*.[7] The incorporation of two deuterium atoms into the dihydro acid **3** according to the conditions of Komae and Nigam[8] established the assignment.

(1) Antitumor Agents. III. Previous paper: R. W. Doskotch and F. S. El-Feraly, *J. Pharm. Sci.*, in press. This investigation was supported by Public Health Service Research Grants CA-08133 from the National Cancer Institute and FR-00328 from Special Research Resources for purchase of the nmr spectrometer (Varian A-60A).

(2) National Institutes of Health Predoctoral Fellow, 1967–1968.

(3) R. W. Doskotch and C. D. Hufford, *J. Pharm. Sci.*, **58**, 186 (1969).

(4) P. G. Deuel and T. A. Geissman, *J. Amer. Chem. Soc.*, **79**, 3778 (1957); T. A. Geissman and R. Mukherjee, *J. Org. Chem.*, **33**, 656 (1968).

(5) (a) H. Abu-Shady and T. O. Soine, *J. Amer. Pharm. Assoc.*, **42**, 387 (1953); (b) L. Bernardi and G. Büchi, *Experientia*, **13**, 466 (1967).

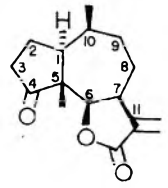
(6) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Amer. Chem. Soc.*, **84**, 2601 (1962).

(7) (a) W. Herz in "Recent Advances in Phytochemistry," T. J. Mabry, Ed., Appleton-Century-Crofts, New York, N. Y., 1968, p 229; (b) J. Romo and A. Romo de Vivar in "Progress in the Chemistry of Organic Natural Products," Vol. 25, L. Zechmeister, Ed., Springer-Verlag, New York, N. Y., 1967, pp 90–130.

(8) H. Komae and I. C. Nigam, *J. Org. Chem.*, **33**, 1771 (1968).

TABLE I

NMR PEAKS OF DAMSINIC ACID AND ITS DERIVATIVES[a]



1

Compd	C-5 CH_3	C-10 CH_3	C-11 CH_3	H-6	H-7	C-11 $=CH_2$	Miscellaneous
2	1.06	1.05 d (7.0)			2.83 m	5.63 6.27	11.23 (COOH)
3	1.01	1.02 d (6.6)	1.18 d (6.7)				10.47 (COOH)
4	1.04	1.05 d (7.0)				5.51 6.08	3.74 ($COOCH_3$)
5a	0.99	1.03 d (7)			2.9 m		3.77 ($COOCH_3$) 4.6 m[b] (CH_2CH_2N)
5b	1.02	1.03 d (7)			2.6 m		3.77 ($COOCH_3$) 4.5 m[b] (CH_2CH_2N)
6	1.01	1.02 d (6.3)			2.73 m		9.91 (COOH)
7	0.88	0.83 d (7)[c]	0.93 d (7)[c]				2.1 m[d] (OH)
9	1.17	1.16 d (6.8)	1.11 d (7.2)	4.54 d (5.4)			2.88 dq (7.2, 8.0,[e] H_{11})
11	1.12	1.09 d (6.8)[c]	1.24 d (6.7)[c]	4.44 d (8.2)			
12	0.98	0.95 d (7)[c]	0.97 d (7)[c]				3.4 m[d] (OH)
13	1.07	1.05 d (6.4)					3.15 d (4.8,[f] NCH_3) 7.4 m[d] (NH)
14	1.03	1.04 d (6.2)					2.78 d (4.7,[f] NCH_3) 5.51 m[d] (NH)
15a	1.27	1.15 d (7.3)		5.45 d (6.2)			4.75 m[b] (CH_2CH_2N)
15b	1.47	1.15 d (7.1)		4.79 d (9.1)	2.96 m		4.7 m[b] (CH_2CH_2N)

[a] Chemical shifts (δ, parts per million) were taken in $CDCl_3$ on Varian A-60A or HA100 instruments with TMS as internal standard; singlets are unmarked, d = doublet, m = multiplet with center given, q = quartet; coupling constants are given in parentheses in hertz. [b] The value recorded is the center of the multiplet of overlapping peaks for the four protons. [c] Values in row may be interchanged. [d] Lost in D_2O. [e] Two overlapping quartets forming five peaks are clearly visible in the 100-MHz spectrum. [f] Collapses to a singlet in D_2O.

The stereochemistry of the ring junction in damsinic acid was assigned as *trans* in keeping with other pseudoguaianolides[7b] on the basis of comparison of its ORD and CD curves with those of damsin. Both gave positive Cotton-effect curves with the first extremum at 315 mμ (a 37.7°) and 327 mμ (a 39.9°), respectively. The assignment for damsin derivatives was originally based on ORD studies[6] in comparison with appropriate steroid models.[9] The absolute stereochemistry follows from ambrosin (2,3-dehydrodamsin), whose 3-bromo derivative was subjected to X-ray analysis.[10]

Attempts to convert both damsin (**1**) and damsinic acid (**2**) into a common product, such as pseudoguaiane, for determining the configuration at C-7 and C-10 failed, but our findings are of interest to be recorded. Catalytic hydrogenation of damsin (**1**) under both heterogeneous[3,5] (Pd on charcoal) and homogeneous[11] [tris(triphenylphosphine)rhodium chloride] conditions results in poor yields of dihydrodamsin (**9**); the main product is dihydroisoambrosin (isodamsin, **10**). However, catalytic heterogeneous hydrogenation under alkaline conditions in which the lactone is opened gave no isodamsin, but instead gave dihydrodamsin (**9**) and 11-epidihydrodamsin (**11**).[12] The latter substance was prepared by Romo, *et al.*,[13] by Raney nickel desulfurization of the addition product of damsin and toluenethiol. Lithium aluminum hydride reduction of dihydrodamsin (**9**) gave the triol **12**, whose mesylate on reduction with the same reagent gave products of S–O bond cleavage. Similar products were obtained from the mesylate and tosylate of the diol **7**. Complete replacement of the tosylate by iodide in diol **7** ditosylate was likewise unsuccessful.

The stereochemistry at C-7 was established by CD studies.[14] In particular the curves of N-methyl thionamides have been shown to be related to the asymmetry at the α carbon,[16] and the corresponding derivative **13** of bisnordamsinic acid (**6**) was prepared *via* the amide **14**. The CD curve of **13** showed a weak negative band at 338 mμ ([θ] −200°) for the n → π^* absorption, the "optically active" band of the thione group. Since a negative Cotton effect in these deriva-

(9) C. Djerassi, R. Riniker and B. Riniker, *J. Amer. Chem. Soc.*, **78**, 6362 (1956).

(10) M. T. Emerson, W. Herz, C. N. Caughlan and R. W. Witters, *Tetrahedron Lett.*, 6151 (1966).

(11) J. F. Biellman and M. J. Jung, *J. Amer. Chem. Soc.*, **90**, 1673 (1968).

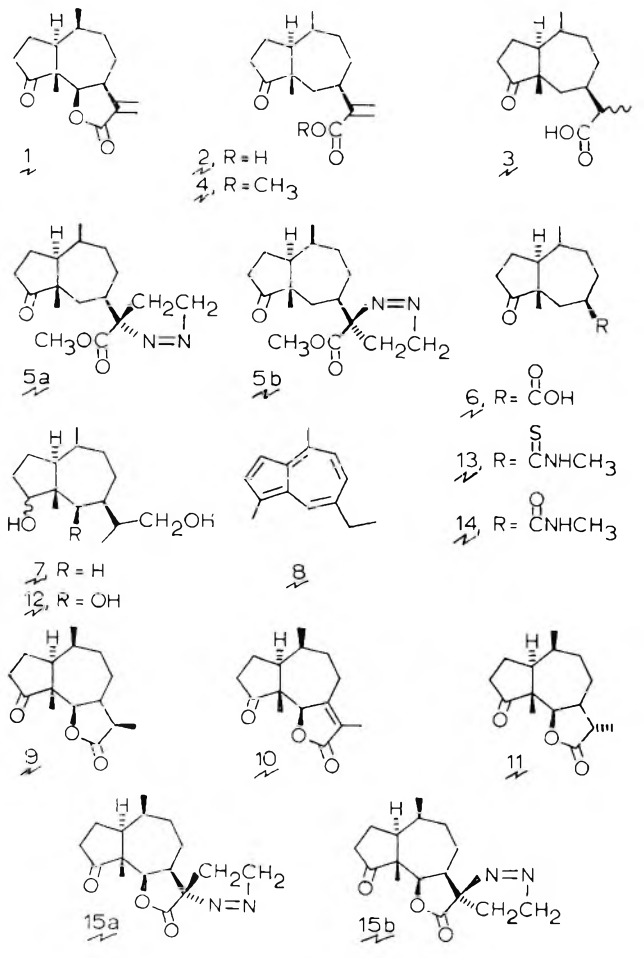
(12) Undoubtedly, dihydrodamsinic acid (**3**) is a mixture of the two C-11 epimers, but these are not separated by the paper chromatographic systems employed.

(13) J. Romo, A. Romo de Vivar, A. Velez, and E. Urbina, *Can. J. Chem.*, **46**, 1535 (1968).

(14) Damsinic acid (**2**) shows a weak Cotton-effect peak at 245 mμ ([θ] +300°) in addition to that for the ketone at 295 mμ ([θ] +3750°). This weak peak has been ascribed to the n → π^* transition of the carbonyl of α,β-unsaturated carboxylic acids by U. Weiss and H. Ziffer [*J. Org. Chem.*, **28**, 1248 (1963)], but no example of acids with exocyclic methylenes were studied. Damsin (**1**) likewise exhibits a weak peak at 240 mμ ([θ] +420°); the n → π^* absorption of the lactone carbonyl and its sign is a function not only of the C-7 configuration but also depends on the ring fusion (*cis* or *trans*) and the position of ring closure (C-6 or C-8).[15] Conclusions reached in the case of **2** would reflect the rotomer population distribution and not simply the stereochemistry at C-7.

(15) T. G. Waddell, W. Stocklin, and T. A. Geissman, *Tetrahedron Lett.*, 1313 (1969).

(16) J. V. Burakevich and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 51 (1965).



tives where only hydrocarbon substituents are at the asymmetric center corresponds to an *R* configuration,[17] the substituent at C-7 in damsinic acid can be said to have the β designation. The asymmetry at C-7 in damsinic acid and damsin is therefore the same. Two additional Cotton-effect peaks of high intensity were observed at 296 (n $\rightarrow \pi^*$ of the ketone) and 259 mμ ($\pi \rightarrow \pi^*$ of the thione).

The configuration at C-10 remained to be determined, and paucity of starting material prevented an extended study. However, on biogenetic grounds the methyl group very likely is β, since all of the sesquiterpenes isolated to date from *Ambrosia* spp. have this configuration.[7a]

Paper chromatographic examination of the reaction mixture from damsinic acid and diazomethane revealed the presence of two pyrazoline esters, **5a** and **5b**, which were purified by partition column chromatography. Both exhibit spectral properties (ir, nmr) consistent with C-11 epimeric structures. Their CD curves are shown in Figure 1, and the stereochemical assignment was made with the aid of the CD results from the pyrazolines of damsin.

The major pyrazoline (**15a**) of damsin readily crystallizes from the reaction mixture, but the minor isomer **15b** was obtained only after partition chromatography of the mother liquor residue. The product ratio was *ca.* 17:1, with the major isomer taken to be that formed by 1,3-dipolar addition of diazomethane from the sterically less hindered α side. The structure assignments were supported by the following spectroscopic data.

(17) R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956).

The chemical-shift differences of the C-5 methyl and the H-6 and H-7 protons in the nmr spectra of the two substances were primary evidence for the choices. Dreiding models of the two isomers indicated that, in **15a**, H-6 is situated along the longitudinal axis of the diazene (–N=N–) group. By analogy with an ethylene group, a deshielding would be expected along that axis. The H-6 proton was found in **15a** at δ 5.45, while in **15b** it appeared at δ 4.79. A similar but less intense deshielding exists for the H-7 proton (δ 2.69) in **15a** but not in **15b** (δ 2.96). If the diazene group is responsible for these chemical-shift differences, a similar effect should be observed for the C-5 methyl, but not for the reverse isomers. This indeed is the case, for one finds the peak at δ 1.47 in **15b** and at δ 1.27 in **15a**. Both isomers gave identical mass spectra.

The CD curves for the damsin pyrazolines are shown in Figure 1. It was therefore possible to make the stereochemical assignment for the methyl damsinate pyrazolines on the basis of these curves.[18]

Experimental Section

Melting points taken in capillaries were determined with a Thomas–Hoover apparatus and are uncorrected. Elemental analyses were performed by Mr. Joseph F. Alicino. Infrared spectra were taken in chloroform on a Perkin-Elmer Model 237 or 257 spectrophotometer, and ultraviolet spectra were obtained in methanol on a Cary Model 15 spectrophotometer. The nmr spectra were measured in deuteriochloroform on a Varian A-60A instrument with TMS as internal standard; chemical shifts are reported in δ (parts per million) units. The ORD, CD, and optical rotation values were determined in methanol on a Jasco Model ORD/UV-5 spectropolarimeter. Gas chromatography (glpc) was performed with an F & M Model 500 instrument equipped with a flame-ionization detector on 10% silicone gum rubber (SE-30) on Chromosorb W (80–100 mesh). Mass spectra were obtained on an AEI MS-9 double-focusing instrument and samples were introduced *via* the direct inlet probe.

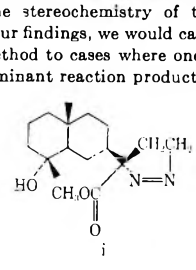
Damsinic Acid (2).—The detailed isolation procedure from *Ambrosia ambrosioides* and the physical properties are published.[3] The substance was obtained in a yield of 0.01% of the dried plant material. The nmr peaks are given in Table I.

Dihydrodamsinic Acid (3).—A solution of 500 mg of **2** in 5 ml of ethanol was added to 170 mg of 5% palladium on charcoal in 50 ml of ethanol. Hydrogen uptake at room temperature and 1-atm pressure ceased after 1 molar equiv was absorbed. The catalyst was removed by filtration and the residue from the filtrate was crystallized from hexane to give 250 mg of **3**: mp 108–109°; $[\alpha]^{25}D$ +121° (*c* 0.27, CH_3OH); uv max 290 mμ (ϵ 35); ir 1735 (cyclopentanone C=O) and 1700 cm^{-1} (carboxylic acid C=O).

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.53; H, 9.63.

Methyl Damsinate (4).—A solution of 38 mg of **2** in 2 ml of ether was treated with 1 equiv of ethereal diazomethane for 10

(18) After this study was completed, a report appeared by M. Suchy, L. Dolejs, V. Herout, F. Sorm, G. Snatzke, and J. Himmelreich, *Collect. Czech Chem. Commun.*, **34**, 229 (1969), and G. Snatzke, *Riechst. Aromen, Koerperpflegem.*, **19**, 1 (1969), on the CD properties of a number of sesquiterpene lactones and their pyrazolines, including that of the major damsin pyrazoline derivative **15a**. Of interest to us was that only one pyrazoline from methyl iliciate (i) was recorded. These authors indicate that the sign of the Cotton-effect curve at *ca.* 330 mμ for the pyrazoline may be used to assist in determining the stereochemistry of the lactone junctions (*e.g.*, jurineolide). In light of our findings, we would caution against the indiscriminate extension of this method to cases where one pyrazoline derivative does not constitute the predominant reaction product.



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min. Removal of the ether and crystallization from aqueous ethanol gave 33 mg of **4**: mp 48–49°; $[\alpha]^{25}D$ +96° (*c* 0.32, CH_3OH); uv max 285 mμ (ε 50); ir 1740 (cyclopentanone C=O) and 1720 and 1626 cm^{-1} (α,β-unsaturated ester).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.60; H, 8.88.

Pyrazolines of Methyl Damsinate (5a and b).—A solution of 200 mg of **2** in 3 ml of ether was treated with a fourfold excess of ethereal diazomethane for 4 days at 5°. Removal of the solvent gave an amorphous residue that indicated two compounds (Zimmerman's reagent) on examination by paper chromatography [$HCONH_2$ and 5:1 C_6H_6–petroleum ether (bp 60–70°)], R_f 0.71 and 0.56.[19] The mixture was separated on a partition column (20 g of Celite 545[20]) employing the same solvent system. The fraction with R_f 0.71 (91 mg) crystallized from isopropyl ether to give 54 mg of **5a** as colorless needles: mp 130–131°; $[\alpha]^{25}D$ −6° (c 0.28, CH_3OH); uv max 324 mμ (ε 173); ir 1740 (double intensity, cyclopentanone and ester C=O) and 1560 cm^{-1} (N=N); ORD Φ_{400} −1240°, Φ_{335} −10,600° (trough), Φ_{327} 0°, Φ_{309} +14,200° (peak), Φ_{287} 0°, Φ_{260} −3420° (trough), Φ_{230} 0°, and Φ_{210} +1980° (last reading); CD Θ_{327} −15,600° (peak), Θ_{308} 0°, Θ_{295} +7300°, Θ_{260} +1340° (shoulder), Θ_{248} 0°, Θ_{234} −2080°, and Θ_{220} 0°; mass spectrum (70 eV) *m/e* (rel intensity) 278.1880 (25) [calcd for $C_{17}H_{26}O_3$ (M − N_2) 278.1882], 260 (16), 246 (17), 222 (15), 201 (14), 190 (15), 175 (17), 161 (24), 137 (44), and 121 (34).

Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.75; H, 8.26; N, 9.48.

The column fraction with R_f 0.56 (163 mg) contained compound **5b**, a colorless, viscous oil that resisted crystallization and had the following properties: $[\alpha]^{25}D$ +167° (*c* 0.32, CH_3OH); uv max 324 mμ (ε 199); ir 1740 (double intensity, cyclopentanone and ester C=O) and 1560 cm^{-1} (N=N); ORD Φ_{400} +2300°, Φ_{334} +13,500° (peak), Φ_{320} 0°, Φ_{308} −3370° (shoulder), Φ_{280} −5970° (trough), Φ_{240} −995° (peak), and Φ_{210} −7350° (last reading); CD Θ_{326} +15,000° (peak), Θ_{300} +7450° (shoulder), Θ_{260} +505° (shoulder), and Θ_{234} +3540° (peak); mass spectrum (70 eV) *m/e* (rel intensity) 278.1879 (20) [calcd for $C_{17}H_{26}O_3$ (M − N_2) 278.1882]. The rest of the spectrum was indistinguishable from that of **5a**.

Ozonolysis of 2. A.—Compound **2** (200 mg) in 10 ml of methanol was treated with oxygen containing *ca.* 2% ozone at −78° for 15 min. The reaction mixture was steam distilled and the distillate was collected in a saturated alcoholic solution of dimedone. The solution deposited the dimedone derivative of formaldehyde, yield 18 mg, mp 189–190°, undepressed on admixture with an authentic sample.

B.—A solution of 100 mg of **2** in 10 ml of methanol was ozonized as before and the solvent was evaporated at reduced pressure. The ozonide was decomposed at room temperature by the addition of 2 ml of H_2O and occasionally stirred. After 1 hr the H_2O was removed by evaporation and the residue was chromatographed on a small partition column (20 g of Celite 545, $HCONH_2$ and C_6H_6 as solvents). Crystallization from C_6H_6–hexane yielded 49 mg of bisnordamsinic acid (**6**): mp 130–131°; $[\alpha]^{25}D$ +110° (*c* 0.27, CH_3OH); uv max 296 mμ (ε 30); ir 1735 (cyclopentanone C=O) and 1705 cm^{-1} (carboxylic acid C=O).

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.98; H, 8.72.

$LiAlH_4$ Reduction of 3.—A solution of 500 mg of **3** in 20 ml of tetrahydrofuran was treated with 600 mg of $LiAlH_4$ under reflux for 24 hr. The reaction mixture was cooled, the excess $LiAlH_4$ was decomposed with ethyl acetate, and 3 ml of H_2O was added. The mixture was filtered, the gel was washed with $CHCl_3$, and the combined filtrate and wash were dried (Na_2SO_4). Evaporation of the solvent and crystallization of the residue from C_6H_6–hexane gave 368 mg of the diol **7**: mp 119–120°; $[\alpha]^{25}D$ +54° (c 0.86, CH_3OH); ir 3600 and 3490 cm^{-1} (free and associated OH) and no carbonyl bands.

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.73; H, 11.87.

The oily dimesylate was prepared in the usual manner. The ir spectrum showed no OH absorption, but peaks were present at 1350 and 1170 cm^{-1} (S=O stretching). An amorphous ditosylate was similarly prepared, ir 1595 (Ar) and 1355 and 1175 cm^{-1} (S=O stretching). Both derivatives were treated with $LiAlH_4$ in tetrahydrofuran under reflux for 24 hr, resulting in a mixture showing in the ir OH bands but no S=O stretching peaks. Heating the ditosylate with NaI in acetone at 100° in a sealed tube resulted in recovery of material with tosylate groups (ir).

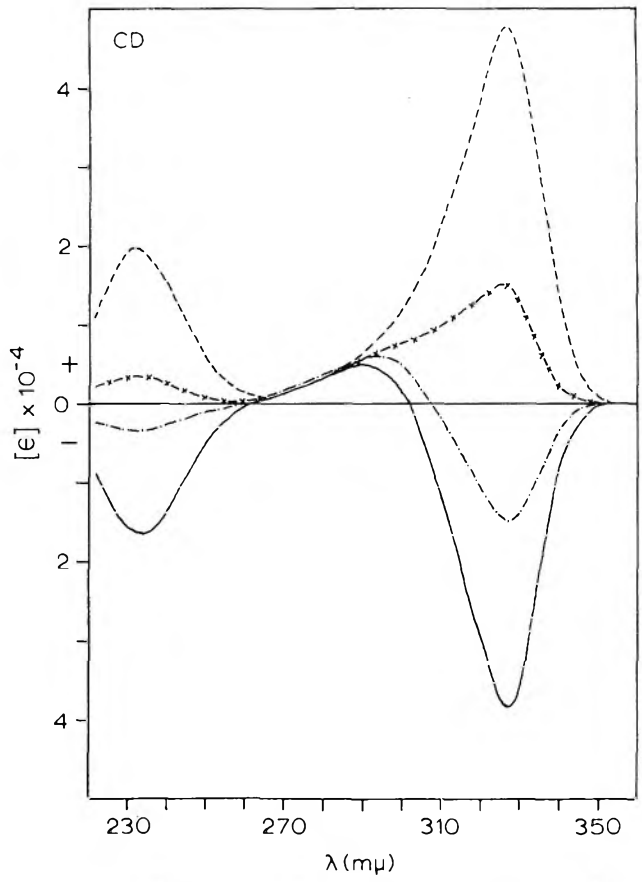

Figure 1.—Circular dichroism curves for methyl damsinate pyrazolines **5a** (-·-·-·-) and **5b** (-×-×-×-×) and damsin pyrazolines **15a** (——) and **15b** (- - - -).

Conversion of 7 into Chamazulene (8).—A 49-mg sample of **7** in 1 ml of anhydrous pyridine was treated with 0.05 ml of $SOCl_2$ for 2 hr at room temperature. The reaction mixture was poured into 5 ml of water and extracted with ether. The ether extract was washed with 3 *N* HCl, 5% $NaHCO_3$, and water and dried (Na_2SO_4). The residue (46 mg) left after evaporation of solvent showed no OH bands in the ir and was thoroughly mixed with 35 mg of 10% palladium on charcoal in a hard-glass test tube. The tube was heated at 320–330° for 1 min and showed a blue vapor. The cooled reaction mixture was extracted with hexane and after removal of the hexane gave a blue-green residue (24 mg). Purification of the residue by preparative tlc (silica gel G, 9:1 *n*-hexane–C_6H_6) resulted in 2 mg of a blue oil which formed a 1,3,5-trinitrobenzene adduct, mp 129–131°. The uv spectrum was identical with that of an authentic sample of the TNB adduct of chamazulene (8).[21] The regenerated azulenes had superimposable uv spectra and identical R_f values (0.53) on tlc (silica gel G, 9:1 *n*-hexane–C_6H_6). In this system guaiazulene had R_f 0.60.

Deuterium Studies on 3.—Sodium metal (125 mg) was added to 1 ml of D_2O. After dissolution, 12 mg of **3** was added and the solution was refluxed for 10 hr. The cooled reaction mixture was acidified with D_2SO_4 and extracted with ether. The combined ether layer was evaporated to dryness, and the residue was dissolved in 2 ml of ethanol, evaporated again, and crystallized from *n*-hexane. The crystalline product (7 mg) was subjected to deuterium-exchange conditions and purification once again.

(19) Reference 3 gives procedures for the paper chromatographic and partition column separations.

(20) A diatomaceous earth from Johns-Manville Corp., New York, N. Y.

(21) Isolated from Chamomile Oil "German," a generous gift from Fritzsche Brothers, Inc., by adsorption chromatography on activity I neutral alumina with *n*-hexane as solvent. The blue band that was collected readily formed the TNB adduct, mp 129–130.5°.[22]

(22) E. Guenther and D. Althausen, "The Essential Oils," Vol. II, D. Van Nostrand Co., New York, N. Y., 1949, pp 132, 133.

The molecular ion of the deuterated product appeared at *m/e* 254, indicating an uptake of two deuterium atoms.

Hydrogenation of Damsin (1) under Alkaline Conditions.—A 546-mg sample of 1 was warmed in 15 ml of 0.1 *N* NaOH on a steam bath to affect lactone ring opening as evidenced by solution forming. The cooled solution was added to a suspension of 300 mg of 5% palladium on charcoal in 40 ml of ethanol containing 2 ml of 0.1 *N* NaOH and hydrogenated. After 10 hr at room temperature and atmospheric pressure, hydrogen uptake ceased. The catalyst was removed by filtration and the ethanol was evaporated from the filtrate at reduced pressure, diluted with 10 ml of H_2O, acidified with HCl, and extracted with $CHCl_3$. The dried (Na_2SO_4) $CHCl_3$-extract residue (550 mg), on paper chromatographic examination (2:1 C_6H_6–hexane and $HCONH_2$) showed two spots with R_f 0.60 and 0.45 (Zimmerman's reagent). A partition column[19] (100 g of Celite 545) employing the same solvent system separated the mixture. The R_f 0.60 band gave 276 mg of tetrahydroambrosin (dihydrodamsin, 9) from *n*-hexane: mp 126–127° (lit.[5a] mp 128°); $[\alpha]^{25}D$ +66° (*c* 0.27, CH_3OH); ir 1770 (γ-lactone C=O) and 1740 cm^{-1} (cyclopentanone C=O).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.17; H, 9.14.

The band with R_f 0.45 gave from isopropyl ether 66 mg of 11-epitetrahydroambrosin (11-epidihydrodamsin, 11): mp 116–117° (lit.[13] mp 115°); ir 1770 (γ-lactone C=O) and 1740 cm^{-1} (cyclopentanone C=O). The R_f of damsin in the solvent system employed is also 0.45.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.18; H, 9.08.

$LiAlH_4$ Reduction of 9.—A solution of 185 mg of 9 in 20 ml of tetrahydrofuran was treated with 300 mg of $LiAlH_4$ under reflux for 24 hr. After cooling, the excess reducing agent was decomposed with ethyl acetate followed by the addition of 2 ml of H_2O. The mixture was filtered, the gel was washed with $CHCl_3$, and the wash and filtrate were dried (Na_2SO_4). The residue from the $CHCl_3$ solution crystallized from isopropyl ether to give 100 mg of the triol 12: mp 139–140°; $[\alpha]^{25}D$ +23° (*c* 0.33, CH_3OH); ir 3600 and 3350 cm^{-1} (OH).

Anal. Calcd for $C_{15}H_{28}O_3$: C, 70.27; H, 11.01. Found: C, 70.28; H, 10.69.

The trimesylate of the triol 12 was prepared in the usual manner, giving a heavy oil lacking OH absorption in the ir but showing peaks at 1330 and 1160 cm^{-1} (S=O stretching). Reduction of the trimesylate with $LiAlH_4$ under reflux for 24 hr in tetrahydrofuran gave a mixture that lacked the S=O absorption in the ir and showed peaks in the OH region.

N-Methylthionbisnordamsinamide (13).—A 30-mg sample of 6 was dissolved in 1 ml of dry C_6H_6, and 0.15 ml of $(COCl)_2$ was added. The reaction proceeded at room temperature for 8 hr and then the solvent and excess reagent were evaporated at reduced pressure. The oily acid chloride was redissolved in dry C_6H_6 and excess anhydrous CH_3NH_2 was bubbled in. After 10 min at room temperature the reaction solution was extracted with dilute base and H_2O. The dried (Na_2SO_4) C_6H_6 solution on evaporation yielded 16 mg of the amide 14 as an oil: homogeneous on tlc and paper chromatogaphic analysis; ir 3455 (NH), 1733 (ketone C=O), and 1665 and 1525 cm^{-1} (amide C=O).

The amide 14 (16 mg) in 1 ml of xylene was treated with 12 mg of sulfurated potash and 10 mg of phosphorus pentasulfide according to the method of Burakevich and Djerassi.[16] The reaction residue was purified twice by tlc (silica gel G, 4:1 C_6H_6–EtOAc), and the eluted band (R_f 0.20) gave the thioamide 13 (7 mg): homogeneous on further tlc and glpc;[23] the mass spectrum (70 eV) *m/e* (rel intensity) 253.1499 (51) (calcd for $C_{14}H_{23}NOS$ *m/e* 253.1500), 238 (15), 220 (28), 204 (12), and 102 (100, C_4H_8NS); CD Θ_{335} −206°, Θ_{297} +4000°, and Θ_{260} +6300°.

Pyrazolines of Damsin (15a and b).—To 329 mg of 1 dissolved in 20 ml of ether, excess ethereal diazomethane was added; the mixture was kept at 5° for 24 hr. The solvent and excess reagent were allowed to evaporate and the residue was crystallized from acetone–hexane to give 218 mg of pyrazoline 15a: mp 133–135° dec; uv max 323 mμ (ε 204); ir 1770 (γ-lactone C=O), 1740 (cyclopentanone C=O), and 1560 cm^{-1} (N=N); mass spectrum (70 eV) *m/e* (rel intensity) 262.1550 (4) [calcd for $C_{16}H_{22}O_3$ (M − N_2) 262.1569], 247.1333 (100) (calcd for $C_{15}H_{19}O_3$ 247.1334), 229 (6), 205 (5), 137 (21), 109 (16), and 97 (32). The mother liquors showed on paper chromatography (C_6H_6–$HCONH_2$, Zimmerman's reagent) an additional substance at R_f 0.54. The major product had R_f 0.65. Employing the same solvent system in a partition column[19] gave the minor pyrazoline 15b, which crystallized (15 mg) from acetone–hexane: mp 146–148° dec; uv max 327 mμ (ε 275); ir 1770 (γ-lactone C=O), 1740 (cyclopentane C=O), and 1555 cm^{-1} (N=N); mass spectrum (70 eV) *m/e* (rel intensity) 262.1564 (6) [calcd for $C_{16}H_{22}O_3$ (M − N_2) 262.1569], 247.1335 (100), 229 (6), 205 (5), 137 (24), 109 (20), and 97 (34). The mass spectra for the two isomers were indistinguishable.

Registry No.—2, 22844-19-5; 3, 22922-35-6; 4, 22844-20-8; 5a, 22844-31-1; 5b, 22844-21-9; 6, 22844-22-0; 7, 22844-23-1; 9, 21848-56-6; 11, 19908-71-5; 12, 22844-26-4; 13, 22844-27-5; 14, 22844-28-6; 15a, 22844-29-7; 15b, 22844-30-0.

Acknowledgment.—We thank Dr. Rodger L. Foltz of Battelle Memorial Institute for the mass spectra.

(23) Less than 2% impurity was detected. On a 4 ft × 0.25 in. column at a temperature of 200° and carrier gas flow rate (He) at 45 ml/min, the retention time for the thicnamide was 5.7 min.

Direct Glycosylation of 1,3,5-Triazinones. A New Approach to the Synthesis of the Nucleoside Antibiotic 5-Azacytidine (4-Amino-1-β-D-ribofuranosyl-1,3,5-triazin-2-one) and Related Derivatives[1]

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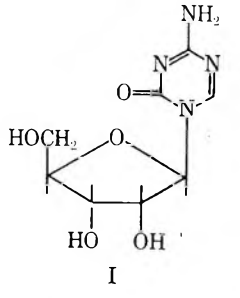
Received June 11, 1969

The first instance of direct glycosylation of the 1,3,5-triazine ring has been described. The synthesis of the nucleoside antibiotic 5-azacytidine (4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2-one, I) has been achieved in 34% yield by treatment of the trimethylsilyl derivative of 4-amino-1,3,5-triazin-2-one (5-azacytosine) with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide in acetonitrile, followed by deblocking with methanolic ammonia. Similar treatment of the trimethylsilyl derivative of 5-azacytosine with 3,5-di-*O*-acetyl-2-deoxyribofuranosyl chloride resulted in the α and β anomers of 2′-deoxy-5-azacytidine, which were clearly distinguished by pmr. In a similar manner, 1-(β-D-ribofuranosyl)cyanuric acid (V) and 1-β-D-ribofuranosyl-3-methylcyanuric acid (VI) were prepared from cyanuric acid and 1-methylcyanuric acid, respectively. Attempts to prepare 4-amino-1-β-D-arabinofuranosyl-1,3,5-triazin-2-one (5-azaarabinofuranosylcytosine) were unsuccessful because 4-amino-1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-1,3,5-triazin-2-one (VII) could not be deblocked without concomitant destruction of the triazine ring. The nucleoside derivatives of the 1,3,5-triazine ring present some interesting nucleosides for future biochemical and biophysical studies.

5-Azacytidine (4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2-one, I) has been isolated from *Streptoverticillium ladakanus*.[2,3] This antibiotic inhibits gram-negative bacteria and is active against T-4 lymphoma and L-1210 leukemia in mice.[2] The identity of I was



I

established[3] by comparison with authentic 5-azacytidine prepared by a lengthy procedure involving ring closure of 1-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)-4-methylisobiuret.[4] The remarkable biological activity of I against experimental leukemia[5-9] has resulted in the selection of 5-azacytidine for clinical trial against leukemia in human subjects.[8,9] 5-Azacytidine inhibits protein synthesis[10] and is incorporated into both RNA and DNA.[11]

Recent studies in this laboratory utilizing various trimethylsilyl pyrimidines in a direct glycosylation procedure has succeeded where other methods have failed.[12-14] The application of this study to the *s*-triazine ring has now resulted in the direct attachment of the D-ribofuranose moiety to the 1,3,5-triazine ring system. 5-Azacytosine[15] was treated with hexamethyldisilazane in a manner similar to that previously employed for 4-amino-6-pyrimidone.[13] The resulting trimethylsilyl derivative (II) was dissolved in acetonitrile and treated with 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide.[16] The crude blocked nucleoside was isolated and treated with methanolic ammonia to give crude I, yield 34%. Recrystallization gave 5-azacytidine, yield 11%, mp 231–233° dec. Rigorous comparison of this product with 5-azacytidine isolated from cultures of *S. ladakanus* proved the samples to be identical.

Utilization of this procedure for the synthesis of 5-aza-2′-deoxycytidine (III) was also successful. Syrupy 1,3,5-tri-*O*-acetyl-2-deoxy-D-ribofuranose[17] was converted into 3,5-di-*O*-acetyl-2-deoxy-D-ribofuranosyl chloride and allowed to react with an excess of the trimethylsilyl derivative of 5-azacytosine in acetonitrile. After 7 days at room temperature the reaction mixture was treated as for the preparation of I and the product was purified *via* column chromatography on silica gel to give a mixture of anomers of 1-(3,5-di-*O*-acetyl-2-deoxy-D-ribofuranosyl)-5-azacytosine. This mixture was treated with ethanolic ammonia to remove the acetyl groups. The resulting α and β anomers were separated by a combination of fractional crystallization and preparative layer chromatography on silica gel to give pure 1-(2-deoxy-α-D-ribofuranosyl)-5-azacytosine (IV) and 2′-deoxy-5-azacytidine [4-amino-1-(2-deoxy-β-D-ribofuranosyl)-1,3,5-triazin-2-one, III]. Assignment of the β configuration to III was made by comparison of the pmr signals observed for the anomeric protons[17] of III and the corresponding α anomer, IV. It should be noted that a lengthy synthesis of 5-aza-2′-deoxycytidine has been reported[18] in a preliminary communication *via* 1-(3,5-di-*O*-*p*-toluyl-2-deoxy-D-ribofuranosyl)-4-methylisobiuret. However, no yield was

(1) Supported by Research Grants CA 08109-02 and CA 08109-03 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) L. J. Hanka, J. S. Evans, D. J. Mason, and A. Dietz, *Antimicrob. Ag. Chemother.*, 619 (1966).

(3) M. E. Bergy and R. R. Herr, *ibid.*, 625 (1966).

(4) A. Piskala and F. Sorm, *Collect. Czech. Chem. Commun.*, **29**, 2060 (1964).

(5) J. S. Evans and L. J. Hanka, *Experientia*, **24**, 922 (1968).

(6) F. Sorm and J. Vesely, *Neoplasma*, **22**, 53 (1966).

(7) J. Vesely, A. Cihak, and F. Sorm, *Biochem. Pharmacol.*, **17**, 519 (1968).

(8) J. Vesely, A. Cihak, and F. Sorm, *Cancer Res.*, **28**, 1995 (1968).

(9) A. Goldin, H. B. Wood, Jr., and R. Engle, *Cancer Chemother. Rept.*, [2] **1**, 13, 14, 233, 268 (1968).

(10) J. Doskocil, V. Paces, and F. Sorm, *Biochim. Biophys. Acta*, **145**, 771 1967).

(11) V. Paces, J. Doskocil and F. Sorm, *ibid.*, **161**, 352 (1968).

(12) M. W. Winkley and R. K. Robins, *J. Org. Chem.*, **33**, 2822 (1968).

(13) M. W. Winkley and R. K. Robins, *ibid.*, **34**, 431 (1969).

(14) M. W. Winkley and R. K. Robins, *J. Chem. Soc., C*, 791 (1969).

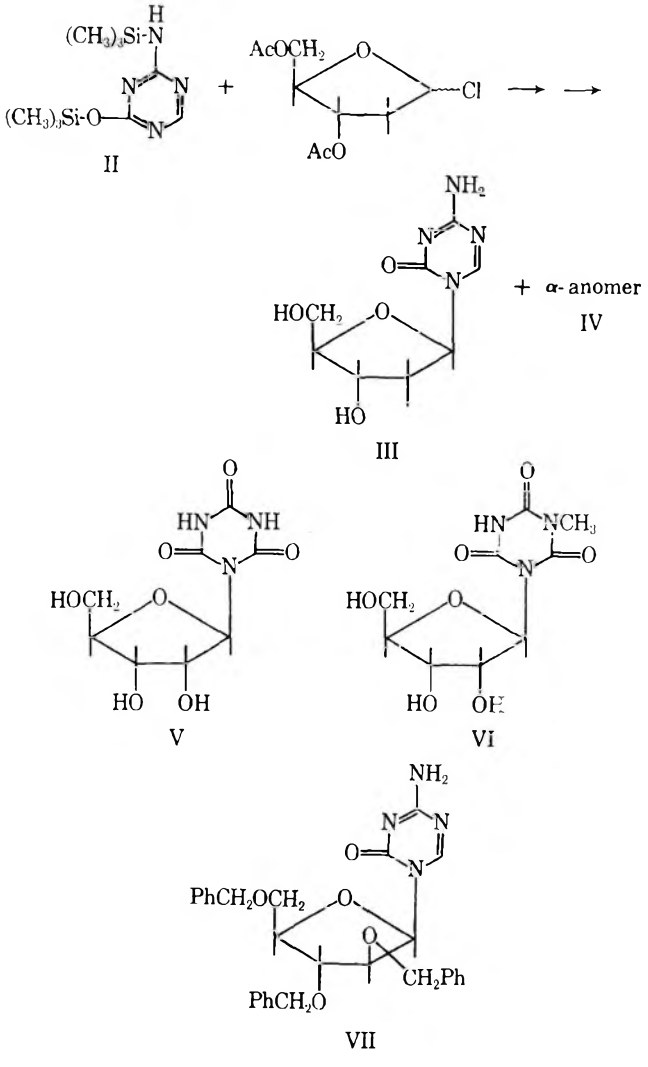
(15) R. Hartenstein and I. F. Fridowich, *J. Org. Chem.*, **32**, 1953 (1967).

(16) R. D. Guthrie and S. C. Smith, *Chem. Ind.* (London), 547 (1968).

(17) M. J. Robins and R. K. Robins, *J. Amer. Chem. Soc.*, **87**, 4934 (1965).

(18) J. Pliml and F. Sorm, *Collect. Czech. Chem. Commun.*, **29**, 2576 (1964).

given and the authors did not distinguish between the possible two anomers, III and IV.



In an attempt to prepare 1-β-D-arabinofuranosyl-5-azacytosine, 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride[19] and the trimethylsilyl derivative of 5-azacytosine were dissolved in dichloromethane and kept at room temperature for 11 days to give a 47% yield of 1-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-5-azacytosine (VII). Catalytic debenzylation of VII with palladium and hydrogen resulted in destruction of the triazine ring. A fusion reaction of 2,3,5-tri-*O*-acetyl-D-arabinofuranosyl chloride with the trimethylsilyl derivative of 5-azacytosine gave only the α anomer, 1-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)-5-azacytosine.

Treatment of 2,4,6-tris(trimethylsilyloxy)-1,3,5-triazine, prepared from cyanuric acid, with 2,3,5-tri-O-benzoyl-D-ribofuranosyl bromide gave a 43% yield, after deblocking of 1-(β-D-ribofuranosyl)cyanuric acid (V). This molecule is of particular interest since it is symmetrical. There is essentially no *anti* form to this nucleoside. The structural resemblance to uridine is, however, indeed striking. Such a nucleoside should be of considerable theoretical interest to both biochemists and biophysical chemists, since it has been postulated that certain enzymes *prefer* either the *syn* or *anti* conformation of pyrimidine nucleosides.[20] Further studies on this nucleoside are in progress in our laboratories. For comparative purposes, the compound 1-(β-D-ribofuranosyl)-3-methylcyanuric acid (VI) was similarly prepared from 1-methylcyanuric acid[21] in 39% yield.

It would appear that the silylation procedure of nucleoside synthesis is generally applicable even to ring systems such as 1,3,5-triazine, which have not previously been alkylated by other methods of nucleoside synthesis.

(19) C. P. J. Glaudemans and H. G. Fletcher, Jr. *J. Org. Chem.*, **28**, 3004 (1963).

(20) E. Reich personal communication.

Experimental Section

Melting points were determined with a Thomas–Hoover capillary melting point apparatus and are uncorrected. Specific rotations were measured in a 1-dm tube with a Perkin-Elmer Model 141 automatic digital readout polarimeter. Proton magnetic resonance (pmr) spectra were measured with appropriate internal standards of tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate with a Varian Model A-60 nmr spectrometer. Ultraviolet spectra were determined with a Beckman Model DK-2 spectrometer. Infrared spectra were determined with a Beckman Model IR-5 spectrophotometer. Detection of components on SilicAR 7 GF (Mallinckrodt) and alumina HF 254 (Brinkmann) was by ultraviolet light. Alumina used in columns was obtained from Merck & Co. (suitable for chromatographic absorption). Silica gel was purchased from J. T. Baker Chemical Co. (suitable for chromatographic use). Solvent proportions were by volume. Evaporations were performed under diminished pressure at 35° with a Buchi Rotovapor.

Trimethylsilyl derivatives of various *s*-triazines were prepared using the general procedure of Wittenburg.[17] The *s*-triazines were heated under reflux in an excess of hexamethyldisilazane with a catalytic quantity of ammonium sulfate under anhydrous conditions until complete solution was achieved. The excess hexamethyldisilazane was removed by distillation under diminished pressure and the residue (oil or crystalline solid) was used directly without further purification.

5-Azacytidine (I).—To the trimethylsilyl derivative of 5-azacytosine (prepared from 10 g of 5-azacytosine[15]) was added 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (prepared from 20 g of tetra-*O*-acetyl-D-ribofuranose[16]) in dry acetonitrile (180 ml). After initial stirring, the solution was left at room temperature for 3 days. The solution was evaporated to a syrup. Sodium bicarbonate, water, and ethanol were added. The mixture was evaporated to dryness. Coevaporation with absolute ethanol removed the last traces of water. The residue was extracted with chloroform (Celite used) and the extract was evaporated to dryness. The residue was extracted once more with chloroform and the solvent was removed to give 24.5 g of a foam. To this material was added methanolic ammonia solution (150 ml of methanol saturated at 0° with ammonia). The vessel was sealed and the solution was left at room temperature for 2 hr and then at 5° overnight. The mixture was evaporated to near dryness. To the residue was added methanol and the solid was collected, yield 5.2 g (34%), mp 192–209°. This material was dissolved in warm water and the solution was decolorized with charcoal. Evaporation gave crystals of 5-azacytidine, yield 1.75 g (11%), mp 231–233°. Recrystallization from aqueous ethanol (charcoal) gave pure 5-azacytidine (I), mp 235–237° dec, $[\alpha]^{26}D$ +22.4° (*c* 1.00, water).

Anal. Calcd for $C_8H_{12}N_4O_5$: C, 39.34; H, 4.95; N, 22.94. Found: C, 39.14; H, 4.99; N, 22.91.

A mixture melting point with authentic material[3] showed no depression. The $[\alpha]^{26}D$ (*c* 1, water) value recorded by us for authentic material was +26.6°.[4] The ir, uv, and pmr spectra were identical with those of authentic material.[2,3] The product was shown to be homogeneous by tlc on SilicAR 7GF with ethyl acetate–methanol (4:1) as solvent and it had the same R_f as a marker of authentic material.[3]

1-(3,5-Di-*O*-acetyl-2-deoxy-α,β-D-ribofuranosyl)-5-azacytosine.—Syrupy 2-deoxy-1,5-tri-*O*-acetyl-D-ribofuranose[17] (21 g) was dissolved in dry ether (400 ml) containing acetyl chloride (30 ml) and the solution was saturated with hydrogen chloride at 0° for 1 hr. The sealed solution was left at 0° for 1 day. The solution was evaporated to a syrup which was coevaporated with toluene

(21) W. J. Close, *J. Amer. Chem. Soc.*, **75**, 3617 (1953).

to give a dark-colored, crude glycosyl halide. This product was dissolved in acetonitrile (200 ml) and transferred to the trimethylsilyl derivative of 5-azacytosine (from 15 g of 5-azacytosine). The sealed mixture was stirred at room temperature for 4 days. The mixture was evaporated to a syrup and sodium bicarbonate and ethanol were added. The mixture was evaporated to dryness and the residue was extracted with chloroform. The extract was evaporated to *ca.* 200 ml and applied to a column (40 × 5.0 cm) of silica gel prepacked in chloroform. The column was eluted with chloroform and 200-ml fractions were collected. At fraction 10 the solvent was changed to chloroform–ethyl acetate (9:1), at fraction 20 to ethyl acetate, and at fraction 31 to ethyl acetate–methanol (19:1). Fractions 33–39 were pooled and evaporated to a semicrystalline material. This mixture was extracted with chloroform and the extract was applied to a column (37 × 3.2 cm) of silica gel prepacked in chloroform. Elution was started with chloroform and 200-ml fractions were collected. The solvent was changed to chloroform–ethyl acetate (4:1) at fraction 8 and to ethyl acetate at fraction 12. Fractions 14–25 were evaporated to a small volume, whereupon crystallization occurred. Ether was added to give 2.42 g of white crystals, mp 162–165°.

Anal. Calcd for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 45.90; H, 5.07; N, 17.85.

This product, when examined by tlc on silicAR 7GF with acetone as developer, showed two very closely moving components (typical of anomers): a major, slower moving component and a minor, faster moving component. Attempts at fractional crystallization failed. The mixture exhibited the following spectral data: pmr (DMSO-d_6) δ 1.99 (s) and 2.11 (s, 6, OAc), 2.20–3.10 (m, 2, 2′ H), 4.07–4.36 ("s" at 4.15, "s" at 4.22, and "s" at 4.31, 2, 5′ CH_2OAc), 4.70–5.00 (m, 1, 4′ H), 5.08–5.42 (m, 1, 3′ H), 6.12 (rough q, 1, 1′ H), 7.55 (s) and 7.63 (s, 2, 4 NH_2), and 8.40 (s, 1, 6 H); λ_{max}^{KBr} 1740 cm^{-1} (OAc).

2′-Deoxy-5-azacytidine (III) and the α Anomer (IV).—To a solution of ammonia-saturated (at 0°) ethanol (200 ml) was added 2.76 g of the mixture of 1-(3,5-di-*O*-acetyl-2-deoxy-α,β-D-ribofuranosyl)-5-azacytosine, and the sealed mixture was stirred at 5° for 2 hr to achieve solution. The solution was maintained at −15° for 5 days and then evaporated at 25° to a syrup which was heated at 60° under oil pump vacuum to remove acetamide. A 100-mg portion of the residue (A) was applied to the short edge of a silicAR 7GF plate (2 × 200 × 400 mm) and the plate was developed several times with ethyl acetate–methanol (4:1). Two closely moving zones were observed, one major (α anomer), slower moving zone and a minor, very slightly faster moving (β anomer) zone. Extraction of the smaller zone with methanol and solvent removal gave a minute quantity of crystalline residue (crude β anomer). The remaining crude syrupy mixture of anomers (A) was dissolved in warm methanol and seeded with this material to give white needles of III, yield 0.10 g, mp 189–191°. The mother liquor and washings (ethanol and ether) deposited white prisms (1.05 g) of α anomer contaminated with a faint trace of β anomer. Recrystallization of the β anomer from methanol–2-propanol gave pure product, 2′-deoxy-5-azacytidine (III): mp 191–193°; $[\alpha]^{29}D$ +63.8° (*c* 1.00, water); λ_{max}^{KBr} 1600–1710 cm^{-1} [5-azacytosine absorptions, in the region 1200–4000 cm^{-1} the spectrum was very similar to that of 5-azacytidine (I)]; $\lambda_{max}^{pH\ 1}$ 253 mμ, $\lambda_{max}^{pH\ 4}$ 239 (ε 8200), and $\lambda_{max}^{pH\ 11}$ 253 sh (2300); pmr (D_2O) δ 2.36–2.67 (m, 2, 2′ H), 3.80–3.94 ("d" centered at 3.80 "*J*" = 2.0 cps, "s" at 3.88, 2,5′ CH_2OH), 6.29 (t, 1, *W* = 13.0 cps, $J_{1',2'}$ = 6.5 cps, 1′ H), and 8.58 (s, 1, 6 H).

Anal. Calcd for $C_8H_{12}N_4O_4$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.81; H, 5.15; N, 24.52.

Recrystallization of the crude α anomer (IV) from methanol–2-propanol gave 0.81 g of pure product: mp 177–179°; $[\alpha]^{29}D$ −40.8° (c 1.0, water); ν_{max}^{KBr} 1600–1660 cm^{-1} (5-azacytosine absorptions); $\lambda_{max}^{pH\ 1}$ 253 mμ, $\lambda_{max}^{pH\ 4}$ 239 (ε 8200), and $\lambda_{max}^{pH\ 11}$ 253 sh (2700); pmr (D_2O) δ 2.00–3.12 (m, 2, 2′H), 3.58–3.81 ("s" centered at 3.69 and "s" centered at 3.75, 2, 5 CH_2OH), 4.30–4.65 (m, 2, 3′, and 4′ H), 4.86 (solvent), 6.16 (q, 1, *W* = 9.0 cps, "*J*" = 2.0, 7.0 cps, 1′ H), and 8.48 (s, 1, 6 H).

Anal. Calcd for $C_8H_{12}N_4O_4$: C, 42.10; H, 5.30; N, 24.55. Found: C, 41.86; H, 5.15; N, 24.55.

The various mother liquors were evaporated and applied (*ca.* 100 mg/plate) to the short edge of silicAR 7GF plates (2 × 200 × 400 mm). The plates were developed several times with ethyl acetate–methanol (4:1) until the zones corresponding to the anomers were separated. The zones were excised and extracted with methanol. Solvent removal and crystallization from methanol–ethanol gave an additional 0.12 g of β anomer (III), mp 191–193°, and 0.40 g of α anomer (IV), mp 177–179°.

In a subsequent experiment the procedure was modified as follows. To a solution of ammonia-saturated (at 0°) ethanol (130 ml) was added 1.70 g of 1-(3,5-di-*O*-acetyl-2-deoxy-α,β-D-ribofuranosyl)-5-azacytosine and the sealed mixture was stirred at 5° for 7 hr. The solution was stored at −15° for a further 6 days. The solution was evaporated below 25° to a syrup. This material was dissolved in methanol and the solution was decolorized with charcoal. The solution was evaporated to smaller volume and then coevaporated with ethanol to give 0.77 g of white crystals, mp 175–177° (A), containing largely α anomer. The mother liquor, richer in the β anomer, was evaporated and applied (*ca.* 100 mg/plate) to the short edges of 5 silicAR 7GF plates (2 × 200 × 400 mm). The plates were developed several times with ethyl acetate–methanol (4:1) and the faster moving of the two barely separated zones was excised and extracted with methanol. Solvent removal and crystallization of the residue from methanol–ethanol gave 56.7 mg (4%) of 2′-deoxy-5-azacytidine (III), mp 193–194°. The crystalline material (A) was also subjected to a similar separation to give 33.6 mg (3%) of β anomer (III), mp 191–192°. The slower moving zone was treated similarly to give a total yield of 0.65 g (52%) of α anomer (IV), mp 181–182°.

1-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)-5-azacytosine (VII).—To the trimethylsilyl derivative of 5-azacytosine (prepared from 7.5 g of 5-azacytosine) was added 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride [prepared from 15.0 g of 2,3,5-tri-*O*-benzyl-1-*p*-nitrobenzoyl-D-arabinofuranose[19] in dry dichloromethane (125 ml)] and the resulting solution was protected from moisture and left at room temperature for 11 days. The solution was evaporated to dryness and the residue was treated with sodium bicarbonate, water, and ethanol. The mixture was evaporated to dryness and the residue was coevaporated with ethanol. The residue was extracted with chloroform and the chloroform extract was evaporated to dryness. The residue was extracted once more with chloroform and the extract was applied to a column (40 × 3.3 cm) of silica gel prepacked in chloroform. Fractions (200 ml each) were collected and the fractionation was monitored by tlc on SilicAR 7GF with chloroform–ethyl acetate (4:1) as developer. Elution was started with chloroform. At fraction 39 the eluting solvent was changed to chloroform–ethyl acetate (9:1). Fractions 8–43, which contained a single nucleosidic component, were evaporated to dryness. The residue was crystallized from ethanol–ether to yield 6.39 g (47%) of white crystals, mp 141–143°. Recrystallization from ethanol gave pure VII: mp 142–143°; pmr ($CDCl_3$) δ 3.60 (d, 2, "*J*" = 5.5 cps, 5′ CH_2OH), 3.93–4.32 (m, 3, 2′, 3′, and 4′ H), 4.38 (s, 2, $PhCH_2$), 4.48 (s, 2, $PhCH_2$), 4.51 (s, 2, $PhCH_2$), 6.31 (d, 1, *J* = 4.0 cps, 1′ H), 7.06–7.47 (m, 15, PhH), 7.69 (broad s, 2, 4 NH_2), and 8.26 (s, 1, 6 H).

Anal. Calcd for $C_{29}H_{30}N_4O_6$: C, 67.69; H, 5.88; N, 10.89. Found: C, 67.60; H, 5.82; N, 11.10.

1-(β-D-Ribofuranosyl)cyanuric Acid (V).—To the trimethylsilyl derivative of cyanuric acid (from 15 g of cyanuric acid) was added 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (from 40 g of 1-*O*-acetyl-2-3,5-tri-*O*-benzoyl-β-D-ribofuranose) in dry acetonitrile (250 ml). After sealing and initial stirring, the solution was left at room temperature for 8 days. The solvent was evaporated to a syrup and absolute ethanol was added to the residue. The mixture was evaporated to dryness and extracted (Celite filtration) with chloroform. The solvent was removed and the residue, redissolved in chloroform, was applied to a column (48.5 × 5.0 cm) of silica gel prepacked in chloroform. Fractions (200 ml each) were collected and the fractionation was monitored by tlc on silicAR 7 GF with ethyl acetate–chloroform (3:7) as developer. At fraction 16 the solvent was changed to chloroform–ethyl acetate (9:1) and at fraction 25 to chloroform–ethyl acetate (4:1). Fractions 14–34 were pooled and evaporated, yielding 22.60 g of a dry syrup. A portion (16.0 g) was dissolved in methanol (250 ml) saturated at (0°) with ammonia and left in a pressure vessel for 4 days. The solution was filtered and the filtrate was evaporated to smaller volume, whereupon crystallization of the product occurred. The mixture was coevaporated with absolute ethanol to yield 6.25 g (43%) of V, mp 222–223° dec. Recrystallization from water–ethanol gave pure material: mp 229–230° dec; $[\alpha]^{26}D$ 24.3° (*c* 1, water); ν_{max}^{KBr} 1680 and 1770 cm^{-1} (C=O of heterocycle); pmr (D_2O) δ 3.57–4.23 (m, 3, 4′ H and 5′ CH_2OH, 5 CH_2OH as "s" at 3.85), 4.38 (t, 1, *W*

= 12.0 cps, $J_{3',2'}$ = 6.0 cps, 3′ H), 4.55–4.85 (m, solvent and 2′ H), and 6.22 (d, 1, $J_{1',2'}$ = 3.5 cps, 1′ H).

Anal. Calcd for $C_8H_{11}N_3O_7$: C, 36.79; H, 4.25; N, 16.09. Found: C, 36.48; H, 3.92; N, 15.85.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)cyanuric Acid.—The remaining portion of the crude benzoate (above, 6.60 g) was crystallized from chloroform–ethyl acetate–heptane to yield 4.44 g of white crystals, mp 211–21°. The product was dissolved in a mixture of methanol and ethyl acetate and the solution was decolorized. The solution was evaporated to small volume and heptane was added. Pure product was deposited as white needles: mp 211–213°; ν_{max}^{KBr} 1655 and 1770 cm^{-1} (C=O of heterocycle, and benzoate); pmr (DMSO-d_6) δ 4.50–5.00 [m, 3, 4′ H overlapping 5′ CH_2OH (s) centered at 4.75], 6.13–6.47 (m, 2, 2′ and 3′ H), 6.57 (s, 1, $J_{1',2'}$ < 1 cps, 1′ H), 7.22–8.26 (m, 15, benzoate), and 11.94 (s, 2, NH).

Anal. Calcd for $C_{29}H_{23}N_3O_{10}$: C, 60.73; H, 4.04; N, 7.33. Found: C, 60.91; H, 4.18; N, 7.18.

1-(β-D-Ribofuranosyl)-3-methylcyanuric Acid (VI).—To the trimethylsilyl derivative of 1-methylcyanuric acid (prepared from 5 g of 1-methylcyanuric acid[21]) was added 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (prepared from 10 g of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose) in dry acetonitrile (150 ml). The sealed mixture was stirred initially and then left at room temperature for 2 weeks. The solution was evaporated to a syrup and the syrup was treated with absolute ethanol (50 ml). The mixture was evaporated to dryness and the residue was extracted with chloroform. Evaporation provided a syrup which was redissolved in chloroform, and the solution was applied to a column (40 × 3.3 cm) of silica gel prepacked in chloroform. The fractionation was monitored by tlc on SilicAR 7 GF with chloroform–ethyl acetate (7:3) as developer. Fractions of 200 ml each were collected up to fraction 4. Fractions 5 and 6 were of 100-ml volume. Fractions 7–12 were again of 200-ml volume. Fractions 6–12 were pooled and evaporated to give 8.37 g of a white, homogeneous foam: pmr ($CDCl_3$) δ 3.23 (s, 3, N_3CH_3), 4.50–4.88 (m, 3, 4′ H and 5′ CH_2OH), 6.05–6.30 (m, 2, 2′ and 3′ H), 6.48 (s, 1, $J_{1',2'}$ < 1 cps, 1′ H), 7.10–7.60 (m, 9, benzoate), and 7.77 (m, 6, benzoate). This material was dissolved in ammonia-saturated (at 0°) methanol (100 ml) and left at room temperature for 4 days in a sealed vessel. The solution was filtered through Celite and the filtrate was evaporated to a syrup. This syrup was dissolved in a mixture of chloroform and water. The aqueous solution was further extracted three times with chloroform and then evaporated to dryness. The residue was coevaporated with absolute ethanol and the residue was stirred in ether (200 ml) for several days. The resulting white powder (3.40 g) was collected and crystallized from methanol–2-propanol, yield 2.05 g (39%), mp 144–146°. This material was dissolved in methanol and the solution was decolorized with activated carbon. After solvent removal the syrup was crystallized from methanol–2-propanol: mp 144–146°; $[\alpha]^{31}D$ −21.5° (c 1, water); ν_{max}^{KBr} 1680 and 1720 cm^{-1} (C=O of heterocycle); pmr (D_2O) δ 3.26 (s, 3, N_3CH_3), 3.80–4.15 [m, 3, 5′ CH_2OH (s) at 3.83 overlapped by 4′ H], 4.40 (t, 1, $J_{3',2'}$ = 2.3 cps, 3′ H), 4.53–5.00 (m, 2′ H and solvent), and 6.11 (d, 1, $J_{1',2'}$ = 3.5 cps, 1′ H).

Anal. Calcd for $C_9H_{13}N_3O_7$: C, 39.27; H, 4.76; N, 15.27. Found: C, 39.19; H, 4.82; N, 15.39.

1-(2,3,5-Tri-*O*-acetyl-α-D-arabinofuranosyl)-5-azacytosine.—To a solution of sodium (0.5 g) in anhydrous methanol (500 ml) was added methyl 2,3,5-tri-*O*-benzoyl-D-arabinofuranoside[22] (84 g) and the solution was heated under reflux for 45 min. To the stirred cooled solution was added portionwise Dowex 50 (H^+, X4, 200–400 mesh) until the solution was neutral. The resin was filtered off and washed with methanol. The filtrate and washings were evaporated to a syrup. The syrup was dissolved in chloroform and extracted with chloroform several times. The aqueous layer was evaporated to a syrup and the syrup was dried by coevaporation with ethanol and then with dry pyridine. The dry syrup was treated overnight with acetic anhydride (200 ml)–pyridine (200 ml). The solution was poured onto ice and the mixture was extracted with chloroform. The chloroform extract was washed consecutively with water, ice-cold 2 *N* hydrochloric acid, water-saturated sodium bicarbonate solution, and water. The dried ($MgSO_4$) solution was evaporated to give syrupy methyl 2,3,5-tri-*O*-acetyl-D-arabinofuranoside.

(22) H. G. Fletcher, Jr., in "Methods in Carbohydrate Chemistry," Vol. 2, M. L. Wolfrom and R. L. Whistler, Ed., Academic Press Inc., New York, N. Y., 1963, p 228.

This syrup was dissolved in a mixture of acetic anhydride (150 ml) and acetic acid (550 ml). Concentrated sulfuric acid (35 ml) was added dropwise to the ice-cold solution and the solution was left at room temperature overnight. The solution was poured onto ice and the mixture was extracted with chloroform. The chloroform extract was stirred with excess saturated sodium bicarbonate overnight at 5°. The extract was washed with water and dried ($MgSO_4$). Solvent removal afforded 64 g of 1,2,3,5-tetra-*O*-acetyl-D-arabinofuranose as an oil.

Dry hydrogen chloride gas was bubbled through an ice-cold solution of 53 g of the above syrup in ether (1 l.) containing acetyl chloride (100 ml) until the solution was saturated (*ca.* 1 hr). The solution was sealed and maintained at 0° for 6 days. The solution was evaporated and the residue was coevaporated with toluene.

This syrup was dissolved in toluene (150–200 ml) and transferred to the trimethylsilyl derivative of 5-azacytosine (prepared from 25 g of 5-azacytosine). An aspirator vacuum was applied to the magnetically stirred solution and the temperature was quickly raised to 195° using an oil bath. The temperature was maintained at 195° for 25 min. Ethanol and sodium bicarbonate were added to the residue. The mixture was evaporated to dryness and the residue was extracted with chloroform (Celite). The chloroform extract was evaporated to smaller volume and applied to a column (6̸9 × 4.0 m) of silica gel prepacked in chloroform. Fractions (200 ml each) were collected and the fractionation was monitored by tlc on silicAR 7 GF with ethyl acetate–methanol (9:1) as developer. At fraction 31 the eluting solvent was changed to chloroform–ethyl acetate (9:1), at fraction 41 to chloroform–ethyl acetate (7:3), at fraction 46 to ethyl acetate, and at fraction 64 to ethyl acetate–methanol (19:1). Fractions 44–74 were collected and evaporated to a syrup which was crystallized from ethyl acetate–ether, yield 2.77 g, mp 165–168°. The mother liquor was evaporated and the residue was dissolved in chloroform. Silica gel was added and the mixture was evaporated to give a free-running powder. This material was added to a dry column of silica gel (43.5 × 4.0 cm) so that the total column size was 66.0 × 4.0 cm. Elution was started with chloroform and 200-ml fractions were collected. At fraction 5 the solvent was changed to chloroform–ethyl acetate (9:1), at fraction 9 to chloroform–ethyl acetate (7:3), at fraction 13 to ethyl acetate (1:1), at fraction 21 to ethyl acetate–chloroform (7:3), at fraction 35 to ethyl acetate, and at fraction 60 to ethyl acetate–methanol (98:2). Fractions 36–66 were evaporated to a syrup which was crystallized as above to give 1.80 g, mp 163–165°.

The mother liquor was evaporated to a syrup and dissolved in chloroform. Silica gel was added and the mixture was evaporated to give a free-running powder. This material was added to a dry column (25 × 3.3 cm) of silica gel so that the total column size was 44.0 × 3.3 cm. The elution was started with chloroform and 200-ml fractions were collected. At fraction 6 the solvent was changed to chloroform–ethyl acetate (9:1), at fraction 11 to chloroform–ethyl acetate (7:3), at fraction 15 to chloroform–ethyl acetate (3:7), and at fraction 26 to ethyl acetate. Fractions 22–30 were evaporated and crystallized as above to give 0.65 g, mp 170–171°. The various crystalline materials were combined and dissolved in chloroform. The solution was decolorized and evaporated to a syrup, which was crystallized from ethyl acetate–ether to give 4.85 g (8%), mp 166–168°. A further crystallization gave pure product: mp 167–168°; pmr ($CDCl_3$) δ 2.10 (s, 3, Ac), 2.18 (s, 6, Ac), 4.33 ("d", 2, "*J*" = 5.5 cps, 5′ CH_2OH), 4.61–4.91 (m, 1, 4 H), 5.20–5.38 (m, 1, 3′ H), 5.62–5.80 (m, 1, 2′ H), 5.95 (d, 1, $J_{1',2}$ = 2.5 cps, 1′ H), 6.73 (s, 2, 4 NH_2), and 8.21 (s, 1, 6 H).

Anal. Calcd for $C_{14}H_{18}N_4O_8$: C, 45.40; H, 4.90; N, 15.13. Found: C, 45.14; H, 4.74; N, 15.04.

1-(2,3-Isopropylidene-β-D-ribofuranosyl)cyanuric Acid.—1-(β-D-Ribofuranosyl)cyanuric acid (6.25 g) was dissolved in a mixture of dimethylformamide (20 ml) and dimethoxypropane (18 ml) containing 15 drops of a solution of 4 *M* hydrogen chloride in dioxane. The sealed solution was left at room temperature for 3 days. Sodium bicarbonate (5 g) was added and the mixture was stirred for 2 hours. The solution was filtered through Celite and the filter was washed with 1-butanol. The filtrate was evaporated to dryness under oil pump vacuum. The residue was dissolved in ethanol (100 ml) containing glacial acetic acid (5 ml). The solution was heated on a steam bath for 5 min and then left overnight at room temperature. The solvent was removed and the residue was coevaporated with toluene. The residue was dissolved in chloroform and silica gel (40 g) was added. The

mixture was then evaporated to give a free-running powder. This material was added to a dry column of silica gel (41 × 3.3 cm) so that the final size was 61 × 3.3 cm. The column was eluted with chloroform and 100-ml fractions were collected. At fraction 11 the solvent was changed to chloroform–methanol (9:1). Fractions 15–20, which were homogeneous as judged by tlc on SilicAR 7GF with ethyl acetate developer (detection with sulfuric acid), were evaporated to dryness. The syrupy residue was crystallized from ethanol–heptane to yield 6.36 g (88%) of white product, mp 179–181°. This material was recrystallized from ethanol–heptane to give pure product: mp 180–181°; λ_{max}^{KBr} 1680–1800 cm^{-1} (C=O of cyanuric acid); pmr (DMSO-d_6) δ 1.32 (s, 3, CCH_3), 1.52 (s, 3, CCH_3), 3.54 ("d," 2, "J" = 6.5 cps, 5′ CH_2OH), 3.80–4.18 (m, 1, 4′ H), 4.54–4.93 (m, 2, 3′ H and 5′ CH_2OH), 5.17 (d, 1, $J_{2',3'}$ = 6.0 cps, 2′ H), 6.18 (s, 1, $J_{1',2'}$ <1 cps, 1′ H), and 11.84 (broad, s, 2, NH).

Anal. Calcd for $C_{11}H_{15}N_3O_7$: C, 43.85; H, 5.02; N, 13.95. Found: C, 44.21; H, 5.45; N, 14.20.

1-(2,3-*O*-Isopropylidene-5-methylsulfonyl-β-D-ribofuranosyl)-cyanuric Acid.—To a stirred solution of 1-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)cyanuric acid (6.32 g) in dry pyridine (50 ml) at 0° was added dropwise methylsulfonyl chloride (1.80 ml) and the resulting solution was sealed and stored at 0° for 36 hr. Absolute ethanol (a few drops) was added and the solution was left overnight at 0°. The solution was evaporated to dryness and the residue was coevaporated with toluene. The dried (oil pump vacuum) residue was dissolved in methanol and silica gel was added. The mixture was evaporated to give a free-running powder which was added to a column (51 × 3.5 cm) of silica gel so that the final dimensions were 72 × 3.5 cm. Elution was started with chloroform. Fractions (200 ml each) were collected and the fractionation was monitored by tlc on SilicAR 7GF with ethyl acetate–chloroform (7:3) as developer (detection by sulfuric acid). At fraction 9 the solvent was changed to chloroform–ethyl acetate (4:1) and at fraction 14 to ethyl acetate. Fractions 16–19, which were of 100-ml volume and which contained a single component, were pooled and evaporated to a foam. Crystallization from ethyl acetate–heptane yielded 7.06 g (89%) of white crystals, mp 194–196°. These crystals were dissolved in methanol and the solution was decolorized. After solvent removal, the product was crystallized from ethanol–heptane to give pure material: mp 195–197°; ν_{max}^{KBr} 1710–1760 cm^{-1}; pmr (DMSO-d_6) 1.33 (s, 3, CCH_3), 1.52 (s, 3, CCH_3), 3.20 (s, 1, 5′ CH_3SO_2), 4.10–4.60 [m, 3, 5′ CH_2O (s) at 4.36 overlapped by 4′ H], 4.74–4.98 (m, 1, 3′ H), 5.21 (d, 1, $J_{2',3'}$ = 7.0 cps, 2′ H), 6.14 (s, 1, $J_{1',2'}$ <1 cps, 1′ H), and 11.66 (s, 2, NH).

Anal. Calcd for $C_{12}H_{17}N_3O_9S$: C, 37.98; H, 4.52; N, 11.08. Found: C, 37.88; H, 4.42; N, 11.04.

Registry No.—I, 320-67-2; III, 2353-33-5; IV, 22432-95-7; V, 22432-96-8; VI, 22432-97-9; VII, 22432-98-0; 1-(3,5-di-*O*-acetyl-2-deoxy-α,β-D-ribofuranosyl)-5-azacytosine, 22432-93-5; 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)cyanuric acid, 22432-99-1; 1-(2,3,5-tri-*O*-acetyl-α-D-arabinofuranosyl)-5-azacytosine, 22433-00-7; 1-(2,3-isopropylidene-β-D-ribofuranosyl)cyanuric acid, 22433-01-8; 1-(2,3-*O*-isopropylidene-5-methylsulfonyl-β-D-ribofuranosyl)cyanuric acid, 22433-02-9.

Synthesis of 21-Hydroxymethylprogesterone

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Received June 18, 1969

The synthesis of 21-hydroxymethylprogesterone was accomplished by two pathways, from progesterone and from 3β-acetoxy-5-pregnen-20-one. The preferred method involved the formylation and subsequent borohydride reduction of the 3-monoketal of progesterone. This diol was subsequently tritylated, oxidized, and hydrolyzed to yield 21-hydroxymethylprogesterone.

The C-17 side chains of the progestational and adrenocortical steroid hormones may be compared with the lowest members of the deoxy sugar and sugar series, respectively. Elongation of these side chains by addition of hydroxymethyl groups would yield homologs of the steroid-substituted carbohydrates. The higher hydroxymethyl homologs of progesterone and cortisol would have side chains which may be pictured as 1-substituted deoxy ketoses and 1-substituted ketoses, respectively. We wish to report the synthesis of 21-hydroxymethylprogesterone (**7a**), our initial objective in these studies.

A simple, direct method has been reported for the synthesis of 21-hydroxymethylcortisol by condensation of cortisol with formaldehyde.[2] When we attempted this method with pregnenolone and formaldehyde, we recovered only starting steroid. Our further studies with this method will be the subject of a separate paper. We did not obtain monohydroxymethylation in the desired position.

Very few primary aliphatic α-unsubstituted β-hydroxy ketones have been reported in the literature.[3] We presumed that 21-hydroxymethylprogesterone would be quite labile and that synthesis by indirect methods would be very sensitive to manipulations involved in protecting the other functional groups in the molecule. This did not prove to be the case.

The addition of the hydroxymethyl group on C-21 was accomplished by condensation of the 17β-acetyl group of pregnenolone acetate (**1**) with formate ester[4] followed by reduction with borohydride to the triol **2a** in the reaction medium (Scheme I). A number of routes were considered in order to utilize this condensation reaction for the synthesis of 21-hydroxymethylprogesterone. That the formate condensation occurs on C-21 has been demonstrated by Hirai, *et al.*,[5] as well as from evidence below.

One approach was to form the 20,21a-acetonide derivative[6] of the triol **2a** in order to oxidize selectively the Δ^5-3β-hydroxyl to the Δ^4-3-ketone by the Oppenauer method. Hydrolysis of the acetonide **4** yielded the diol ketone **5a**. The overall yield of this method to this point was so low that we turned to other approaches. An attempt to shortcut this pathway by tritylation of

(1) (a) Senior Postdoctoral Fellow, 1965–1967, supported by Grant 5 TU-MH6418, National Institutes of Health.

(2) S. Noguchi and K. Morita, *Chem. Pharm. Bull.* (Tokyo), **11**, 1235 (1963).

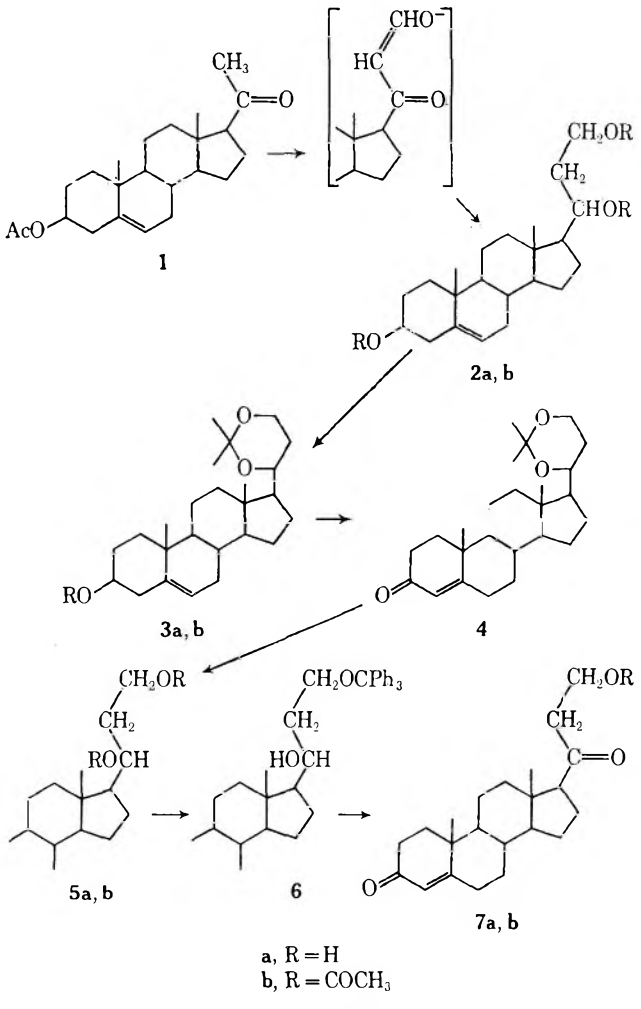
(3) See, *e.g.*, T. White and R. N. Howard, *J. Chem. Soc.*, 25 (1943), and the patent literature for 1-hydroxybutan-3-one.

(4) L. Ruzicka, U. S. Patent 2,398,861 (1946); W. Bockmühl, G. Ehrhart, and H. Ruschig, German Patent 871,451 (1953); N. J. Doorenbos and L. Milewich, *J. Org. Chem.*, **31**, 3193 (1966).

(5) S. Hirai, R. G. Harvey, and E. V. Jensen, *Tetrahedron*, **22**, 1625 (1966).

(6) M. Tanabe and B. Bigley, *J. Amer. Chem. Soc.*, **83**, 756 (1961); A. Hampton, J. C. Fratantoni, P. M. Carroll, and S. Wang, *ibid.*, **87**, 5481 (1965).

SCHEME I



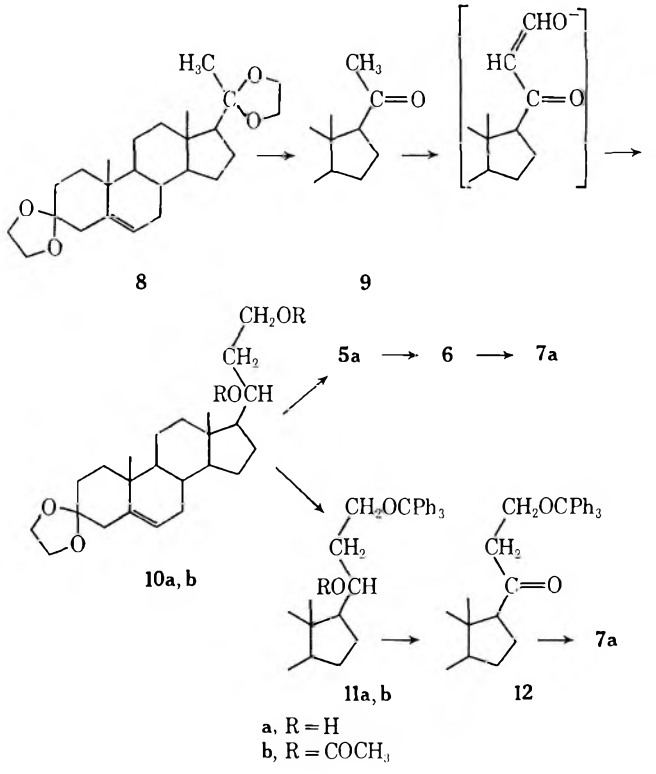
the triol **2a** followed by oxidation of both the C-3 and C-20 hydroxyls simultaneously was unsuccessful.

The more fruitful method was to start with progesterone and mask the 3-ketone with an ethylene ketal derivative **9** prepared by selective hydrolysis of the 3,20-bisketal of progesterone (**8**) (Scheme II). Condensation of the 3-monoketal **9** with isoamyl formate followed by borohydride reduction yielded the 20,21a-dihydroxy 3-ethylene ketal **10a**. On hydrolysis this yielded the same diol ketone **5a** as the first method. The configuration of the 20-hydroxyl is presumed to be β, since sodium borohydride reduction of the 20-ketones yields almost exclusively the 20β-ols.[7] From nmr spectral data the characteristic upfield shift for the C-18 methyl of 0.11 ppm is observed following acetylation of the 20β,21a-diol 3-ketone **5a** to the 20β,21a-diacetoxy 3-ketone **5b**, substantiating the 20β configuration for the hydroxyl group.[8] There is indication of some 20α-hydroxyl formation from the minor product which was separated on tlc but not characterized further. By protecting the C-21a primary hydroxyl of **5a** by tritylation, we selectively oxidized the C-20 hydroxyl with chromic acid–pyridine to the trityl diketone, which was not isolated. Mild hydrolysis of the trityl group gave the desired 21-hydroxymethylprogesterone (**7a**) in 59% yield from **10a**.

(7) See, *e.g.*, L. F. Fieser and M. Fieser," Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p 568.

(8) See C. H. Robinson and P. Hofer, *Chem. Ind.* (London), 377 (1966); H. Lee and M. E. Wolff, *J. Org. Chem.*, **32**, 192 (1967).

SCHEME II



It was surprising that no other products were observed on tlc. This was an indication of the relative stability of this β-hydroxy ketone.

The above method was simplified by removing the ketal group simultaneously with the trityl group in the synthesis. The 20β,21a-diol 3-ketal **10a** was tritylated, then oxidized at C-20 to the 21a-trityl 20-ketone 3-ketal **12**. Mild acid hydrolysis removed both the trityl and the ketal to yield 21-hydroxymethylprogesterone. This method gave the best overall yields (63% from **10a**).

The difficulties anticipated in the removal of protective groups in the β-hydroxy keto steroids were not realized. In fact, the 21a-hydroxy 20-keto steroid appears to be much more stable than anticipated and to be quite resistant to the usual dehydration procedures. Neither mild acid nor alkali appears to alter this structure.

Experimental Section

Analyses were determined by Spang Microanalytical Laboratory, Ann Arbor, Mich. Ir spectra were recorded with a Perkin-Elmer Model 21 spectrophotometer; nmr spectra with a Varian Model A-60 spectrometer in $CDCl_3$ with $SiMe_4$ as internal standard; and ORD spectra with a Cary Model 60 spectropolarimeter in dioxane unless otherwise stated. Melting points were determined on a Kofler hot stage. For tlc, silica gel GF was used, and, for silica gel columns, SilicAR cc-7, 100–200 mesh, was used.

21-Methyl-5-pregnene-3β,20β,21a-triol (2a).[9]—A solution of 30 g (84 mmol) of pregnenolone acetate (**1**) in 1.3 l. of anhydrous benzene was distilled to remove about 100 ml of a benzene azeotrope. To the cooled solution, under nitrogen, were added with stirring 10.92 g of sodium hydride (55% in oil) and 33.3 ml of freshly distilled isoamyl formate. The mixture was refluxed for 12 hr and cooled, and to it 9.5 g of sodium borohydride and 500 ml of methanol were added. The mixture was stirred overnight, diluted with 150 ml of water, neutralized with sulfuric acid, and concentrated *in vacuo*. The solid residue was washed

(9) We wish to acknowledge the generous assistance of Mr. A. S. Tarendash in the preparation of this substance.

with water, dried *in vacuo*, and crystallized from acetone, affording 9.8 g (33.6%) of product **2a**, which was sufficiently pure for the subsequent steps. A sample was recrystallized from acetone, mp 183–185° (softening at 178°), ir (KBr) 3.01 μ (OH).

Anal. Calcd for $C_{22}H_{36}O_3 \cdot {}^1/_2H_2O$: C, 73.96; H, 10.43. Found: C, 73.88; H, 10.21.

The triol **2a** was acetylated to the triacetate **2b** in 66% yield, mp 139–143.5° (softening at 137°), ir (CS_2) 5.74 (ester C=O) and 8.10 μ (ester COC).

Anal. Calcd for $C_{28}H_{42}O_6$: C, 70.86; H, 8.92. Found: C, 70.78; H, 8.77.

20β,21a-Isopropylidenedioxy-21-methyl-5-pregnen-3β-ol (3a). Method A.—To a solution of 383 mg (1.1 mmol) of triol **2a** in 3 ml of dimethylformamide were added 5 ml of 2,2-dimethoxypropane and 10 mg of *p*-toluenesulfonic acid. The solution was stirred for 75 min, neutralized with dilute sodium bicarbonate, and extracted with benzene. The extract was washed with water, dried ($MgSO_4$), and concentrated. The residue (403 mg) was chromatographed on 20 g of alumina (Merck) and the methylene chloride eluate gave 302 mg of crude product, which on crystallization from acetone yielded 185 mg (48%) of **3a**, mp 190–192° subl, ir (CS_2) 2.82 (OH) and 7.29 μ (acetonide).

Anal. Calcd for $C_{25}H_{40}O_3$: C, 77.27; H, 10.38. Found: C, 77.11; H, 10.27.

Method B.—A suspension of 3.48 g (10 mmol) of **2a**, 400 ml of acetone, 15 ml of 2,2-dimethoxypropane, and 340 mg of di(*p*-nitrophenyl) phosphate was stirred for 5 hr (dissolution occurring in 20 min) at room temperature. After addition of 200 mg of sodium bicarbonate, the solution was concentrated *in vacuo*. The residue was taken up in ether, washed with water, dried ($MgSO_4$), and concentrated. After crystallization from methylene chloride or acetone, 2.85 g (73%) of **3a** was obtained, mp 191–193° and identical in ir spectrum and chromatographic mobility with product from method A.

The acetate **3b** was prepared in quantitative yield from **3a**: mp 188–193° subl; ir (CS_2) 5.77 (ester C=O), 7.29 (acetonide), and 8.09 μ (ester COC); nmr δ 5.44 (br, 1, C-6), 3.84 (m, 2, C-21a), 2.03 (s, 3, CH_3CO), 1.47 (s, 3, acetonide CH_3 axial), 1.35 (s, 3, CH_3 equatorial), 1.02 (s, 3, C-19), and 0.73 (s, 3, C-18).

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H· 9.83. Found: C, 75.33; H, 9.91.

Oppenauer Oxidation of 3a.—A solution of 176 mg (0.45 mmol) of **3a**, 30 ml of toluene, and 5 ml of cyclohexanone (freshly distilled reagents) was distilled to remove *ca.* 3 ml of toluene. After addition of 200 mg of aluminum isopropoxide, the solution was refluxed for 2 hr and allowed to stand overnight. A yellow, gum residue was obtained after concentration *in vacuo*. To this was added 70 ml of 10% Rochelle salt solution and 150 ml of ether. The ethereal solution was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel and eluted with 1% acetone in benzene. The product obtained was crystallized from acetone, yielding 17.6 mg (10%) of chromatographically pure **4**: mp 183–186° subl; ir (CS_2) 5.96 (C=O) and 7.28 μ (acetonide); nmr δ 5.79 (br, 1, C-4), 1.49 (s, 3, acetonide, CH_3 axial), 1.36 (s, 3, CH_3 equatorial), 1.21 (C-19), and 0.73 (C-18).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91. Found: C, 77.58; H, 9.94.

20β,21a-Dihydroxy-21-methyl-4-pregnen-3-one (5a).—A solution of 23.4 mg (0.061 mmol) of acetonide **4** in 1 ml of 90% acetic acid was allowed to stand at room temperature for 3 hr. The process of concentrating *in vacuo*, adding benzene, and reconcentrating was repeated three times. The product, obtained in quantitative yield, was crystallized from acetone, mp 198–201°; when compared with **5a** from series II there was no depression in melting point on admixture and ir spectra were identical.

21-Hydroxymethylprogesterone (7a) Prepared from Diol Ketone 5a.—A solution of 1.328 g of diol ketone **5a** in 20 ml of pyridine (freshly distilled) was partially distilled and replenished with pyridine twice. After 1.175 g of trityl chloride was added, the solution was allowed to stand for 3 days. The trityl hydroxy ketone **6** proved to be very deliquescent and was not characterized further. The pyridine solution of **6** was added to a solution of 500 mg of CrO_3 in 20 ml of pyridine. Two more portions of 500 mg of CrO_3 in pyridine were added over a period of 7 days until the reaction was complete according to tlc. After 10 ml of methanol was added, the solution was concentrated *in vacuo* and extracted with ether. The extract was filtered, washed with water, concentrated, and hydrolyzed with 20 ml of 70% acetic acid over 4 days. The residue was concentrated *in vacuo*, extracted with ether, washed, dried, and chromatographed on 45 g of silica gel. From the benzene–acetone (9:1) fraction was obtained 911 mg (69%) of **7a**, crystallized from acetone, mp 138–139°; when compared with **7a** prepared from **10a**, there was no depression in melting point on admixture and ir spectra were identical.

5-Pregnene-3,20-dione 3-Ethylene Ketal (9).[10]—To 100 mg (0.25 mmol) of progesterone bisethylene ketal (**8**)[11] in 25 ml of water-saturated benzene was added 2.5 ml of 0.01 *M* *p*-toluenesulfonic acid in ether. After the mixture was stirred for 70 min at room temperature, 50 ml of benzene and 50 ml of 10% $NaHCO_3$ were added. The organic phase was washed well with water, dried, (K_2CO_3), and concentrated, yielding 86 mg (96%) of a product sufficiently pure for the subsequent reactions. Crystallization from methanol and then from acetone gave **9**, mp 174.5–176.5° (lit. mp 180–181°,[12a] 178–180°[12b]).

20β,21a-Dihydroxy-21-methyl-5-pregnen-3-one 3-Ethylene Ketal (10a).—A solution of 4.89 g (13.62 mmol) of the 3-monoethylene ketal (**9**) of progesterone in 550 ml of dry benzene was distilled to remove *ca.* 50 ml of a benzene azeotrope. To the cooled solution under a nitrogen atmosphere was added with stirring 1.82 g of sodium hydride (55% in oil) and 5.5 ml of freshly distilled isoamyl formate. The mixture was refluxed for 4 hr and cooled, and 3.6 g of sodium borohydride and 100 ml of methanol were added and the resultant mixture was stirred overnight. After the mixture was concentrated under reduced pressure and 600 ml of water was added, a suspension was formed which was extracted thoroughly with ether until no solid remained. The combined ether solution was washed with water, dried ($MgSO_4$), and concentrated. In later work methylene chloride was used for the extraction because of greater solubilizing properties. The crude product was crystallized from acetone, affording 5.19 g (97.4%) of product sufficiently homogeneous to use in subsequent steps. A sample for analysis was prepared by chromatography on alumina (Merck) from the fraction eluted with methanol–methylene chloride (1:1). A small amount of what is probably the 20α isomer of **10a** was separated by chromatography. Two recrystallizations of the major fraction (90%) from acetone yielded **10a**: mp 196–199.5° subl; ir ($CHCl_3$) 2.80 (sh) and 2.88 μ (OH); nmr δ 5.4 (br, 1, C-6), 3.95 (ketal), 3.88 (t, 2, J = 6 cps, C-21a), 1.04 (C-19), and 0.79 (C-18).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.81; H, 9.81. Found: C, 74.02; H, 9.80.

Acetylation of the diol ketal **10a** gave a quantitative yield of the diacetate **10b**: mp 164–168°; ir (CS_2) 5.74 (ester C=O), 8.06, and 8.16 μ (ester COC); nmr δ 5.37 (br, 1, C-6), 5.07 (br, 1, C-20), 4.11 (t, 2, J = 7 cps, C-21a), 3.96 (ketal), 2.05 (acetates), 1.02 (C-19), and 0.69 (C-18).

Anal. Calcd for $C_{28}H_{42}O_6$: C, 70.86; H, 8.92. Found: C, 70.76; H, 8.80.

Hydrolysis of Ketal 10a.—A solution of 700 mg of ketal **10a** in 100 ml of 80% acetic acid, after standing for 24 hr at room temperature, was diluted with two 100-ml portions of water and extracted thoroughly with methylene chloride. The extract was washed well with Na_2CO_3 and water, concentrated to dryness *in vacuo*, and crystallized from acetone. Three crops yielded 527 mg (85%). On chromatography on Woelm neutral alumina (activity I), the CH_2Cl_2–MeOH (9:1) fraction gave a nearly quantitative yield of the diol ketone **5a**, recrystallized twice from acetone as needles: mp 203.5–204.5°; ir ($CHCl_3$) 2.88 (OH), 6.02 (C=O), and 6.20 μ (C=C); nmr δ 5.75 (br, 1, C-4), 3.88 (t, 2, J = 5 cps, C-21a), 2.76 (OH), 2.29 (C-21), 1.2 (C-19), and 0.83 (C-18); ORD (*c* 0.056) $[\Phi]_{589}$ +285°, $[\Phi]_{420-405}$ +525° (broad peak), $[\Phi]_{364}$ −453°, $[\Phi]_{357}$ −262°, $[\Phi]_{350}$ −755°, $[\Phi]_{336}$ + 1244° (sh), $[\Phi]_{322}$ +3480° (sh), $[\Phi]_{308}$ +5816° (sh), and $[\Phi]_{275}$ +8540°.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.45; H, 9.61.

The diacetate **5b** was prepared in the usual way: mp 122–126°; ir (CS_2) 5.74, 8.09, and 8.16 μ (ester C=O, COC); nmr

(10) This procedure is a modification of the method of J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **45**, 331 (1962).

(11) W. S. Allen, S. Bernstein, and R. Littell, *J. Amer. Chem. Soc.*, **76**, 6116 (1954).

(12) (a) F. Sondheimer, M. Velasco, and G. Rosenkranz, *ibid.*, **77**, 192 (1955); (b) A. Bowers, L. C. Ibanez, and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

δ 5.75 (br, 1, C-4), 4.11 (t, 2, J = 7 cps, C-21a), 2.29 (t, 2, J = 7 cps, C-21), 2.05 (acetates), 1.19 (C-19), and 0.72 (C-18).

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.53; H, 8.90. Found: C, 72.65; H, 9.09.

Tritylation of 20β,21a-dihydroxy-21-methyl-5-pregnen-3-one 3-Ethylene Ketal (10a).—A solution of 4.22 g (10.8 mmol) of diol ketal **10a** in 75 ml of dry pyridine was partially distilled *in vacuo* and replenished with pyridine to a volume of 100 ml. To this was added 3.47 g of freshly crystallized trityl chloride and the solution was allowed to stand for 40 hr. Another 0.5 g of trityl chloride was added and 24 hr later no starting material remained according to tlc [acetone–benzene (1:4)]. The pyridine was removed *in vacuo* and the addition and distillation of benzene *in vacuo* was repeated three times. The residue was taken up in 150 ml of methylene chloride, washed with 5% $NaHCO_3$ solution and water, dried ($MgSO_4$), and concentrated to dryness. After crystallizing from acetone, 4.82 g of **11a** was obtained in two crops, mp 187–191°. The total yield of 6.0 g (88.3%) included a third crop of crystals, mp 179–183°. A sample was recrystallized from acetone for analysis: mp 188–191°; ir (CS_2) 2.86 (OH), 3.30, 3.33, 13.48, and 14.23 μ (aryl); nmr δ 7.23–7.53 (trityl), 5.4 (broad, 1, C-6), 3.95 (ketal), 3.35 (t, 2, J = 6 cps, C-21a), 1.05 (C-19), and 0.78 (C-18).

Anal. Calcd for $C_{43}H_{52}O_4$: C, 81.61; H, 8.28. Found: C, 81.63; H, 8.18.

The acetate **11b** was prepared from **11a** in quantitative yield and crystallized from acetone as colorless needles: mp 193–194°; ir (CS_2) 3.30, 3.34, 13.47, and 14.23 (aryl), 5.76 (ester C=O), and 8.10 μ (ester COC); nmr δ 7.2–7.5 (trityl), 5.36 (broad, 1, C-6), 4.95 (broad, 1, C-20), 3.93 (ketal), 3.12 (t, 2, C-21a), 1.84 (acetate),[13] 1.01 (C-19), and 0.64 (C-18).

Anal. Calcd for $C_{45}H_{54}O_5$: C, 80.08; H, 8.06. Found: C, 80.09; H, 8.12.

Chromium Trioxide Oxidation of 11a.—A solution of 2.26 g (3.58 mmol) of hydroxy trityl ketal **11a** in 40 ml of dry pyridine was added dropwise to a solution of 1.41 g (14.1 mmol) of chromium trioxide in 30 ml of dry pyridine and allowed to stand overnight at room temperature. After 300 ml of ether and 10 ml of methanol were added, the precipitate formed was filtered and washed with ether. The combined ether solution was washed with water and dried, and the solvent was removed *in vacuo*. The product solidified when treated with acetone–cold methanol and weighed 2.06 g (91%). This was sufficiently pure for the next step. Various attempts to prepare an analytical sample failed. From silica gel chromatography a homogeneous substance **12** was obtained from the benzene fraction: mp 78.5–81.5°; ir (CS_2) 3.29, 3.32, 13.47, and 14.22 (aryl), and 5.86 μ (20 C=O); nmr δ 7.2–7.6 (trityl), 5.4 (br, 1, C-6), 3.96 (ketal), 3.44 (t, 2, J = 6 cps, C-21a), 2.62 (t, 2, J = 6 cps, C-21), 1.03 (C-19), and 0.63 (C-18).

21-Hydroxymethylprogesterone (7a).—Hydrolysis of 1.72 g (2.73 mmol) of 21-trityloxymethylprogesterone 3-ethylene ketal (**12**) in 100 ml of 80% acetic acid was complete after the solution had been shaken for 17 hr at room temperature. After 100 ml of water was added, the solution was extracted with ether and the organic extract was washed with dilute Na_2CO_3 and water, dried ($MgSO_4$), and concentrated *in vacuo* to a yellowish gum. The residue was chromatographed on silica gel, and the fraction eluted with acetone–benzene (1:4) yielded 726 mg (78%) of **7a**, which was crystallized from acetone: mp 140.5–141.5°; uv max (MeOH) 241 mμ (ε 17,800); ir (CS_2) 2.82 (OH), 5.90 (20 C=O), and 5.96 μ (3 C=O); nmr δ 5.74 (br, 1, C-4), 3.85 (t, 2, J = 5 cps, C-21a), 2.62 (t, 2, J = 5 cps, C-21), 1.19 (C-19), and 0.69 (C-18); ORD (c 0.0527) $[\Phi]_{589}$ + 550°, $[\Phi]_{365}$ +1540°, $[\Phi]_{356}$ +2000°, $[\Phi]_{351}$ +1870°, $[\Phi]_{312}$ +15,200°, $[\Phi]_{273}$ +780°.

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.54; H, 9.57.

Acetylation of **7a** resulted in a quantitative yield of the acetate **7b**, which crystallized from acetone in orthorhombic prisms: mp 129–129.5°; ir (CS_2) 5.73 (ester C=O) and 8.14 (ester COC), 5.86 (20 C=O), and 5.96 μ (3 C=O); nmr δ 5.78 (br, 1, C-4), 4.38 (t, 2, J = 6 cps, C-21a), 2.72 (t, 2, J = 6 cps, C-21), 2.04 (acetate), 1.20 (C-19), and 0.71 (C-18).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.39; H, 8.75.

Registry No.—**2a**, 22486-07-3; **2b**, 22528-31-0; **3a**, 22486-08-4; **3b**, 22486-09-5; **4**, 22486-10-8; **5a**, 22486-11-9; **5b**, 22486-12-0; **7a**, 22486-13-1; **7b**, 22486-15-3; **10a**, 22486-16-4; **10b**, 22485-90-1; **11a**, 22485-91-2; **11b**, 22485-92-3; **12**, 22528-29-6.

(13) The acetate protons shifted upfield by 0.20 ppm in the presence of a trityl group. See, *e.g.*, D. Horton, J. B. Hughes, J. S. Jewell, K. D. Philips, and W. N. Turner, *J. Org. Chem.*, **32**, 1073 (1967).

Photochemistry of 5-Norbornenylacetone and 5-Norbornenylacetaldehyde

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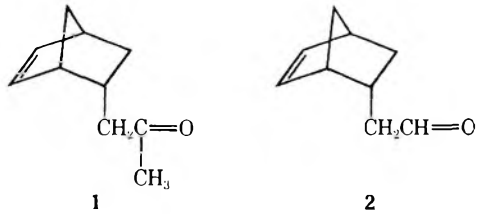
Received July 24, 1969

Irradiation of the δ,ε-unsaturated carbonyl compounds **1** and **2** led to mixtures of oxetanes as the major photoproducts.

As part of a broad study of the photochemical behavior of unsaturated polycyclic ketones,[1] it was of interest to examine the two norbornene systems **1** and **2**. It was hoped that studies of these systems would be informative as to the intramolecular modes of interaction of the excited carbonyl groups with the double bond. More specifically, for example, one has the possibility



1 **2**

of intramolecular energy transfer[2] from the triplet state of the carbonyl group of **1** (E_T = 80–82 kcal/mol[3]) to the norbornene double bond ($E_T \cong$ 72 kcal/mol[4]). On the other hand, triplet transfer from the aldehyde function of **2** ($E_T \cong$ 69 kcal/mol[5]) would be expected to be considerably less efficient. Substantive product differences in the two cases would serve as a basis for interpretations as to the nature of the transfer process. Lastly, our interest in these systems was enhanced by the intriguing chemical possibilities, *e.g.*, Norrish Type II cleavage or cyclobutanol formation, which might

(1) R. R. Sauers, W. Schinski, and M. M. Mason, *Tetrahedron Lett.*, 79 (1969).

(2) H. Morrison, *J. Amer. Chem. Soc.*, **87**, 932 (1965); P. A. Leermakers, J.-P. Montillier, and R. D. Rauh, *Mol. Photochem.*, **1**, 57 (1969); D. O. Cowan and A. A. Baum, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, No. P 117.

(3) R. F. Borkman and D. R. Kearns, *J. Chem. Phys.*, **44**, 945 (1966).

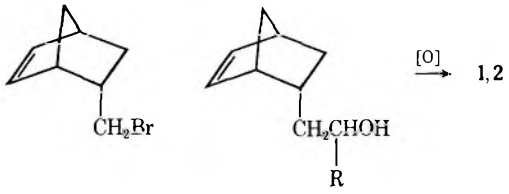
(4) See D. R. Arnold, *Advan. Photochem.*, **6**, 301 (1968).

(5) J. D. Borman, J. H. Stanley, W. V. Sherman, and S. G. Cohen, *J. Amer. Chem. Soc.*, **85**, 4010 (1963).

follow intramolecular abstractions of the γ hydrogen at the bridgeheads.

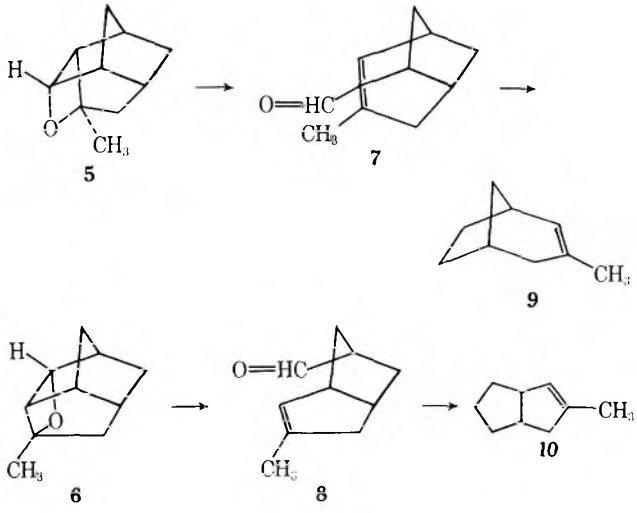
Results and Discussion

Ketone **1** was prepared by chromic acid oxidation of the alcohols (**4a**) obtained from the reaction of the Grignard reagent of bromomethylnorbornene (**3**) with acetaldehyde. Aldehyde **2** was obtained by mild oxidation of 5-norbornenylethanol (**4b**).[6] Preparative



1 **4a**, R = CH_3; **b**, R = H

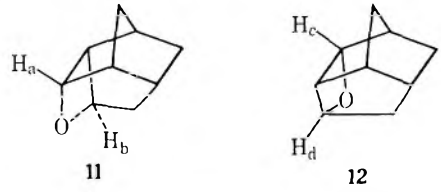
photolyses were carried out on nitrogen-purged solutions of **1** or **2** in benzene or ether with Corex-filtered light. Under these conditions, **1** was consumed with the concurrent production of a 2:1 mixture of products. A careful search revealed only trace amounts of acetone and norbornadiene, the expected products of a Norrish Type II cleavage. That the two major products were isomeric with **1** was demonstrated by elemental analyses on samples obtained by fractional distillation of the product. From a consideration of infrared and nmr spectral data, it was clear that these isomers were oxetanes. Since the problem of differentiating between the two possible oxetanes **5** and **6** could not be unambiguously resolved by analysis of the spectral data, a chemical means was devised. The key reaction involved acid-catalyzed cleavage of the oxetane ring,[7] a process which would be expected to lead to the isomeric aldehydes **7** and **8**. Since the parent hydrocarbons



5 **7** **9** **6** **8** **10**

3-methylbicyclo[3.2.1]oct-2-ene (**9**) and 3-methylbicyclo[3.3.0]oct-2-ene (**10**) are both known compounds,[8] the desired correlations could be achieved by decarbonylation reactions. Experimentally, it was found that the major oxetane gave **9** after rearrangement and decarbonylation, a fact which verifies the assignment of **5** to this isomer. Similarly, the minor isomer must be **6**, since olefin **10** was produced on rearrangement and decarbonylation.

Finally, irradiation of the aldehyde **2** led to two isomeric oxetanes in a ratio of 22:78. Analysis of the nmr spectral parameters in the low-field region suggested that the major isomer corresponded to structure **11**, since the observed broad doublet at δ 4.50 (J = 6 cps) assigned to H_a and H_b bore resemblance to the gross structure of the multiplet (doublet of triplets, J = 7.5, 1.5, and 1.5 cps) for the analogous proton in **5**. Similarly, the low-field proton in **6** (q, J = 7.5 and 4.5 cps) had a counterpart, H_c, in the low-field region of **12** (q, J = 8 and 5 cps). The remaining proton, H_d (t, J = 4 cps), had no counterpart in the spectra of either **5** or **6**. This analysis, while self-consistent, is not regarded as definitive. The basic arguments would not be altered if the structural assignments for **11** and **12** were reversed, however.



11 **12**

Thus no significant differences in product type were observed for the two photolyses. Nevertheless, the results are of interest in that they extend the limits of the intramolecular Paterno–Büchi reaction in the sense that photocyclizations of δ,ϵ-unsaturated ketones have not previously been observed to lead to products of the types represented by **6** and **12**. Moreover, they represent relatively simple examples of carbonyl systems which possess γ-hydrogen atoms but which do not undergo appreciable Norrish Type II reactions.[9] Owing to the wide variations in the efficiency of Type II eliminations in cyclic compounds, speculations as to the role of the double bond in the cases at hand would be premature.[10]

Experimental Section

Elemental analyses were done by Micro-Tech Laboratories, Skokie, Ill. Infrared spectra were determined as films or as noted on a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance data were obtained from a Varian Model A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard. Gas chromatograms were determined on an Aerograph A-90 P instrument using 12 ft × 0.25 in. columns of Carbowax 20 M on Chromosorb G or as noted. Melting points were determined on a Mel-Temp apparatus and are uncorrected.

exo,endo-**5-Norbornenylacetaldehyde** (**2**).—An ice-cold solution of 32.3 g (0.23 mol) of *exo,endo*-**4b**[6] in 1.5 l. of acetone was treated with 60 ml of 8.0 N Jones reagent[11] over a period of 70 min. The resulting mixture was diluted with 4.5 l. of water and extracted with chloroform. The extracts were washed with

(6) R. R. Sauers, R. M. Hawthorne, and B. I. Dentz, *J. Org. Chem.*, **32**, 4071 (1967); E. Allred and J. Marichich, *Tetrahedron Lett.*, 949 (1963).

(7) G. Büchi, C. G. Inman, and E. S. Lipinsky, *J. Amer. Chem. Soc.*, **76**, 4237 (1954). Traces of acid present in unpurified carbon tetrachloride smoothly catalyzed these rearrangements.

(8) For a reference to **9**, see W. Kraus and R. Dewald, *Justus Liebigs Ann. Chem.*, **689**, 21 (1965). H. C. Brown and W. J. Hammar [*J. Amer. Chem. Soc.*, **89**, 1524 (1967)] have reported the synthesis of **10**.

(9) For a discussion and other examples, see A. Padwa and D. Eastman, *ibid.*, **91**, 463 (1969).

(10) A quantitative study of this problem is in progress in these laboratories with A. Rousseau. For a recent discussion and references on the intermolecular mechanism of carbonyl–olefin energy transfer, see J. Saltiel, K. R. Neuberger, and M. Wrighton, *ibid.*, **91**, 3659 (1969).

(11) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

sodium bicarbonate solution and dried over $MgSO_4$. Evaporation of the extracts gave 5.40 g (17%) of an oil: bp 57° (1.5 mm); nmr δ 9.71 (m, HC=O), 5.92 (m, HC=C), 2.82 (s), and 2.6–0.55 (m); ir 5.78 (C=O) and 13.92 (C=C) μ. Gc analysis (152°) showed an *exo/endo* ratio of 17:83.

Satisfactory elemental analysis of **2** could not be obtained owing to rapid air oxidation.

The 2,4-dinitrophenylhydrazone was prepared, mp 131–130°.

Anal. Calcd for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.10; N, 17.71. Found: C, 57.14; H, 5.34; N, 17.47.

***exo,endo*-5-Norbornenylacetone (1). A.**—A solution of 13.1 g (0.096 mol) of **2** in 20 ml of dry ether was added to the Grignard reagent prepared from 20.6 g (0.14 mol) of methyl iodide and 3.89 g (0.16 g-atom) of magnesium in 20 ml of ether. The resulting solution was heated at reflux for 1 hr, at which time it was poured onto a mixture of ice and hydrochloric acid. The crude alcohols (**4a**) were extracted into ether which was dried and evaporated.

A small sample of *exo,endo*-1-(5-norbornenyl)propan-2-ol (**4a**) was purified by gas chromatography: nmr δ 5.98 (m, HC=C), 3.70 (m, HCO), 2.75–0.6 (m), and 1.10 (d, J = 7 cps, CH_3); ir 2.92 (m, OH), 3.25 (w, HC=), 8.90 (m, CO), and 13.98 μ (s, HC=CH).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C 78.51; H, 10.49.

The crude alcohol was dissolved in 200 ml of acetone and treated with 31 ml of Jones reagent[11] at 0–10°. After the mixture had been stirred for 10 min, enough isopropyl alcohol to destroy the excess reagent was added. The resulting mixture was poured into 1 l. of water followed by ether extraction. The dried extracts were evaporated and the residue was distilled to yield 7.42 g (51%) of **1**: bp 64–65° (0.6–0.5 mm); nmr δ 6.03 (m, HC=), 3.0–0.3 (m), and 2.09 (CH_3); ir 5.83 (s, C=O) and 13.98 (s, HC=CH) μ. Gc analysis (153°) showed a 15:85 ratio of *exo/endo* isomers.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.22; H, 9.53.

B.[12]—The Grignard reagent of 5-bromomethylnorbornene (15% *exo*)[13] was prepared from 153 g (0.82 mol) and 21.9 g (0.90 g-atom) of magnesium in 500 ml of ether. A solution of 66 g (1.22 mol) of freshly distilled acetaldehyde in 70 ml of ether was added over a 20-min period to the cooled (5–10°) Grignard solution. The resulting mixture was heated at reflux for 15 min and poured over a mixture of ice and hydrochloric acid. The product was extracted into ether which was washed with sodium bicarbonate solution and dried over $MgSO_4$. The crude product obtained on evaporation showed four components on gc analysis (153°)—*exo* and *endo*-**1** and *exo* and *endo* alcohols **4a**.

The entire product was oxidized as above in 2 l. of acetone with 200 ml of Jones[11] reagent to yield 69.34 g (56%) of ketone **1**, bp 80–83° (15 mm).

Photolyses.—Preparative-scale irradiations were carried out in cyclindrical flasks equipped with nitrogen inlet tubes at the bottom. The lamps used were 450-W (type L) Hanovia medium-pressure mercury arcs which were housed in a water-cooled immersion cell equipped with a Corex 9700 filter sleeve. The compound to be irradiated was dissolved in dry benzene or ether and the solution was purged with dry, oxygen-free nitrogen for 15 min before irradiation was commenced.

Irradiation of 1.—A solution of 12.04 g of **1** in 1 l. of ether was irradiated for 20 hr. Gc analysis (150°) revealed only a trace of starting materials and two new peaks in the ratio 2:1. An nmr spectrum of the concentrated reaction mixture revealed two singlets at 1.37 and 1.22 ppm in the ratio of *ca.* 1:2. Distillation of the crude photosylate at 2 mm gave a 7.52-g (62%) fraction, bp 42–65°, which was essentially pure oxetanes. A nonvolatile residue of 4.32 g remained. The pure oxetanes could be obtained by fractional distillation on a spinning-band column (18 in. × 6 mm).

3-Methyl-4-oxatetracyclo[5.2.1.0.^{3,6}0^{5,9}]decane (5) gave the following data: bp 68–73° (6 mm); nmr δ 4.41 (d, of t, J = 7.5, 1.5, and 1.5 cps, HCO), 1.22 (s, CH_3), and 2.6–1.0 (m); ir (film) 9.10 (m), 9.52 (s), 9.71 (s), 9.85 (m), 10.48 (m), 11.28 (m), and 12.18 μ (s).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.25; H, 9.44.

5-Methyl-6-oxatetracyclo[5.3.0.0.^{3,9}0^{5,8}]decane (6) gave the following data: bp 63–64° (6 mm); nmr δ 4.57 (q, J = 7.5 and 4.5 cps, HCO), 1.37 (s, CH_3), and 2.9–1.1 (m); ir (film) 8.74 (m), 9.56 (m), 10.03 (s), 10.13 (s), 10.78 (s), 11.06 (m), and 12.08 μ (s).

Anal. Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.83; H, 9.36.

Irradiation of *endo*-1.—A 30-mg sample of *endo*-**1** was collected by preparative gc, $\lambda_{max}^{CH_3OH}$ 279 nm (ϵ 27). A deoxygenated solution in 0.30 ml of benzene was prepared and irradiated in a Pyrex nmr tube with the 3000-Å source of a Rayonet photochemical reactor[14] for 22 hr. Gc analysis revealed that 80% of the ketone had been consumed but that only trace amounts (<0.1%) of acetone and norbornadiene could be detected.

Irradiation of 2.—Irradiation of 5.40 g of **2** in 1 l. of benzene for 3 hr gave 2.41 g (≐5%) of a solid which contained a trace of starting material. A pentane solution of the product was washed with dilute potassium permanganate until the color persisted. The acidic materials were removed by washing with aqueous sodium carbonate and the extracts were dried and evaporated to give 1.45 g of a mixture of **11** and **12**. An analytical sample was prepared by sublimation at 55° (1.5 mm).

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.38; H, 9.06.

Gc analysis (152°) indicated the presence of two components in a ratio of 22:78. Small samples of the two isomers were collected for spectral purposes. The minor isomer, mp 143–150°, was assigned structure **12** (6-oxatetracyclo[5.3.0.0.^{3,9}0^{5,8}]decane): nmr δ 4.70 (q, J = 8 and 5 cps, HCO), 4.88 (t, J = 4 cps, HCO), and 3.5–1.4 (m); ir (Nujol) 8.50 (m), 8.98 (m), 9.68 (m), 10.18 (s), 11.43 (m), 11.91 (m), and 12.15 μ (m).

The major component, mp 153–164°, was assigned structure **11** (4-oxatetracyclo[5.2.1.0.^{3,6}0^{5,9}]decane): nmr δ 4.50 (d, J = 6 cps, HCO) and 3.5–1.0 (m); ir (Nujol) 9.42 (w), 9.93 (m), 10.20 (m), 11.33 (m), 11.96 (m), and 12.58 μ (m).

3-Methyl-*cis*-bicyclo[3.3.0]oct-2-ene-7-carboxaldehyde (8).—A solution of **6** in carbon tetrachloride[7] was allowed to stand at 25° for 42 hr. At the end of this period, rearrangement to **8** was complete as shown by gc: nmr δ 9.50 (d, J = 2 cps, HC=O), 5.10 (m, HC=C), and 3.5–1.0 (m); ir 3.69 (w) and 5.78 μ (s).

The **2,4-dinitrophenylhydrazine** was prepared by addition of **6** directly to an acid solution of 2,4-DNPH in ethanol; after crystallization from ethanol the melting point was 176–177.5°.

Anal. Calcd for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.06; H, 5.35; N, 16.46.

3-Methylbicyclo[3.2.1]oct-2-ene-6-carboxaldehyde (7).—The aldehyde was prepared as above. Gc analysis indicated two peaks in a 3:1 ratio which are presumed to be epimers: nmr δ 9.63 (d, J = 2 cps, HC=O), 5.52 (d, J = 7 cps, HC=C), and 3.0–1.4 (m); ir 3.70 (w) and 5.80 μ (s).

The 2,4-dinitrophenylhydrazone was prepared as above, mp 153–155°.

Anal. Found: C, 58.03; H, 5.38; N, 17.17.

3-Methylbicyclo[3.3.0]oct-2-ene (10).—A mixture of 0.81 g of **8** and 0.20 g of 10% palladium on carbon was heated at 150°[15] in a short-path distillation apparatus. The bath temperature was gradually raised to 190°, at which time the evolution of gas appeared to cease. A vacuum was applied, whereupon 0.84 g of distillate was obtained. Preparative gc (Apiezon L, 125°) indicated one major product with a small shoulder. The ir spectrum of the collected material was virtually identical with that of an authentic sample of **10**;[8] the nmr spectrum was identical with that of an authentic sample except for a small doublet at δ 0.95 in the decarbonylation product.

3-Methylbicyclo[3.2.1]oct-2-ene (9).—A 0.75-g sample of mixed aldehydes (<10% **8**) was heated at 138° for 4 hr with 0.35 ml of *t*-butyl peroxide.[16] An additional 0.17 ml of peroxide was added followed by heating for 20 hr. Preparative gc (Apiezon L, 148°) revealed one major component, which was collected (0.105 g). The ir spectrum of this material was virtually identical with that of an authentic sample of **9**.[8] About 10% **10** was present in this product, as determined by integration of the nmr spectrum in the δ 5.0 region.

(12) This method proved to be the more convenient one owing to the availability of the starting materials.

(13) K. Alder and E. Windemuth, *Chem. Ber.*, **71**, 1939 (1938).

(14) Obtained from the Southern New England Ultraviolet Co., Middletown, Conn.

(15) J. Wilt and V. P. Abegg, *J. Org. Chem.*, **33**, 925 (1968).

(16) J. A. Berson and C. J. Olsen, *J. Amer. Chem. Soc.*, **84**, 3178 (1962).

Registry No.—*endo*-**1**, 22842-22-4; *endo*-**2**, 15507-07-0; 2,4-dinitrophenylhydrazone of *endo*-**2**, 22842-24-6; **5**, 22842-30-4; **6**, 22842-31-5; **7**, 22842-32-6; 2,4-dinitrophenylhydrazone of **7**, 22842-33-7; **8**, 22842-25-7; 2,4-dinitrophenylhydrazone of **8**, 22842-26-8; **11**, 22842-34-8; **12**, 22842-35-9.

Acknowledgments.—Financial support from the following agencies is gratefully acknowledged: Cities Service Co., Merck & Co., and the donors of the Petroleum Research Fund (1676-A1), administered by the American Chemical Society. We are grateful to Professors H. C. Brown and W. Kraus for spectral data.

Notes

Pyrazole Product Ratio Analysis of the Reaction of Diazomethane with Methyl *cis*- and *trans*-β-Chloroacrylates

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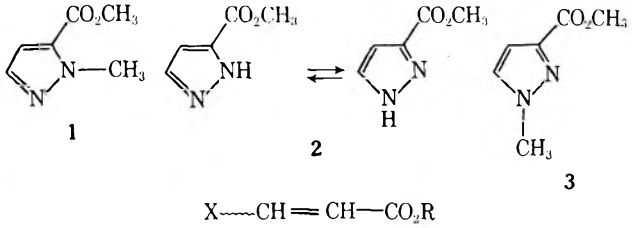
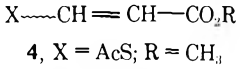
Received May 20, 1969

Carbomethoxypyrazoles **1**, **2**, and **3** are obtained upon reaction of appropriately substituted methyl acrylates (*i.e.*, **4** and **5**) with excess diazomethane in ether.[1,2] However, the mechanism of pyrazole formation remains obscure. To probe into the nature of the intermediates in pyrazole formation, we studied the reaction of methyl *cis*- and *trans*-β-chloroacrylates **6** with diazomethane.

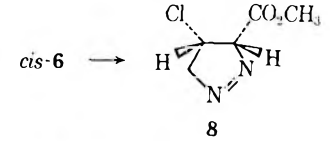


1 **2** **3**

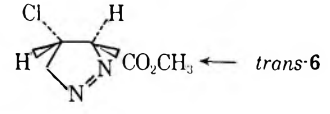


4, X = AcS; R = CH_3
5, X = Br; R = CH_3
6, X = Cl; R = CH_3
7, X = Cl; R = H

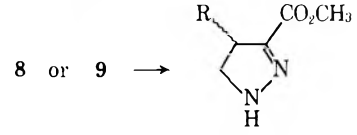
Concerted addition of diazomethane to *cis*- and *trans*-**6** is expected to yield intermediate 1-pyrazolines **8** and **9**, respectively. This conclusion is supported by the observation that activated olefins containing a β substituent which is not a leaving group react with diazomethane to yield 1-pyrazolines with retention of geometrical configuration.[3] 1-Pyrazolines may readily isomerize to 2-pyrazolines.[4,5] This isomerization, which is apparently very fast,[6] would yield the 2-pyrazoline **10** as a common intermediate from either *cis*- or *trans*-**6**. Attempts, in our laboratories, to detect intermediate 1- or 2-pyrazolines spectrophotometrically failed. We therefore investigated the pyrazole product ratios, which we suspected would yield indirect evidence for the nature of the intermediates in pyrazole formation. If pyrazolines **8** and **9** are indeed formed during the reaction sequence, product analysis[1] should reflect the presence of these intermediates which are expected to eliminate HCl at different rates. Significant differences in pyrazole product ratio should only be observed if there are large differences in rates of elimination of HCl from intermediate stereoisomeric 1-pyrazolines and one of the elimination rates is faster than isomerization (**8** or **9** → **10**).



cis-**6** → **8**



trans-**6** → **9**



8 or **9** → **10**, R = Cl; **11**, R = H

Results and Discussion

Methyl *cis*-β-chloroacrylate (**6**) was prepared by cuprous chloride catalyzed addition of HCl to propiolic acid followed by esterification in methanol.[7] The *trans* isomer **6** was prepared in a similar manner from *trans*-β-chloroacrylic acid (**7**) obtained by isomerization of *cis*-**7** in 6 *N* HCl.[7] A mixture of *cis* and *trans* isomers **6** could also be prepared by catalytic addition of HCl to methyl propiolate. Spinning-band distillation afforded pure *cis* and *trans* isomers in 60 and 5% yields, respectively. The purity of the geometrical β-chloro esters was confirmed by gas–liquid partition chromatography and by comparison with reported nmr spectra.[7]

Reaction of 10 m*M* *cis*-**6** in 36–43 m*M* distilled diazomethane–ether in a Dry Ice–acetone bath for 4 hr,

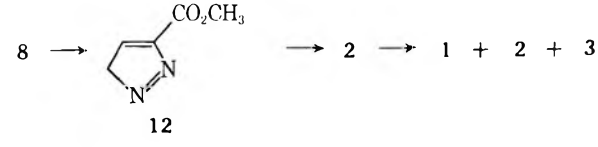
(1) D. T. Witiak and M. C. Lu, *J. Org. Chem.*, **33**, 4451 (1968).
(2) H. von Pechman and E. Burkard, *Ber.*, **33**, 3594 (1900).
(3) T. V. VanAuken and R. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **84**, 3736 (1962).
(4) L. I. Smith and W. Pings, *J. Org. Chem.*, **2**, 23 (1937).
(5) L. I. Smith and K. L. Howard, *J. Amer. Chem. Soc.*, **65**, 159 (1943).
(6) L. I. Smith and K. L. Howard, *ibid.*, **65**, 165 (1943).
(7) A. N. Kurtz, W. E. Billups, R. B. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).

followed by standing at room temperature for 70 hr, affords, by gas–liquid partition chromatography, 1-methyl-5-carbomethoxypyrazole (**1**), 3-carbomethoxypyrazole (**2**), and 1-methyl-3-carbomethoxypyrazole (**3**) in a ratio of 2.20:1.34:1.00 (43.8, 36.5, and 19.7%, respectively). No starting material was detected. Reaction of 10 m*M* *trans*-**6** under identical conditions afforded only pyrazoles **1** and **2** in a ratio of 1.00:9.87 (9.2 and 90.8%, respectively). No starting material or 1-methyl-3-carbomethoxypyrazole (**3**) was detected. This difference in pyrazole product ratios, which is dependent upon the configuration of the starting β-chloro ester, is evidence for the lack of a common intermediate 2-pyrazoline **10** and/or an identical reaction pathway for the two geometrical isomers of **6**; the differences in pyrazole product ratios must be mainly a reflection of the ease of elimination of HCl from intermediate 1-pyrazolines **8** and **9**.

Support for this interpretation is derived from the following observations. Reaction of 10 m*M* 3-carbomethoxypyrazole (**2**) in 36–43 m*M* distilled diazomethane–ether under identical conditions described when *cis*- or *trans*-**6** served as starting material afforded pyrazoles **1**, **2**, and **3** in a ratio of 2.26:1.94:1.00 (43.5, 37.4, and 19.2%, respectively).[8] This ratio is nearly the same as the pyrazole product ratio observed when *cis*-**6** served as starting material. Under identical reaction conditions, but employing equimolar (10 m*M*) concentrations of 3-carbomethoxypyrazole (**2**) and diazomethane, the ratio obtained for **1**, **2**, and **3** was 1.53:6.90:1.00, respectively; *i.e.*, even at low concentrations of diazomethane, **3** was obtained as one of the products. When *trans*-**6** served as the reactant, no 1-methyl-3-carbomethoxypyrazole (**3**) was formed.

To determine whether intermediate 1- or 2-pyrazolines could undergo such methylation, we subjected methyl acrylate to identical reaction conditions, removed the solvent under reduced pressure, and converted the residual pyrazolines into pyrazoles by bromination followed by elimination of HBr.[2] Gas–liquid partition chromatography showed 1-methyl-5-carbomethoxypyrazole (**1**) and 3-carbomethoxypyrazole (**2**) to be present in 11.6 and 76.8% yield, respectively. No 1-methyl-3-carbomethoxypyrazole (**3**) was detected; therefore, the 1-pyrazoline does not yield **3**. 3-Carbomethoxy-2-pyrazoline (**11**) was also prepared in pure form and subjected to methylation under the same conditions. After removal of the solvent, the residual pyrazolines were similarly converted into pyrazoles. Product ratio analysis again revealed the absence of **3** and the presence of **1** and **2** in 7.6 and 86.6% yield, respectively. The product ratios when **11** served as starting material were similar to the ratios observed when *trans*-**6** served as starting material. Since **3** is not obtained from intermediate 1- or 2-pyrazolines, it must result from methylation of pyrazole **2** when *cis*-**6** serves as the reactant.

Cromwell and coworkers have evidence suggesting that *trans* elimination (under acidic conditions) of appropriately substituted 4-aminopyrazolines is more rapid than *cis* elimination.[9] When methyl β-(acetylthio)acrylates were employed as starting material, product ratio analysis suggested *cis* elimination of thiolacetic acid from the intermediate 1-pyrazoline to be the more facile process.[1] Since large differences in pyrazole product ratio were not observed when stereoisomeric methyl β-(acetylthio)acrylates served as the reactant, but were observed when the acetylthio group was replaced by chloride, it seems that *trans* elimination of the acetylthio group also takes place readily. With the β-chloroacrylates, results obtained are consistent with the proposal that the 1-pyrazoline **8**, derived from *cis*-**6**, undergoes a relatively rapid *trans* elimination of HCl, affording, after rapid isomerization of intermediate **12**, 3-carbomethoxypyrazole (**2**). The intermediate 1-pyrazoline **8** is methylated to the same extent (*via* **3**) as when **3** itself serves as the reactant. Such *trans* elimination of HCl is apparently faster than isomerization (**8** → **10**) and involves the more acidic proton α to the carbomethoxy group, since the relative configuration of this proton represents the only difference between intermediates **8** and **9**. With intermediate **9**, derived from *trans*-**6**, elimination of HCl is considerably slower and most likely takes place during solvent (and diazomethane) removal, since pyrazole **3** was not detected as one of the reaction products. The elimination of HCl may in fact occur during or after isomerization (**9** → **10**).



Experimental Section

cis-β-**Chloroacrylic acid** (**7**) was prepared by cuprous chloride catalyzed addition of HCl to propiolic acid according to a published method: mp 59–60° (lit.[7] mp 60.8–61.4°).

trans-β-**Chloroacrylic acid** (**7**) was prepared from *cis*-**7** by heating in 6 *N* HCl for 6 hr: mp 85–86.5° (lit.[7] mp 85–86°).

Methyl *cis*-β-chloroacrylate (**6**) was prepared by heating *cis*-**7** in methanol containing a few drops of concentrated H_2SO_4: bp 85–86° (90 mm) [lit.[7] bp 79–83° (78 mm)]. Alternatively, methyl *cis*-β-chloroacrylate (**6**) may be prepared from methyl propiolate. To a solution of 2.0 g of CuCl in 40 ml of concentrated HCl was added 15.0 g (0.19 mol) of methyl propiolate during 15 min with constant stirring at a temperature of 8–12°. After standing at 0° overnight, the mixture was extracted with chloroform, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue (14.0 g) was distilled using a spinning-band column, affording 13.0 g (62%) of pure *cis*-**6** and 1.0 g (4.5%) of *trans*-**6**.

Methyl *trans*-β-chloroacrylate (**6**) was prepared from *trans*-**7** in a manner similar to the preparation of the *cis* isomer **6**: bp 60–62° (100 mm) [lit.[7] bp 74–75° (131 mm)].

Reaction of Methyl *cis*-β-Chloroacrylate (**6**) **with Distilled Diazomethane in Ether.**—To 200 ml of the distilled ether–diazomethane ($3.6–4.3 \times 10^{-2}$ mol) solution[10] was added 1.2 g (1.0×10^{-2} mol) of methyl *cis*-β-chloroacrylate (**6**) in 100 ml of dry ether. The flask containing *cis*-**6** was washed with 50 ml of dry ether and added to the reaction flask to make 350 ml. The reaction mixture was kept in a Dry Ice–acetone bath for 4 hr and then allowed to stand at room temperature for 70 hr. The solvent was removed under reduced pressure and the residue was dissolved in 25 ml of dry chloroform. The chloroform solution was analyzed by gas–liquid partition chromatography on silicone gum rubber (UC-W98) on Chromosorb W (80–100 mesh) with a 4 ft × 0.25 in. glass column with column temperature of 120°, detector temperature of 240°, injection port temperature of 250°, inlet pressure of 35 psi, and carrier gas (He)

(8) This pyrazole product ratio is dependent upon the concentration of diazomethane and the reaction conditions employed. Under somewhat different conditions (see ref 1), other ratios are obtained.

(9) N. H. Cromwell, N. G. Barker, R. A. Wankel, P. J Vanderhorst, F. W. Olson, and J. H. Anglin, Jr., *J. Amer. Chem. Soc.*, **73**, 1044 (1951).

(10) H. A. Blatt, Ed., "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1955, p 165.

flow rate of 45 ml/min. Retention times of 0.90 min for 1-methyl-5-carbomethoxypyrazole (1), 1.5 min for 3-carbomethoxypyrazole (2), and 2.30 min for 1-methyl-3-carbomethoxypyrazole (3) were obtained. These retention times are similar to those previously reported.[1] The peak ratio for 1/2/3 was 2.2:1.34:1.0 (43.8:36.5:19.7%), respectively.

Reaction of Methyl *trans*-β-Chloroacrylate (6) with Distilled Diazomethane in Ether.—Reaction conditions employed were the same as in the reaction of *cis*-6 with distilled ether–diazomethane. Gas–liquid partition chromatography under identical conditions afforded 1-methyl-5-carbomethoxypyrazole (1) and 3-carbomethoxypyrazole (2) in a ratio of 9.87:1.00 (90.8:9.2%), respectively. No 1-methyl-3-carbomethoxypyrazole (3) was detected.

Pyrazoline and Pyrazole Formation When Methyl Acrylate Served as Starting Material.—One gram (1.1×10^{-2} mol) of methyl acrylate was treated with distilled ether–diazomethane ($3.6–4.3 \times 10^{-2}$ mol) under conditions identical with those described for the reaction of methyl *cis*-β-chloroacrylate (6) with distilled diazomethane in ether. The solvent was removed under reduced pressure and the residue containing pyrazolines was brominated by dropwise addition of 1.0 g (0.55×10^{-2} mol) of Br_2 in 10 ml of dry CCl_4 according to the method of Pechman and Burkard.[2] The reaction temperature was maintained at 0° for 0.5 hr and then the solution was allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was dissolved in 25 ml of dry chloroform. Gas–liquid partition chromatography showed 1-methyl-5-carbomethoxypyrazole (1), 11.6%, and 3-carbomethoxypyrazole (2), 76.8%. No 1-methyl-3-carbomethoxypyrazole (3) was detected. Uncharacterized compounds represented a total of 11.6% of the reaction mixture.

Pyrazole Formation When 3-Carbomethoxy-2-pyrazoline (11) Served as Starting Material.—3-Carbomethoxy-2-pyrazoline was prepared from 2.1 g (2.4×10^{-2} mol) of methyl acrylate under the same reaction conditions as described previously. The solvent was removed under reduced pressure and the residue was crystallized from 95% ethanol, affording 1.8 g (60%) of 3-carbomethoxy-2-pyrazoline (11), mp 61–63° (lit.[2] mp 63–66°). One gram (7.9×10^{-3} mol) of 3-carbomethoxy-2-pyrazoline (11) was treated in distilled ether–diazomethane (2.5×10^{-2} mol) under conditions identical with the reaction conditions described for *cis*-6 with distilled diazomethane in ether. The solvent was removed under reduced pressure and the residue was brominated by addition of 1.0 g (0.55×10^{-2} mol) of Br_2 in 10 ml of dry CCl_4 as above. Gas–liquid partition chromatography showed 1-methyl-5-carbomethoxypyrazole (1), 7.6%, and 3-carbomethoxypyrazole (2), 89.6%. No 1-methyl-3-carbomethoxypyrazole was detected. Uncharacterized compounds represented a total of 2.8% of the reaction mixture.

Registry No.—Diazomethane, 334-88-3; *cis*-6, 3510-44-9; *trans*-6, 5135-18-2.

Acknowledgment.—We are grateful to the Environmental Control Administration, National Institutes of Health, Rockville, Md., for support of this work through Grant EC-00115.

Isomeric Transition Metal Complexes of *trans*-2-(2′-Quinolyl)-methylene-3-quinuclidinones[1]

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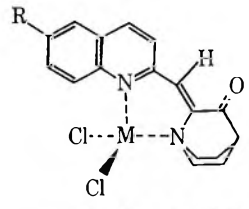
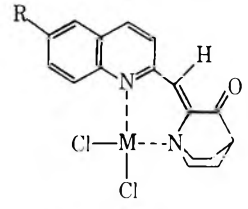
Received April 14, 1969

Tetrahedral–square-planar equilibria have been identified and studied with a variety of tetracoordinate nickel(II) complexes in solution.[2] In comparatively fewer instances, both isomers of a given complex have been isolated in pure form.[3] This has been accomplished with bis(alkyldiphenylphosphine)nickel(II) dihalides. It has now been observed that both the tetrahedral and square planar nickel(II) dichloride complexes of the bidendate ligand *trans*-2-(2′-quinolyl)methylene-3-quinuclidinone and of its 6′-methoxy derivative are very easily prepared in pure crystalline form.

2-(6′-Methoxy-2′-quinolyl)methylene-3-quinuclidinone was synthesized in the course of a project concerned with antimalarials of the quinolinemethanol class by the base-catalyzed condensation of 6-methoxyquinoline-2-carboxaldehyde[4] with 3-quinuclidinone. In order to prove the anticipated *trans* stereochemistry of the product, its cobalt, nickel, and copper dichloride complexes were prepared. Since these exhibit normal (1710–1720 cm^{-1}) carbonyl stretching frequencies in their infrared spectra, both nitrogen atoms and not the carbonyl oxygen are involved in coordination, whence the *trans* geometry must obtain.





1, M = CO; R = OCH_3
2, M = Ni; R = OCH_3
5, M = CO; R = H
6, M = Ni; R = H

3, M = Cu; R = OCH_3
4, M = Ni; R = OCH_3
7, M = Cu; R = H
8, M = Ni; R = H

The complexes were prepared by combining ethanol solutions of the metal dichlorides with solutions of the ligand. They crystallized out immediately. The cobalt complex **1** is deep green and may be recrystallized without change from chloroform–ethanol. The nickel complex **2** is maroon and has an infrared spectrum (Nujol) identical with that of the cobalt complex. The copper complex **3** is brown-yellow and has an entirely different infrared spectrum from those of complexes **1** and **2**. Given the propensity of cobalt(II) to form tetrahedral complexes and of copper(II) to form square-planar complexes,[5] tetrahedral stereochemistry can be assigned to complexes **1** and **2** and square-planar stereochemistry to complex **3**. When the maroon nickel complex **2** is recrystallized from methylene chloride–ethanol, it changes color and yields yellow-brown crystals of a complex having an infrared spectrum virtually identical with that of the copper complex **3**. On this basis it is assigned the square-planar structure **4**.

The isomerization of **2** to **4** is irreversible, the latter evidently being the more stable isomer, and the successful preparation of isomer **2** is contingent on the use of

(1) Synthetic Quinine Analogs II, supported by the U. S. Army Medical Research and Development Command, Contract DADA-17-68-C-80-45. Part I: D. R. Bender and D. L. Coffen, *J. Org. Chem.*, **33**, 2504 (1968).

(2) M. C. Browning, R. F. B. Davies, D. J. Morgan, L. E. Sutton, and L. M. Venanzi, *J. Chem. Soc.*, 4816 (1961); R. H. Holm and K. Swaminathan, *Inorg. Chem.*, **2**, 181 (1963); A. Chakrovorty and R. H. Holm, *ibid.*, **3**, 1010 (1964); D. R. Eaton, W. D. Phillips, and D. J. Caldwell, *J. Amer. Chem. Soc.*, **85**, 397 (1963); L. Sacconi, M. Ciampolini, and N. Nardi, *ibid.*, **86**, 819 (1964).

(3) M. C. Browning, J. R. Mellor, D. J. Morgan, S. A. J. Pratt, L. E. Sutton, and L. M. Venanzi, *J. Chem. Soc.*, 693 (1962); R. E. Hayter and F. S. Humiec, *Inorg. Chem.*, **4**, 1701 (1965).

(4) W. Mathes and W. Sauermilch, *Chem. Ber.*, **90**, 758 (1957).

(5) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1966, pp 865, 899.

a hot solvent in which the complex has low solubility. Boiling absolute ethyl alcohol served admirably up to the time a crystalline sample of isomer **4** was prepared. Thereafter, boiling *n*-butyl alcohol was necessary for further preparations of **2** in the same laboratory.

Since the methoxyl group in the series **1**–**4** is essentially an artifact arising from our interest in quinine analogs, the ligand lacking this additional functional group was also synthesized. Again a single geometrical isomer (*trans*) was obtained, which readily yielded the series of complexes **5**–**8**. The nickel complex **6** undergoes the same facile isomerization to complex **8** described above for the isomeric pair **2** and **4**. Magnetic moments of four of the complexes, **1**, **6**, **7**, and **8**, were measured[6] to confirm the structural assignments made on the basis of infrared spectral data, and, in reasonable agreement[7] with the assigned structures, magnetic moments of 3.98, 3.34, 1.74, and 0.65 BM, respectively, were observed. The small moment observed for complex **8** suggests that it is not entirely diamagnetic. Possibly a small amount of the tetrahedral geometry is admixed with the square-planar geometry.

Experimental Section[8]

trans-**2-(6′-Methoxy-2′-quinolyl)methylene-3-quinuclidinone.**—A solution of sodium (50 mg) in absolute ethanol (2 ml) was added to a solution of 6-methoxyquinoline-2-carboxyaldehyde[4] (187 mg, 1 mmol) and 3-quinuclidinone[9] (125 mg, 1 mmol) in absolute ethanol (10 ml) and heated under reflux for 2 hr. The solution was cooled and scratched to induce crystallization, and the product was filtered out and washed with water and cold ethanol to give 246 mg (84%) of yellow crystals: mp 185–186°; ir ν_{max} 1700, 1615, 1555, 1495, 1240, 1215, 1090, 1025, and 830 cm^{-1}; nmr ($CDCl_3$) 2.05 (m, 4 H), 2.67 (quintuplet, 1 H), 3.15 (m, 4 H), 3.95 (s, 3 H), 7.08 (d, 1 H), 7.40 (m plus s, 2 H), 8.05 (d, 2 H), and 8.75 ppm (d, 1 H).

Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.65; H, 6.16; N, 9.52. Found: C, 73.80; H, 6.16; N, 9.40.

Cobalt Complex 1.—A solution of cobaltous chloride hexahydrate (81 mg, 0.34 mmol) in ethanol (2 ml) was added to a warm solution of the ligand (100 mg, 0.34 mmol) in ethanol (5 ml). The product was filtered and washed with ethanol, giving 133 mg (92%) of green powder. Recrystallization from chloroform–ethanol gave lustrous green crystals: mp 316° dec; ir ν_{max} 1710, 1620, 1580, 1375, 1245, 1235, 1165, 1130, 1095, 1020, 938, 867, 819, 764, 754, and 688 cm^{-1}. An nmr spectrum was precluded by low solubility.

Anal. Calcd for $C_{18}H_{18}Cl_2CoN_2O_2$: C, 50.96; H, 4.28; Cl, 16.72; N, 6.60. Found: C, 51.22; H, 4.30; Cl, 17.04; N, 6.73.

Nickel Complex 2.—A hot solution of nickelous chloride hexahydrate (81 mg, 0.34 mmol) in ethanol (1 ml) was added to a boiling solution of the ligand (100 mg, 0.34 mmol) in 1-butanol (1 ml). The product was filtered and washed with ethanol, giving 131 mg (91%) of maroon needles: mp 310° dec; ir ν_{max} 1710, 1620, 1580, 1375, 1245, 1235, 1165, 1130, 1095, 1020, 938, 868, 816, 764, 755, and 687 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}Cl_2N_2NiO_2$: C, 50.99; H, 4.28; Cl, 16.73; N, 6.61. Found: C, 51.06; H, 4.32; Cl, 16.44; N, 6.43.

Copper Complex 3.—A solution of cupric chloride dihydrate (58 mg, 0.34 mmol) in ethanol (2 ml) was added to a warm solution of ligand (100 mg, 0.34 mmol) in ethanol (5 ml). The product was filtered and washed with ethanol, giving 138 mg (95%) of small khaki crystals: mp 297–298°; ir ν_{max} 1720, 1645, 1625, 1500, 1380, 1245, 1135, 1090, 1025, 910, 888, 875, 850, 833, 819, 781, 772, 755, and 690 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}Cl_2CuN_2O_2$: C, 50.42; H, 4.23; Cl, 16.54; N, 6.53. Found: C, 50.47; H, 4.05; Cl, 16.33; N, 6.39.

Nickel Complex 4.—The nickel complex **2** (131 mg) was taken up in boiling methylene chloride (25 ml), giving a brown solution. This was concentrated with gradual addition of ethanol, causing the isomeric complex to separate in yellow-brown plates. The product was filtered and washed with ethanol, giving 120 mg (92%): mp >360°; ir ν_{max} 1720, 1645, 1625, 1500, 1380, 1245, 1135, 1090, 1025, 910, 885, 871, 850, 835, 818, 782, 763, 757, and 690 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}Cl_2N_2NiO_2$: C, 50.99; H, 4.28; Cl, 16.73; N, 6.61. Found: C, 51.21; H, 4.02; Cl, 16.92; N, 6.57.

trans-**2-(2′-Quinolyl)methylene-3-quinuclidinone.**—A solution of sodium (347 mg) in absolute ethanol (10 ml) was added to a solution of quinoline-2-carboxaldehyde[10] (1.572 g, 0.01 mol) and 3-quinuclidinone[9] (1.612 g, 0.01 mol) in absolute ethanol (25 ml) and heated under reflux for 0.5 hr. The solution was cooled and treated with water (50 ml) to induce crystallization, and the product was filtered out and washed with alcohol to give 2.187 g (83%) of yellow crystals: mp 150–151°; ir ν_{max} 1710, 1640, 1240, 1170, 1090, 830, 810, and 758 cm^{-1}; nmr ($CDCl_3$) 2.03 (m, 4 H), 2.67 (quintuplet, 1 H), 3.08 (m, 4 H), 7.36 (s, 1 H), 7.63 (m, 3 H), 8.08 (d, 2 H), and 8.71 ppm (d, 1 H).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.46; H, 6.10; N, 10.52.

Cobalt Complex 5.—A solution of cobaltous chloride hexahydrate (0.237 g, 0.001 mol) in ethanol (12 ml) was added to a warm solution of the ligand (0.264 g, 0.001 mol) in ethanol (10 ml). The product was filtered and washed with ethanol, giving 0.379 g (96%) of green powder. Recrystallization from $CHCl_3$–ethanol gave deep green crystals: mp 325° dec; ir ν_{max} 1710, 1640, 1590, 1370, 1240, 1210, 1165, 1090, 1015, 935, 855, 832, 807, 788, 760, and 745 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}Cl_2CoN_2O$: C, 51.80; H, 4.09; N, 7.11; Cl, 17.99. Found: C, 51.80; H, 4.02; N, 7.05; Cl, 18.18.

Nickel Complex 6.—A hot solution of nickelous chloride hexahydrate (0.095 g, 0.4 mmol) in absolute ethanol (1.5 ml) was added to a warm solution of the ligand (0.106 g, 0.4 mmol) in *n*-butyl alcohol (4 ml). The resulting maroon solution was quickly cooled in a cold-water bath. The product was filtered and vacuum dried, giving 0.141 g (89%) of maroon crystals: mp 310° dec; ir ν_{max} 1720, 1645, 1595, 1370, 1245, 935, 868, 855, 835, 810, 790, 780, 760, and 743 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}Cl_2N_2NiO$: C, 51.83; H, 4.09; Cl, 18.00; N, 7.11. Found: C, 51.88; H, 4.03; Cl, 18.15; N, 7.11.

Copper Complex 7.—A solution of cupric chloride dihydrate (0.085 g, 0.5 mmol) in ethanol (4 ml) was added to a warm solution of the ligand (0.132 g, 0.5 mol) in ethanol (7 ml). The product was filtered and washed with ethanol, giving 0.189 g (95%) of small gold crystals: mp 233° dec; ir ν_{max} 1720, 1640, 1595, 1495, 1370, 1240, 1090, 908, 855, 828, 783, 766, and 755 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}Cl_2CuN_2O$: C, 51.20; H, 4.04; Cl, 17.80; N, 7.03. Found: C, 51.03; H, 3.96; Cl, 17.96; N, 6.90.

Nickel Complex 8.—The nickel complex **6** (50 mg) was dissolved in boiling chloroform (35 ml), giving a rose-colored solution. This was concentrated with concurrent addition of absolute ethanol, causing the isomeric complex to separate in yellow-brown crystals. The product was filtered and washed with ethanol, giving 43 mg (86%): mp >360°; ir ν_{max} 1710, 1645, 1595, 1500, 1370, 1238, 1160, 1140, 1085, 1020, 915, 886, 860, 830, 810, 780, 755, and 738 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}Cl_2N_2NiO$: C, 51.83; H, 4.09; Cl, 18.00; N, 7.11. Found: C, 51.81; H, 4.08; Cl, 17.96; N, 7.04.

(6) Magnetic susceptibilities were measured at room temperatures with a Gouy balance using solid samples in glass tubes. The apparatus was calibrated with mercury tetrathiocyanato cobaltate. For a detailed description, see B. N. Figgis and R. S. Nyholm, *J. Chem. Soc.*, 4190 (1958). No allowance was made for diamagnetic contributions in calculating magnetic moments from the observed susceptibilities.

(7) See ref 5, p 636–637.

(8) Melting points are uncorrected. Infrared spectra were measured as Nujol mulls on a Perkin-Elmer Infracord Model 137; stronger bands are listed. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

(9) Obtained from Aldrich Chemical Co., Inc., Milwaukee, Wis., as the hydrochloride.

(10) H. Kaplan, *J. Amer. Chem. Soc.*, **63**, 2654 (1941).

Registry No.—*trans*-2-(6′-Methoxy-2′-quinolyl)-methylene-3-quinclidinone, 22058-77-1; *trans*-2-(2′-quinolyl)methylene-3-quinuclidinone, 22058-81-7; **1**, 22143-13-1; **2**, 22058-78-2; **3**, 22058-79-3; **5**, 22058-80-6; **6**, 22143-14-2; **7**, 22058-82-8.

4-(4-Nitrophenylazo)benzoic Acid. Improved Synthesis of Its Acid Chloride and Spectroscopic Properties of Its Esters[1]

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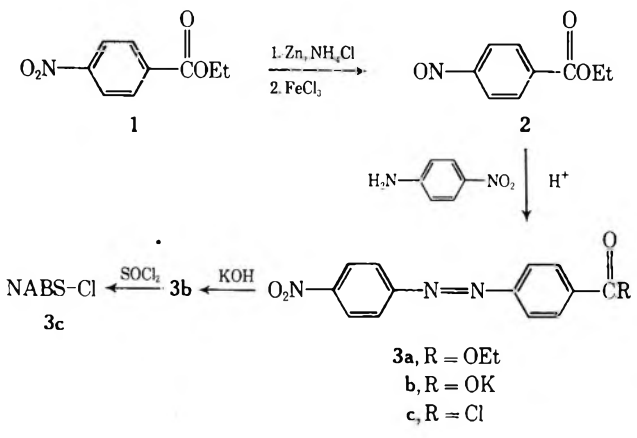
Received July 7, 1969

The synthesis of 4-(4-nitrophenylazo)benzoyl chloride (NABS–Cl)[2] and its use in the formation of esters was described[3] in 1955. Since then, NABS–Cl has been employed advantageously for the derivatization of other aliphatic[4] and aromatic[5] alcohols, thiols,[6] sugars,[7] amines,[8] and amino acid methyl esters;[9] NABS–hydrazide has been prepared and used to prepare derivatives of aldehydes and ketones.[10] The esters are usually solid,[11] their bright red-orange color makes them highly suitable for chromatographic purification,[4,12] and their molecular weight[13] may be determined from the ultraviolet absorption of the NABS chromophore. These properties make NABS–Cl a desirable reagent in the isolation and characterization of natural products.[12,14]

Synthesis of NABS–Cl.—In connection with work on the structure of sirenin,[14a] it became necessary to synthesize NABS–Cl in quantity as shown in Scheme I. Our attempts to obtain the 65–70% yield reported[3] for the conversion of **1** into **2** on the original 5-g scale resulted in an average yield (ten experiments) of 15%; larger scale reactions gave even lower yields. Other attempts[5a] to increase the scale of the reaction have also resulted in lower yields of **2**. A 65% yield is claimed[5a] using modified conditions, but these also failed in our hands. Consequently we examined this reaction in detail and now report conditions which reliably lead to 60–65% yields on up to a 40-g scale. In particular, vigorous stirring, closely controlled temperature, and a nitrogen atmosphere are required. Also, the use of ammonium chloride[15] in place of the originally recommended acetic acid reduced the acid-catalyzed side reactions of the intermediate ethyl *p*-hydroxylaminobenzoate, which was then oxidized to **2** using a decreased quantity of ferric chloride in the cold.

SCHEME I



No major changes were required in the subsequent steps. The crude, thoroughly dried NABS ester **3a** was purified by chromatography on alumina, and the most effect purification of the final NABS chloride (**3c**) was accomplished by vacuum sublimation.

Ultraviolet Absorption of NABS Esters.—The light-activated isomerization of substituted *trans*-azobenzenes to a photostationary equilibrium mixture of *cis* and *trans* isomers has been established.[16] In the presence of ordinary laboratory fluorescent light, solutions of *trans*-*p*-phenylazobenzoates (PAB esters) of aliphatic[17] and aromatic[5b] alcohols are isomerized, and the isomers are chromatographically separable.[17] Consequently, *trans*-4-(4-nitrophenylazo)benzoates (NABS esters) would be expected to behave similarly, and thus special precautions would be necessary to exclude light during handling of the solutions when precise chromatographic and spectroscopic determinations were being made.

About 3×10^{-3} *M* solutions of NABS ethyl ester (**3a**) were exposed to laboratory fluorescent light and the absorbance at 330 nm was noted as a function of time. A variety of solvents—benzene, ether, ethyl acetate, ethanol, and acetic acid—was used, and in each case photostationary equilibrium was reached after 2 hr with about a 5% decrease in absorbance.

The equilibrium mixture, showing a yellow spot at R_f 0.14 and a red-orange spot at R_f 0.37 on silica gel–benzene thin layer chromatography, can be thermally isomerized[6a] at room temperature in the dark for 30 hr to an all-*trans* solution which shows only

(1) Supported in part by the National Science Foundation.

(2) Abbreviated from its German name, 4-nitroazobenzolcarbonsaure-4-chlorid: A. Butenandt, R. Beckmann, and D. Stamm, *Z. Physiol. Chem.*, **324**, 84 (1961).

(3) E. Hecker, *Ber.*, **88**, 1666 (1955).

(4) E. S. Amin and E. Hecker, *ibid.*, **89**, 695 (1956); E. Hecker and R. Lattrell, *ibid.*, **96**, 639 (1963).

(5) (a) R. Pohloudek-Fabini and P. Muenchow, *Pharmazie*, **18**, 734 (1963); (b) P. Muenchow and R. Pohloudek-Fabini, *ibid.*, **19**, 386 (1964).

(6) E. S. Amin, *J. Chem. Soc.*, 4769 (1958).

(7) E. S. Amin, *ibid.*, 5544 (1961).

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(9) E. S. Amin, *J. Chem. Soc.*, 1953 (1960).

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(13) A. Butenandt, R. Beckmann, and E. Hecker, *Z. Physiol. Chem.*, **324**, 71 (1961); W. Kloepffer, H. Esterbauer, and E. Schauenstein, *Fette, Seifen, Anstrichmittel*, **67**, 198 (1965).

(14) (a) W. H. Nutting, H. Rapoport, and L. Machlis, *J. Amer. Chem. Soc.*, **90**, 6434 (1968). (b) E. Hecker, *Angew. Chem.*, **68**, 682 (1956); E. Clarke and E. Hecker, *Naturwissenschaften*, **52**, 446 (1965); A. Butenandt and Tam, *Z. Physiol. Chem.*, **308**, 277 (1957); S. M. A. D. Zayed and T. M. Hussein, *ibid.*, **341**, 91 (1965); A. Butenandt and H. Rembold, *ibid.*, **308**, 284 (1957).

(15) G. H. Coleman, C. M. McCloskey, and F. A. Stuart, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 668.

(16) (a) W. R. Brode, J. H. Gould, and G. M. Wyman, *J. Amer. Chem. Soc.*, **74**, 4641 (1952); **75**, 1856 (1953); (b) G. Zimmerman, L. Chow, and U. Paik, *ibid.*, **80**, 3528 (1958).

(17) I. Katz and M. Keeney, *Anal. Chem.*, **36**, 231 (1964).

TABLE I

SPECTROSCOPIC PROPERTIES OF NABS ESTERS

Alcohol	Registry no.	Uv ϵ_{max} at 330 nm[a]	Nmr, δ, ppm: Carbinol protons, In alcohol	Carbinol protons, In ester	=CH	=CCH₂	-CCH₂
Methanol	22428-39-3	31,300	3.47	3.95	...	...	...
1-Hexanol	22428-40-6	32,200	3.55	4.33	...	...	0.92[b]
Ethanol	22428-41-7	32,000	3.70	4.44	...	...	1.43[c]
2-Propanol	22428-38-2	32,000	3.97	5.29	...	...	1.40[d]
Cyclohexanol	222867-6-6	32,200	3.55	5.14	...	...	...
Geraniol	22286-78-8	32,200	4.12	4.90	5.14[e]	1.62	...
					5.54[c]	1.68	
						1.81	
Nerol	22286-79-9	32,500	4.10	4.82	5.09[e]	1.60	...
					5.49[c]	1.66	
						1.80	
cis-2-Methyl-2-penten-1-ol	22286-80-2	32,300	4.00	4.80	5.46[c]	1.85	1.00[c]
2-Methylenepentanol	22286-77-7	32,300	4.00	4.80	5.02	...	0.97[c]
					5.14		
trans-2-Methyl-2-penten-1-ol	22286-81-3	32,400	3.92	4.74	5.58[c]	1.76	1.00[c]

[a] All values are in 95% ethanol and are to within ±200. [b] t, $J \cong 5$ Hz. [c] t, $J \cong 7$ Hz. [d] d, $J \cong 6$ Hz. [e] $W_{1/2} = 7$ Hz.

one red-orange spot. Progress of the isomerization is followed by the increase in absorbance at 330 nm. This demonstrates the *cis–trans* light-activated equilibrium for NABS esters and provides a procedure to ensure that the spectroscopic and chromatographic measurements are being made on only the *trans* isomer.

In order to compare the ultraviolet absorption properties of the *cis* with the *trans* isomer, preparative thin layer chromatography on silica gel G–benzene was used to obtain a small sample of the *cis* isomer. However, the normal procedure used to measure an extinction coefficient involved sufficient heat and light to isomerize the sample to nearly all *trans* isomer. By immediately making the measurement at room temperature after desorption of the *cis* isomer from the silica gel at 0°, a λ_{max} of 262 nm (ε 13,900) in methanol–chloroform (9:1) was obtained. Isomerizing the solution of *cis*-NABS ethyl ester (**3a**) to its *trans* form allowed the concentration to be calculated from the extinction coefficient of *trans*-NABS ethyl ester (**3a**) as determined in this solvent. Within 2 hr after the measurement on *cis*-**3a** was made, tlc showed a small amount of *trans*-**3a** to be present. The *cis* extinction coefficient therefore is a minimum value and may be as high as 14,900, estimating from tlc that as much as 10% *trans*[18] isomer may have been present when the measurement was made. Using the value ε 13,900, the photostationary equilibrium mixture contains approximately 6% *cis* isomer. If one examines the spectra for the isomerization of *trans*-**3a** to the equilibrium mixture, the decrease in absorbance at 330 nm is accompanied by an increase in absorbance at 262 nm.

Since there is no mention[3] of any precautions to shield solutions of NABS esters from light for the extinction coefficient measurements, the high uncertainty in ε of ±800 in 30,880 (ethanol) could be due to some isomerized solutions, which would also lead to a lower average value for the extinction coefficient.

Consequently, NABS esters of representative saturated primary and secondary alcohols as well as primary allylic alcohols were prepared to redetermine the extinction coefficients and to assess any effect of structure of the alcohol upon the extinction coefficient of the corresponding NABS ester. In particular, the difference in the reported[19] values for NABS nerol and NABS geraniol (ε 28,800 and 31,600, respectively) was much greater than would be expected from experimental error or from the lowering of extinction coefficient of NABS nerol owing to *trans–cis* light-activated isomerization of the NABS chromophore. This suggested a possible effect of the configuration of the allylic double bond upon the extinction coefficient of the NABS ester.

The NABS esters of primary alcohols were prepared in 85–95% yield in most cases and the reaction time was reduced from 24[3] to 0.6–1 hr. However, the 33% yield of NABS 2-propanol (0.6-hr reaction time) indicates that secondary alcohols require a longer reaction time for comparable yields. A simplified work-up was developed by directly chromatographing the crude reaction product.

The redetermined extinction coefficients of NABS esters are presented in Table I. Except for NABS methanol, an average value of 32,200 ± 400 was found. Thus there is no effect of the structure of the aliphatic alcohols upon their NABS ester chromophore. The 4% increase to 32,200 in the extinction coefficient is in accord with the 4% decrease in absorbance observed for NABS ethyl ester in ethanol solution exposed to light. The lower value of 30,880[3] is thus attributed primarily to the *cis–trans* light-activated isomerization of the NABS chromophore. Protection of the NABS ester solutions from light has not only increased the extinction coefficient but also decreased the uncertainty by 50%. The significantly smaller extinction coefficient of NABS methanol may be a true difference, since methanol is the only proton-substituted primary alcohol in the series of alkyl-substituted primary alcohols.

Nmr Properties of NABS Esters.—An additional advantage of characterizing alcohols as NABS esters has been found. The carbinol protons of alcohols, when converted into their NABS ester, fall into groups

(18) If all the absorbance at 330 nm (ε 6000) is due to *trans*-**3a**, as much as 19% may be present, and then *cis*-**3a** would have ε 17,100 and *trans*-**3a** would have ε 4800 at 262 nm.

(19) A. Mondon and G. Teege, *Ber.*, **91**, 1014 (1958).

in the nmr spectrum according to the type of alcohol, as shown in Tables I and II. If the chemical shift

TABLE II
NMR SIGNAL OF THE CARBINOL PROTONS OF NABS ESTERS ACCORDING TO THE TYPE OF ALCOHOL

NABS ester of alcohol	δ of carbinol proton
Primary saturated	3.95–4.44
Primary allylic	4.74–4.90
Secondary saturated	5.14–5.29

of the carbinol proton in the free alcohol is used to classify the type of alcohol, a discrepancy occurs in the case of 2-propanol and cyclohexanol. The former would be classified as a primary allylic alcohol while the latter would be regarded as a primary saturated alcohol. In contrast, conversion of the alcohols into their NABS esters allows a consistent classification according to the type of alcohol.

Experimental Section[20]

Ethyl *p*-Nitrosobenzoate (2).—After 40 g (0.21 mol) of ethyl *p*-nitrobenzoate (1) was dissolved in 560 ml of 2-methoxyethanol, a solution of 17 g of ammonium chloride in 135 ml of water was added and the solution was warmed to 30° in a nitrogen atmosphere. With vigorous stirring (Hershberg-type stirrer), 36 g (0.55 mol) of finely powdered zinc dust was added, by periodically removing the condenser, in small portions over 30 min and the temperature was held at 33–35° by cooling with an ice bath. After addition was completed, the stirring was stopped at 5-min intervals to ascertain the color[21] of the supernatant liquid. When it became colorless, the reaction mixture was suction filtered in a nitrogen atmosphere and the filter cake was washed with 30 ml of 2-methoxyethanol. The combined filtrate and washing was then added dropwise, under a nitrogen atmosphere with rapid stirring over a period of 90 min, to a solution of 84 g (0.52 mol) of anhydrous ferric chloride in 950 ml of water and 240 ml of ethanol maintained at −5° with an ice–methanol bath. After an additional 30 min of stirring, the reaction mixture was poured into 1900 ml of cold water and suction filtered. After being washed with water, the damp precipitate was steam distilled to give 28.8 g (62%) of **2**, mp 79–80.5° after recrystallization from ethanol (lit.[3] mp 83–84°).

Ethyl 4-(4-Nitrophenylazo)benzoate (3a).—Into a flask shielded from the light and equipped with a reflux condenser, magnetic stirring bar, and nitrogen atmosphere were placed 40 g (0.22 mol) of unrecrystallized **2**, 33.6 g (0.24 mol) of *p*-nitroaniline, and a solution of 120 g of trichloroacetic acid in 800 ml of glacial acetic acid. After the solution was stirred and heated at 100° for 4 hr, it was cooled to 30° and then poured into 2400 ml of water. The suspension was filtered and the filter cake was washed with water and air dried on the filter overnight. Drying was completed by dissolving the precipitate in benzene and evaporating to dryness. The residue was then redissolved in benzene and passed through a column of 454 g of alumina (neutral, activity I) and eluted with benzene–ether (1:1) to yield, after evaporation, 58.6 g (81%) of NABS ethyl ester (**3a**), mp 164–165° (lit.[3] mp 162–165°).

Potassium 4-(4-Nitrophenylazo)benzoate (3b).—In a nitrogen atmosphere were placed 70 g (0.23 mol) of NABS ethyl ester (**3a**) dissolved in 3.5 l. of benzene and a solution of 17.3 g of potassium hydroxide in 400 ml of 2-methoxyethanol. The reaction mixture was stirred at room temperature for 15 hr and then filtered. The filter cake was washed with a small amount of 2-methoxyethanol, dried on the filter overnight, and finally placed in a vacuum oven at 120–140° for 5 hr to give 63 g (87.5%) of potassium salt **3b**.

4-(4-Nitrophenylazo)benzoyl Chloride (3c).—Using a flask shielded from light, 9.8 g (0.032 mol) of potassium salt **3b** which had been found with 5.4 g of anhydrous sodium carbonate was treated with 40 ml of thionyl chloride and 40 ml of toluene. After the reaction mixture was refluxed and magnetically stirred for 4 hr, the excess thionyl chloride and toluene were distilled at reduced pressure. The crude product was dissolved in benzene and filtered, and the filtrate was evaporated to dryness. Sublimation at 150° (0.02 mm) gave 6.35 g (69%) of acid chloride **3c**, mp 163–165° in an evacuated capillary (lit.[3] mp 162–163°).

Preparation of NABS Esters.—Geraniol was obtained from the hydrolysis of geranyl acetate (purissima, Aldrich), while the 2-methyl-2-penten-1-ols and 2-methylenepentanol were prepared as described.[22] Except for nerol, other alcohols were commercially available and were dried over Na_2SO_4 or distilled. Pyridine was distilled from *p*-toluenesulfonyl chloride and the benzene was distilled from calcium hydride.

General Procedure.—To the alcohol was added 2 mol of pyridine and sufficient benzene to dissolve 1 mol of NABS-Cl. A 1-mol excess of either the alcohol or NABS-Cl was used. After stirring for *ca.* 1 hr for primary alcohols (secondary alcohols may require 24 hr or longer) in a flask protected from light, the reaction mixture was suction filtered and the filtrate was evaporated *in vacuo*. The residue was then chromatographed on alumina (neutral, activity 2.5) with benzene to afford the NABS ester. The analytical sample was obtained by recrystallization from benzene or benzene–cyclohexane.

In addition to the ethyl ester, the following esters were prepared: **methyl ester**, mp 190–191° (lit.[3] mp 186–187°); ***n*-hexyl ester**, mp 114–115° (lit.[3] mp 110–111°); **isopropyl ester**, mp 183–184° (lit.[3] mp 178–180°); **cyclohexyl ester**, mp 163–164° (lit.[3] mp 164–165°); **geranyl ester**, mp 103–104° (lit.[3] mp 107–109°); and **neryl ester**, mp 88–89° (lit.[3] mp 90–91°). The following esters were prepared and analyzed.

***cis*-2-Methyl-2-penten-1-yl ester** had a melting point of 138–139°.

Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.6; H, 5.4; N, 11.9. Found: C, 64.9; H, 5.3; N, 12.2.

2-Methylenepentyl ester had a melting point of 105–106°.

Anal. Calcd for $C_{19}N_{19}N_3O_4$: C, 64.6; H, 5.4; N, 11.9. Found: C, 64.8; H, 5.1; N, 12.1.

***trans*-2-Methyl-2-penten-1-yl ester** had a melting point of 124–125°.

Anal. Calcd for $C_{19}H_{19}N_3O_4$: C, 64.6; H, 5.4; N, 11.9. Found: C, 64.9; H, 5.1; N, 12.1,

Ultraviolet Measurements for Ethyl *trans*-4-(4-Nitrophenylazo)benzoate (3a). A. Isomerization.—*Ca.* 3×10^{-3} *M* solutions of NABS ethyl ester (**3a**) in 95% ethanol were placed 67 cm from the laboratory fluorescent light. Aliquots (1 ml) were withdrawn periodically and diluted to 100 ml with 95% ethanol before measurement in 1-cm matched cells.

B. Extinction Coefficients.—By heating at 40° in a water bath when necessary, 95% ethanol solutions of known concentration were prepared in aluminum foil covered flasks and stored in the dark at room temperature for at least 24 hr prior to measurement at λ_{max} 330 nm. The values presented in Table I are the result of at least duplicate determinations 24 hr apart on duplicate samples.

Isolation and Extinction Coefficient for Ethyl *cis*-4-(4-Nitrophenylazo)benzoate.—A 0.052 *M* solution of *trans*-NABS ethyl ester (**3a**) in benzene was exposed to laboratory fluorescent light at a distance of 67 cm for *ca.* 10 hr. The mixture was separated by preparative thin layer chromatography on silica gel G plates and developed with benzene in aluminum foil covered tanks at room temperature (*trans* ester, R_f 0.37, red-orange; *cis* ester, R_f 0.14, yellow). After cooling to 0°, the *cis*-NABS ethyl ester was desorbed in near darkness with 5 ml of absolute ethanol and 100 ml of methylene chloride, and the solution was then filtered. The filtrate was evaporated *in vacuo*, with no external heat, in the dark at 20 mm for 30 min and then for 15 min each at 2 mm and 0.020 mm. A portion of the resulting liquid was diluted to

(20) Melting points were taken in capillary tubes and are uncorrected; ultraviolet spectra were determined with a Cary Model 14 Spectrophotometer; nmr spectra were determined in deuteriochloroform on a Varian A-60 spectrometer using internal TMS (δ 0); microanalyses were performed by the Analytical Laboratory, University of California, Berkeley.

(21) The supernatant liquid was yellow at the end of the addition and became colorless in 15–20 min. If more time is required, the stirring may not be sufficiently vigorous and the yield may be low.

(22) K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968). The corresponding NABS esters were prepared by K. C. Chan.

100 ml with methanol–chloroform (9:1, v/v) and its absorbance was determined at 262 nm. After the yellow solution was exposed to laboratory fluorescent light for 2 hr, it was stored in the dark at room temperature for 65 hr. Its absorbance at 330 nm was then measured, from which the concentration of *trans* ester (and hence of the original *cis* ester) was calculated using 32,000 as the extinction coefficient.

Registry No.—3c, 22286-74-4.

Oxygen-Transfer Reactions of Amine N-Oxides. IV. The Pyridine N-Oxide–Trichloroacetic Anhydride Reaction

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Received June 25, 1969

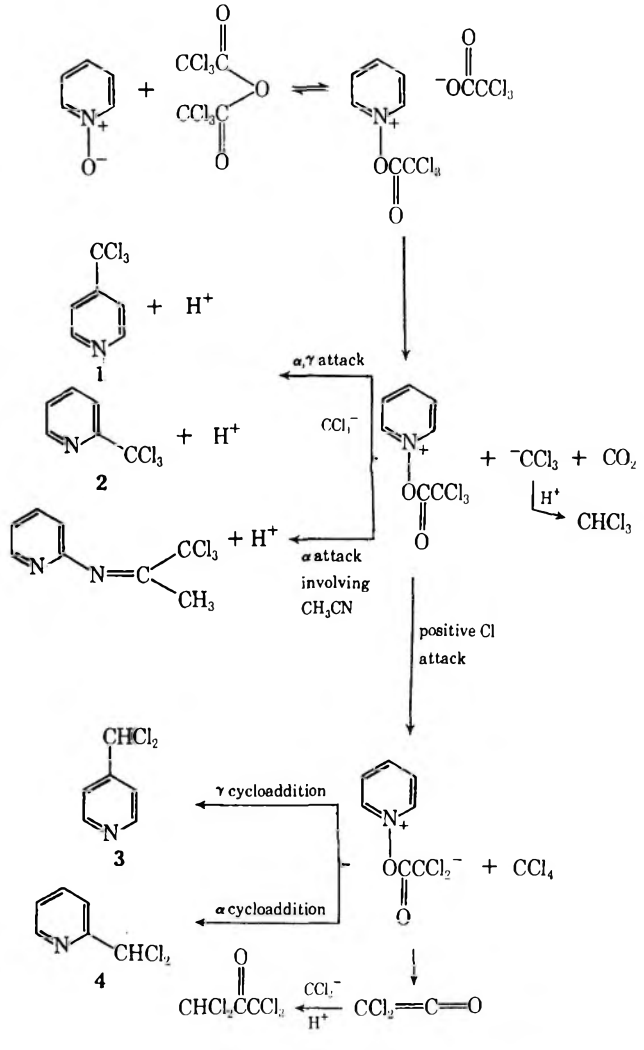
During the course of our general studies[2] on the reactions of N-oxides with acylating agents, we observed[3] a rather unusual reaction between trichloroacetyl chloride and picoline N-oxides which gives picolyl chlorides and carbon dioxide in fairly high yields after a few hours in refluxing chloroform. The chloride product was found to be a result of the high susceptibility of trichloroacetate esters to displacement by chloride ion, and the carbon dioxide was found to be a result of the unexpectedly fast rate of decarboxylation of ammonium trichloroacetate salts in solutions at high concentration. The present report deals with an additional manifestation of the rapid decarboxylation rate of the trichloroacetate ion in the reaction of pyridine N-oxide with trichloroacetic anhydride.

When pyridine N-oxide is refluxed in chloroform in the presence of trichloroacetic anhydride, no appreciable reaction is evident even after several hours. The N-oxide can be largely recovered after such a period. However, when the two reagents are mixed in acetonitrile solvent even at 0°, an exothermic reaction is immediately evident and carbon dioxide evolution begins at once. If the temperature is maintained at 0°, the gas evolution levels off at *ca.* 30%. When the reaction is carried out at 20–30°, 1 equiv of gas is evolved after *ca.* 5 hr.

The resulting product solution contains an exceedingly complex mixture of substituted pyridine derivatives. The products isolated and identified after the complicated work-up procedure, summarized in the Experimental Section, are carbon tetrachloride (40%), chloroform (20%), pentachloroacetone (20%), α-trichloromethylpyridine (10–20%), γ-trichloromethylpyridine (1–4%), α-dichloromethylpyridine (present), γ-dichloromethylpyridine (5%), and α-aminopyridine (4%). These yields are based on amount of N-oxide present initially, since 2 equiv of the anhydride were used in the runs in which quantitative analyses were attempted. No detectable amount of α-trichloroacetoxypyridine, which was synthesized independently, was observed by nmr or infrared. This product is the expected one based on analogy with the acetic anhydride–pyridine N-oxide reaction.[4]

The reaction at hand is apparently not a result of homolytic cleavage of the N–O bond of the acylated N-oxide, since very little carbon dioxide is obtained when the N-oxide is treated with trichloroacetyl chloride. A more likely explanation is that the driving force for the reaction is the exothermic loss of carbon dioxide from free trichloroacetate ion, which is not complexed with its counterion. Scheme I uses this idea in *rationalizing* the products observed.

SCHEME I



That the observation of any reaction at all is definitely coupled to the polarity of the medium was evidenced by slow addition of acetonitrile to a refluxing solution of the reagents in chloroform. Only when the solvent mixture contains *ca.* 50% acetonitrile does carbon dioxide evolution occur at an appreciable rate. The spectral properties of the product residues from

(1) Fellow of the Kosciusko Foundation on leave from Politechnika Wroclawska, Poland, 1966–1967.

(2) T. Koenig and T. Barklow, *Tetrahedron*, in press; T. Koenig, *J. Amer. Chem. Soc.*, **88**, 4045 (1966); T. Koenig, *Tetrahedron Lett.*, No. 29, 2751 (1967); T. Koenig, *ibid.*, No. 35, 3127 (1965).

(3) T. Koenig and J. Wieczorek, *J. Org. Chem.*, **33**, 1530 (1968).

(4) M. Katada, *J. Pharm. Soc., Jap.*, **67**, 51 (1947); J. H. Markgraf, H. B. Brown, S. C. Mohr, and R. G. Peterson, *J. Amer. Chem. Soc.*, **85**, 958 (1963).

these conditions were similar to those from the acetonitrile runs but were not investigated further. This serves to militate against acetonitrile functioning in any stoichiometric way. A more likely role is a polarity effect which allows formation of free trichloroacetate ion. The proposed scheme is by no means uniquely established by experimental facts. Alternative radical chains and carbene mechanisms are also possible. It does seem clear that trichloroacetate ions can be more reactive toward decarboxylation than toward what would seem to be a facile nucleophilic atack on a charged pyridine derivative.

The formation of α-aminopyridine could be a result of attack of one of the pyridine bases on the N-acetoxy pyridinium species, but the product in such cases would not be expected to hydrolyze as readily as the Schiff-base structure shown. The failure of the acid chloride reaction militates against a heterolytic cleavage of the acetoxonium ion with α attack by solvent, as has been observed[5] in picoline N-oxide reactions using benzonitrile solvents. The decarboxylation of pyridinium trichloroacetate[3] does not give **1**, and the anhydride does not react with pyridine to the products found here under similar conditions.

Experimental Section

Infrared spectra were obtained using a Beckman IR-5 spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian A-60 spectrometer. Glpc analyses of chloroform and carbon tetrachloride were carried out at 50° using an Aerograph 90-P and a 10 ft × 0.125 in. column packed with 20% TCEP on firebrick. Analyses were obtained from Berkeley Analytical Laboratories, Berkeley, Calif. Pyridine N-oxide was distilled directly into the reaction flask. Trichloroacetic anhydride was distilled, bp 60° (0.6 mm), immediately before use. Acetonitrile was dried by distillation from phosphorus pentoxide.

2-Trichloromethylpyridine (**2**).—This compound was synthesized by the reaction of 2-picoline with chlorine in acetic acid–sodium acetate[6] and obtained as an oil, bp 98° (15 mm). Nmr spectra of carbon tetrachloride solutions showed the characteristic pattern of a 2-substituted pyridine, an H-6 doublet of doublets at δ 8.71 (J = 4.2 Hz, $J' \cong$ 1.5 Hz) and H-3, -4, and -5 multiplets centered at δ 7.87 and 7.33. It failed to form a picrate.

Anal. Calcd for $C_6H_4NCl_3$: C, 36.67; H, 2.05; N, 7.12; Cl, 54.14. Found: C, 36.92; H, 2.05; N, 6.98; Cl, 53.98.

4-Trichloromethylpyridine (**1**).—The sequence[7] identical with that used for **2** afforded **1** as an oil, bp 78° (10 mm). Nmr spectra of carbon tetrachloride solutions of this material showed the characteristic four-substituted pattern (AA′XX′ system), δ_A, α protons, 8.87, and δ_X, β protons, 8.00 (J = 4.5 Hz, $J' \cong$ 1.8 Hz). It formed a picrate, mp 151–152° (lit.[7] mp 154°).

2-Dichloromethylpyridine (**4**).—Authentic **4** was obtained by reduction[7] of **2**, using stannous chloride, as an oil, bp 90–92° (18 mm). Its nmr spectrum in carbon tetrachloride showed the ω-proton singlet at δ 7.01, an H-6 multiplet at δ 8.65, and H-3, -4, and -5 multiplets at δ 7.87 and 7.39. It formed a picrate, mp 115.5–116° (lit.[8] mp 115–116°).

4-Dichloromethylpyridine (**3**).—Authentic **3** was obtained[7] in low yield from the stannous chloride reduction of **1** as an oil, bp 78–80° (15 mm). Its nmr spectrum in carbon tetrachloride showed the ω-proton singlet at δ 6.81 and the characteristic AA′XX′ pattern of a 4-substituted pyridine, δ_A, α protons, 8.63, and δ_X, β protons, 7.40 (J = 4.0 Hz, $J' \cong$ 1.5 Hz). It formed a picrate, mp 135–136°.

Anal. Calcd for $C_{12}H_8Cl_2N_4O_7$: C, 36.84; H, 2.06; Cl, 18.13; N, 14.32. Found: C, 36.65; H, 1.97; Cl, 18.28; N, 14.14.

α-**Trichloroacetoxypyridine**.—This material was prepared by treatment of an ether suspension of the silver salt of 2-pyridone with trichloroacetyl chloride. The product was distilled, bp 58° (0.7 mm). Its infrared spectrum in chloroform showed carbonyl absorption at 1767 cm^{-1}. The nmr spectra of carbon tetrachloride solutions of this material showed the characteristic pattern of a 2-substituted pyridine, an H-6 doublet of doublets at δ 8.41 (J = 4 Hz, $J' \cong$ 2 Hz) and H-3, -4, and -5 multiplets centered at δ 7.50 and 7.25. The chemical shift of H-6 is distinctly different from that of the products (**2** and **4**) obtained here.

Pyridine N-Oxide–Trichloroacetic Anhydride Reaction.—The anhydride (36.00 g, 0.117 mol) in 20 ml of acetonitrile was added over a 10-min period to 160 ml of solvent containing 5.57 g (0.059 mol) of freshly distilled pyridine N-oxide. The reaction vessel was immersed in a cold-water bath such that the temperature of the reaction mixture did not rise above 30°. (The bath was previously equilibrated as a closed system with a gas buret attached.) In some runs (with equivalent results), the reaction was carried out with a nitrogen sparge through ascarite. Gas evolution was immediately evident and after 5 hr amounted to 1500 ml. The mass spectrum of an aliquot of the condensible portion of this gas indicated that it was essentially pure carbon dioxide containing traces of solvent.

The acetonitrile and volatile components of the product mixture were removed by bulb-to-bulb distillation at room temperature and 1-mm pressure. Glpc analyses showed the presence and amounts of chloroform and carbon tetrachloride. The residue remaining after the bulb-to-bulb distillation was diluted with 10 ml of water, and steam distillation yielded 7.22 g of volatile residue after extraction with methylene chloride, drying, and evaporation of solvent. The nmr spectrum of this material indicated that it contained approximately equal amounts of pentachloroacetone (singlet at δ 6.91) and substituted pyridines (H-6 multiplet centered at δ 8.77). A number of smaller singlets at higher field (δ >6.8) were also present in the nmr spectrum of this mixture.

Treatment of an aliquot of this mixture with picric acid gave the equivalent of 0.27 g (0.69 mmol) of the picrate of γ-trichloromethylpyridine, mp 150–151° when mixed with authentic sample.

Distillation of the steam-volatile residue gave a fraction whose nmr spectrum was nearly free of pyridine protons, bp 65–85° (10 mm). Residistillation of this material gave a cut, bp 68.5° (8 mm), which showed an infrared spectrum in carbon tetrachloride which was identical with that of authentic pentachloroacetone. Its nmr spectrum showed a major singlet at δ 6.91, also identical with that of pentachloroacetone. However, there were two additional singlets at δ 6.63 and 6.13 which could be attributed to the tetrachloroacetone isomers.

The higher boiling fraction from the steam-volatile material was distilled at 54° (0.5 mm). On treatment with picric acid, the picrate of **1** was obtained, mp 150–152°, undepressed when mixed with authentic sample. Removal of the excess picric acid by extraction with bicarbonate gave a residue which showed infrared and nmr spectra identical with those of authentic **2**.

The residue after steam distillation was brought to pH 9 by the addition of potassium carbonate, extracted several times with methylene chloride, and dried. After removal of solvent the residue weighed 2.09 g. This material was chromatographed over Florosil. A fraction which was eluted by ether gave the picrate of γ-dichloromethylpyridine, mp 135–136°, undepressed when mixed with authentic sample. The nmr spectrum was also identical with that of the synthetic material. Other chromatography fractions gave nmr spectra similar to those of authentic α-dichloromethylpyridine, but the picrates from these fractions were those of the γ isomer, which crystallizes more readily. Fractions finally eluted with methanol–ethyl acetate were identical with authentic α-aminopyridine.

Registry No.—Pyridine N-oxide, 694-59-7; trichloroacetic anhydride, 4124-31-6; α-trichloroacetoxypyridine, 22796-45-8; **1**, 22796-40-3; **2**, 4377-37-1; **3**, 22796-42-5; **3** picrate, 22796-43-6; **4**, 4377-35-9.

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Optically Active Selenium-Containing Amino Acids. The Synthesis of L-Selenocystine and L-Selenolanthionine[1-3]

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Received August 11, 1969

During the past few years, increased attention has been given to biologically active selenocysteine-containing peptides.[4-8] In this context it was important to develop synthetic methods which would permit the introduction of selenium into optically active amino acids. Recently, we described a convenient procedure for the preparation of Se-benzyl-L-selenocysteine derivatives. This method, consisting of a nucleophilic displacement of the O-*p*-toluenesulfonate moiety of an O-tosylated L-serine derivative by the benzyl selenolate anion, is advantageous for the preparation of Se-benzyl-L-selenocysteine compounds which bear selectively removable amino- and carboxyl-protecting groups.[7,8]

In order to demonstrate the wider scope for this displacement reaction in the synthesis of selenium-containing amino acids, we investigated the possibility of transforming an O-tosylated L-serine derivative with sodium hydrogen selenide to the corresponding selenocysteine derivative. Such a derivative with its free selenol function would provide a key intermediate, allowing the transformation either to the diselenide by oxidation or to selenides by alkylation. While the former type of reaction would pave the way for a convenient synthesis of L-selenocystine, the latter would offer a route toward the synthesis of dialkylselenides which possess a selenocysteine moiety as the basic skeleton, such as L-selenolanthionine. The latter reaction path would also permit the introduction of selectively removable selenium-protecting groups.

To examine the feasibilty of the above concept, N-carbobenzoxy-O-tosyl-L-serine diphenylmethyl ester (I)[8] was allowed to react with a stoichiometric amount of sodium hydrogen selenide. In view of the ease with which aliphatic selenols oxidize,[9,10] we did not attempt to isolate the N-carbobenzoxy-L-selenocysteine diphenylmethyl ester but instead converted the selenol *in situ* into the corresponding diselenide, bis(diphenylmethyl)bis(N-carbobenzoxy)-L-selenocystinate (IIa). Although the reaction mixture gave a solid corresponding to 85% yield, various preparations of IIa gave different optical rotations, and a close examination of the reaction product on tlc revealed two compounds which exhibit almost identical R_f values. Repeated slow crystallizations of the reaction mixture finally gave IIa in moderate yield with only a trace of by-product. The preparation of II in high yield, completely free of contaminants, and with reproducible optical activity was achieved by the following route. N-Carbobenzoxy-Se-benzoyl-L-selenocysteine diphenylmethyl ester (III)—readily secured by the acylation of N-carbobenzoxy-L-selenocysteine diphenylmethyl ester—was debenzoylated with hydroxylamine and oxidized *in situ* to yield II. The ester II was cleaved with 0.9 *N* hydrogen chloride in nitromethane[11] and the reaction product was isolated as the crystalline bisdicyclohexylammonium salt (IV). The nitrogen function of the free acid of IV was liberated by treatment with hydrogen bromide in glacial acetic acid, and, upon adjustment of the solution of the hydrobromide to pH 5, the L-selenocystine (V) was secured (Scheme I). In addition, L-selenocystine was prepared by another method. While the above route, starting with the fully protected selenocysteine derivative III, proceeded according to the scheme (a) liberation of selenium moiety, (b) oxidative dimerization, (c) liberation of carboxyl group, and (d) liberation of nitrogen moiety, the route described below entails the following steps: (a) liberation of nitrogen and carboxyl moieties, (b) liberation of selenium moiety, and (c) oxidative dimerization. For this purpose the sodium salt of N-carbobenzoxy-L-selenocysteine diphenylmethyl ester was allowed to react with diphenylmethyl bromide to yield N-carbobenzoxy-Se-diphenylmethyl-L-selenocysteine diphenylmethyl ester (VI). Apparently, this alkylation proceeds slowly and a prolonged reaction time is required to obtain VI in high yield. If the reaction time is shortened, II, formed from the unreacted selenol during the work-up procedure of the reaction, is isolated as a major by-product. When diphenylmethyl toluene-*p*-sulfonate,[12] instead of the diphenylmethyl bromide, is used for alkylation, the reaction does not proceed any faster. Decarbobenzoxylation and simultaneous deesterification of VI were achieved by treatment with HBr–AcOH and the resulting Se-diphenylmethyl-L-selenocysteine on reaction with TFA and oxidation *in situ* gave V.

Horn, *et al.*, described the isolation of the sulfur-containing amino acid lanthionine [bis(β-amino-β-carboxyethyl)sulfide] from wool[13] and from several proteins[14,15] after being treated with alkalies. More recently, it has come to light that L-lanthionine may be a

(1) This work was supported by U. S. Public Health Service Grant AM-10080 of the National Institute of Arthritis and Metabolic Diseases and by the U. S. Atomic Energy Commission.

(2) The following abbreviations have been adopted: Z = $C_6H_5CH_2OCO$; Ts = $H_3CC_6H_4SO_2$; DMFA = N,N-dimethylformamide; AcOH = acetic acid; EtOH = ethanol; MeOH = methanol; Et_2O = diethyl ether; EtOAc = ethyl acetate; TFA = trifluoroacetic acid.

(3) (a) This work was presented in part before the First American Peptide Symposium at Yale University, Conn., Aug 1968 (R. Walter and M. Dekker, New York, in press). (b) Since the completion of this work, the synthesis of L-selenolanthionine by an independent route has been reported: G. Zdansky, *Ark. Kemi*, **29**, 443 (1968).

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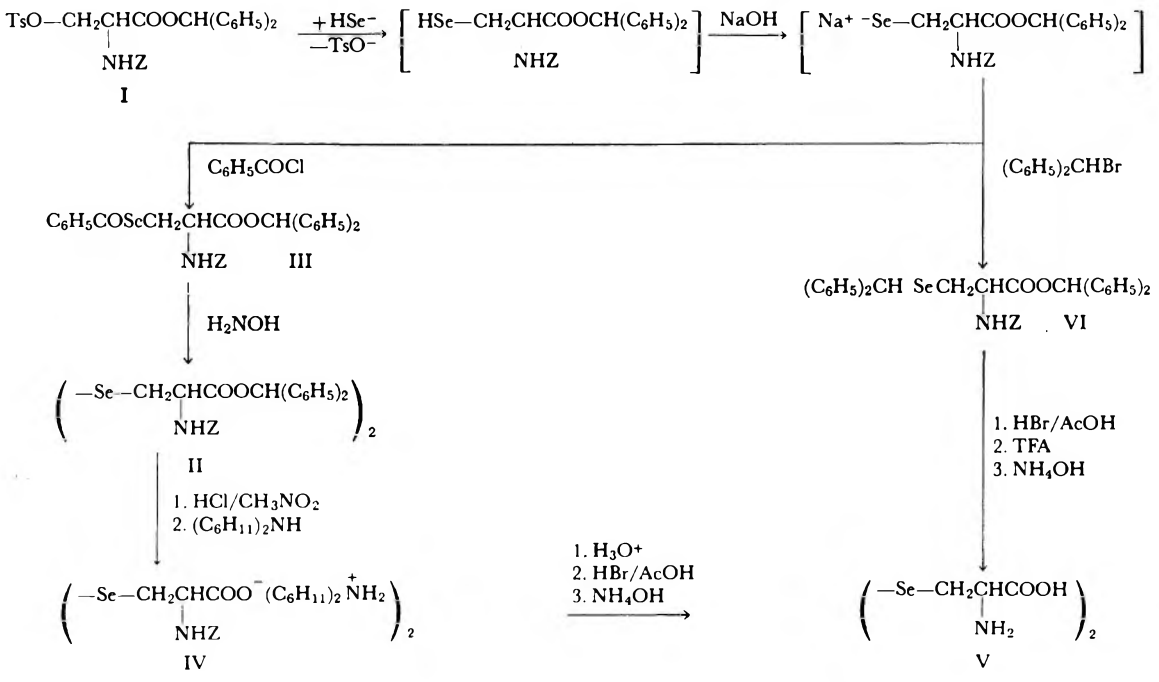
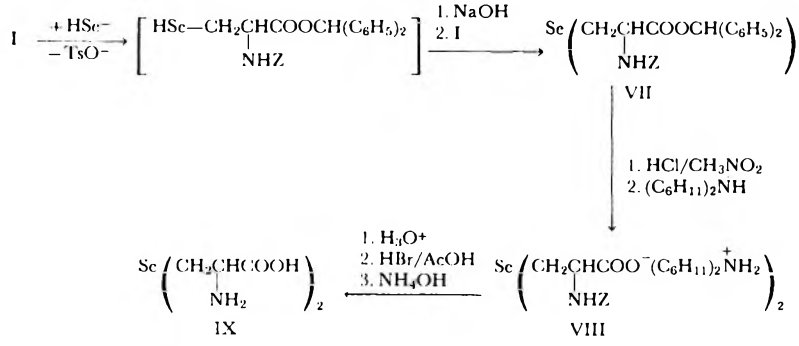
SCHEME I



SCHEME II



naturally occurring amino acid.[16,17] We therefore set out to synthesize the optically active seleno isolog as a further test of our method. The experimental path followed is outlined in Scheme II. The O-tosylated ester I was allowed to react with sodium hydrogen selenide and converted into the selenolate, which in turn was alkylated by addition of a second mole of I. The resulting protected L-selenolanthionine (VII) was hydrolyzed and the bis(N-carbobenzoxy)-L-selenolanthionine was isolated as the crystalline dicyclohexylammonium salt (VIII). The hydrobromide salt, obtained after decarbobenzoxylation of the acid liberated from VIII, was converted into the free base of L-selenolanthionine (IX).

Experimental Section[18]

Preliminary Preparation of Bis(diphenylmethyl)bis(N-carbobenzoxy)-L-selenocystinate (IIa).—Under a hydrogen atmosphere, sodium (0.075 g) was dissolved in EtOH (5 ml) and the resulting mixture was saturated with hydrogen selenide. To this solution, I (1.25 g) dissolved in degassed DMFA (2 ml) was added and the reaction mixture was stirred for an additional 20 min. After the addition of EtOAc (80 ml), the organic phase was extracted with water (three 20-ml portions). The organic phase was separated, dried, and evaporated. The residue crystallized from EtOAc–petroleum ether (bp 30–60°): yield 0.895 g (85%); mp 90–93°; $[\alpha]^{23}D$ −57.4° (2% in DMFA). Examination on tlc with C_6H_6–EtOAc (9:1, v/v) as solvent system revealed two compounds with very close R_f values. Repeated recrystallizations from EtOAc–EtOH gave an almost pure product: yield 0.65 g (62%); mp 96–98°; $[\alpha]^{24}D$ −82.2° (2% in DMFA).

N-Carbobenzoxy-Se-benzoyl-L-selenocysteine Diphenylmethyl Ester (III).—Sodium hydrogen selenide was prepared from sodium (0.065 g) dissolved in absolute EtOH (5 ml) as described above. To the resulting solution, I (1.12 g), which was dissolved in degassed DMFA (2 ml) was added and the reaction mixture was stirred for an additional 30 min. After this period, NaOH (0.1 g) dissolved in degassed water (1 ml) was added, followed by benzoyl chloride (1.13 g) in degassed DMFA (3 ml). The exothermic reaction mixture was stirred under hydrogen inflow for 45 min and then diluted with EtOAc (80 ml). The organic phase was separated and washed with water (three 25-ml portions), dried, and evaporated. The residue was thoroughly extracted with petroleum ether and the remaining solid was crystallized from absolute EtOH: yield 0.9 g (78.3%); mp 82–84°; $[\alpha]^{22}D$ −42.0° (2% in DMFA).

Anal. Calcd for $C_{31}H_{27}NO_6Se$: C, 65.0; H, 4.76; N, 2.45. Found: C, 64.8; H, 4.64; N, 2.40.

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Final Preparation of Bis(diphenylmethyl)bis(N-carbobenzoxy)-L-selenocystinate (II).—Sodium (0.0144 g) was dissolved in anhydrous MeOH (2 ml); to this solution hydroxylamine hydrochloride (0.0434 g) dissolved in MeOH (2 ml) was added. To the stirred reaction mixture N-carbobenzoxy-Se-benzoyl-L-selenocysteine diphenylmethyl ester (0.286 g) in DMFA (2 ml) was added. After 75 min of continued stirring, the light yellow solution was diluted with 75 ml of EtOAc. The organic phase was separated and washed with water (two 25-ml portions) and dried; removal of the solvent gave an oil. Fine, faint yellow needles were obtained by crystallization from MeOH: yield 0.19 g (81%); mp 101–102°; $[\alpha]^{24}D$ −85.2° (2% in DMFA).

Anal. Calcd for $C_{48}H_{44}N_2O_8Se_2$: C, 61.7; H, 4.74; N, 3.00. Found: C, 61.8; H, 4.62; N, 2.93.

Bis(dicyclohexylammonium)bis(N-carbobenzoxy)-L-selenocystinate (IV).—The ester II (0.6 g), dissolved in a solution of 0.9 *N* HCl in nitromethane (10 ml), was kept for 1 hr at room temperature. After this period, thin layer chromatography [C_6H_6–EtOAc (9:1)] revealed the absence of starting material. The nitromethane was evaporated and the oily residue was thoroughly extracted with dilute $NaHCO_3$ solution. The aqueous phase was extracted with Et_2O (two 25-ml portions), separated, and, after acidification with 2 *N* H_2SO_4, extracted with EtOAc (three 20-ml portions). The organic solution was washed two times with small amounts of H_2O, dried with Na_2SO_4, and evaporated. The syrupy residue (0.39 g) was dissolved in MeOH (3 ml), and dicyclohexylamine (0.3 g) dissolved in MeOH (1 ml) was added. Upon addition of Et_2O, a crystalline precipitate resulted, which was collected and recrystallized from MeOH–Et_2O: yield 0.6 g (97%); mp 177–178°; $[\alpha]^{22}D$ −49.5° (1% in MeOH).

Anal. Calcd for $C_{46}H_{70}N_4O_8Se_2$: C, 57.3; H, 7.31; N, 5.81. Found: C, 57.4; H, 7.39; N, 5.71.

L-Selenocystine (V).—The salt IV (0.4 g) was dissolved in a mixture of 1 *N* H_2SO_4 (30 ml) and EtOAc (30 ml). The organic phase was separated, washed three times with a few milliliters of 2 *N* H_2SO_4 and three times with a few milliliters of H_2O, dried over anhydrous Na_2SO_4, and evaporated, and the residue was dried over P_2O_5. The resulting oil was dissolved in dry AcOH (1 ml) and 4 *N* HBr in AcOH (1 ml) was added. During the next 30 min, while the mixture was allowed to stand at room temperature, the HBr salt precipitated partially. Precipitation was completed by addition of Et_2O and the solid material was filtered and repeatedly washed with Et_2O. After being dried under vacuum over KOH and P_2O_5, the HBr salt was dissolved in H_2O (2 ml) and the product was precipitated by adjusting the pH to 5 with dropwise addition of 2 *N* NH_4OH. The canary yellow product was washed with H_2O (2 ml) and dried over P_2O_5 under vacuum: yield 0.125 g (90%); mp 218° dec; $[\alpha]^{25}D$ −162° (1% in 2 *N* HCl) {lit.[19] mp 215° dec; $[\alpha]^{25}D$ −162° (2 *N* HCl)}; ir 2080 (NH_3^+), 1620, and 1580 cm^{-1} (carboxylate).

Anal. Calcd for $C_6H_{12}N_2O_4Se_2$: C, 21.5; H, 3.85; N, 8.36. Found: C, 21.6; H, 3.68; N, 8.52.

Upon amino acid analysis, L-selenocystine emerged at 156.8 ml after the start of the chromatogram; an identical value for the time of emergence was found previously.[20] Glycine, which emerged at 105.6 ml, served as a position marker.

N-Carbobenzoxy-Se-diphenylmethyl-L-selenocysteine Diphenylmethyl Ester (VI).—To the sodium salt of N-carbobenzoxy-L-selenocysteine diphenylmethyl ester prepared from 1.12 g of I (as detailed for the preparation of III) was added 1.0 g of diphenylmethyl bromide dissolved in 2 ml of degassed DMFA. The reaction mixture was stirred under hydrogen for 3 hr and then the tightly stoppered reaction flask was left in the dark for 72 hr at room temperature. The reaction mixture was diluted with EtOAc (100 ml) and washed with water (three 25-ml portions); the organic phase was separated, dried, and evaporated. The resulting oil was chromatographed on a silica gel column; unreacted diphenylmethyl bromide was eluted with C_6H_6 and the product with C_6H_6–EtOAc (99:1, v/v). The fractions containing the product were combined and evaporated, and the resulting oily residue was crystallized from EtOH: yield 1.0 g (79%); mp 104–104.5°; $[\alpha]^{24}D$ −36.5° (2% in DMFA).

Anal. Calcd for $C_{37}H_{33}NO_4Se$: C, 70.0; H, 5.24; N, 2.21. Found: C, 69.7; H, 5.44; N, 2.32.

Alternative Preparation of L-Selenocystine.—To a solution of VI (0.3 g) in dry AcOH (1 ml), 4 *N* HBr in AcOH (1 ml) was added. After 1 hr, the reaction mixture was evaporated and the resulting white solid material was triturated repeatedly with dry Et_2O and then with a few drops of water, yield 0.1 g (63%), mp 149–150°. The infrared spectrum taken in KBr [3020 and 3040 (phenyl stretching), 1620 and 1580 (carboxylate), and 700, and 750 cm^{-1} (phenyl bending)] indicated that the Se-diphenylmethyl-L-selenocysteine was isolated as its zwitterion rather than as the hydrobromide. This compound was suspended in TFA (3 ml) and after addition of phenol (0.4 g) the reaction mixture was heated under reflux for 20 min. The volatile solvent was evaporated under reduced pressure to dryness; the residual liquid was dissolved in water (2 ml) and washed with Et_2O (two 10-ml portions); and the pH was then adjusted to 5 with 2 *N* NH_4OH when a yellow solid was obtained, yield 0.04 g (80%), which had identical physical properties as V described above.

Bis(diphenylmethyl)bis(N-carbobenzoxy)-L-selenolanthionate (VII).—Into absolute EtOH (4 ml) containing sodium (0.055 g) H_2Se was bubbled. Into the solution, I (0.8 g) dissolved in DMFA (2 ml) was introduced. After 10 min of stirring, NaOH (0.068 g) dissolved in H_2O (1 ml) was added followed by I (0.80 g) in DMFA (2 ml). The mixture was stirred for an additional 20 min. The reaction mixture was extracted with EtOAc (50 ml) which was washed with H_2O (one 40-ml and two 10-ml portions), dried, and evaporated. The resulting residue was crystallized from EtOAc–petroleum ether: yield 0.752 g (61.5%); mp 114°; $[\alpha]^{22}D$ −31.7° (1% in DMFA); ir 3335 (NH), 1740 (ester), and 1690 cm^{-1} (urethane).

Anal. Calcd for $C_{48}H_{44}N_2O_8Se$: C, 67.4; H, 5.18; N, 3.27. Found: C, 67.6; H, 5.30; N, 3.19.

Bis(dicyclohexylammonium)bis(N-carbobenzoxy)-L-selenolanthionate (VIII).—A solution of 0.9 *N* HCl in nitromethane (20 ml) containing VII (0.665 g) was kept for 1.5 hr at 25°; then the solvent was evaporated under reduced pressure. The resulting residue was taken up in petroleum ether (15 ml) which was then extracted with half-concentrated $NaHCO_3$ solution (20 ml). The aqueous phase was acidified with 2 *N* H_2SO_4 and extracted with EtOAc (three 20-ml portions). After the combined organic fractions were washed with H_2O (four 10-ml portions), the solution was dried and the solvent was evaporated. Upon dilution of the oily residue (0.381 g) with MeOH (2 ml) and addition of dicyclohexylamine (0.334 g) and Et_2O, a crystalline product resulted which was collected and recrystallized from MeOH–Et_2O: yield 0.61 g (93%); mp 172–173°; $[\alpha]^{22}D$ −0.88° (1% in MeOH); ir 3400 and 3250 (NH), 1715 (urethan), and 1635 cm^{-1} (carboxylate).

Anal. Calcd for $C_{46}H_{70}N_4O_8Se$: C, 62.4; H, 7.96; N, 6.32. Found: C, 62.6; H, 8.08; N, 6.32.

L-Selenolanthionine (IX).—Compound VIII (0.310 g) was dissolved by shaking with a mixture of 2 *N* H_2SO_4 (40 ml) and EtOAc (40 ml). The organic phase was separated, washed repeatedly with a few milliliters of dilute H_2SO_4 and H_2O, dried over anhydrous Na_2SO_4, and evaporated. The resulting residue was dissolved in glacial AcOH (1 ml) and treated with 4 *N* HBr in glacial AcOH (1 ml). After 1 hr at 26°, Et_2O (20 ml) was added and the resulting solid material was washed several times by decantation with Et_2O. The hydrobromide salt was taken up in H_2O (0.5 ml) and the pH of the resulting solution was adjusted to 5 with 2 *N* NH_4OH. The precipitated product was washed with H_2O (0.7 ml): yield 0.065 g (72%); the compound decomposed in solid state between 230 and 270°; $[\alpha]^{21}D$ +34.9° (1% in 5 *N* HCl) [lit.[3b] $[\alpha]^{25}D$ +34.8° (1% in 1 *N* HCl)]; ir 3400 (broad NH), 1630, and 1540 cm^{-1} (carboxylate).

Anal. Calcd for $C_6H_{12}N_2O_4Se$: C, 28.2; H, 5.04; N, 10.9. Found: C, 28.5; H, 4.88; N, 11.0.

Upon amino acid analysis, L-selenolanthionine and glycine emerged at 88.5 and 105.6 ml, respectively, after the start of the chromatogram.

Elution Procedure for Amino Acids.—L-selenocystine and L-selenolanthionine were chromatographed on the Beckman–Spinco Model 120C amino acid analyzer, using Beckman custom research resin PA-28 packed in a 56 × 0.9 cm column. For elution of the amino acids a pH 3.22 ± 0.002 buffer and a pH 4.250 ± 0.002 buffer were used. Both buffers were comprised of 0.20 *N* sodium citrate containing BrIJ 35 (2.0 ml/l.), pentachlorophenol (0.1 ml/l.), and thiodiglycol reagent (5.0 ml/l.). The latter reagent was deleted during the elution of L-selenocystine.[20] The buffer flow rate was set at 68.0 ml/hr and the temperature was maintained during the entire elution procedure at 55°.

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Registry No.—II, 22423-79-6; III, 22423-80-9; IV, 22423-81-0; V, 5034-33-3; VI, 22423-83-2; VII, 22423-84-3; VIII, 22423-85-4; IX, 19641-75-9.

Acknowledgments.—The authors express their appreciation to the following members of these laboratories: Miss Patricia Evans for the preparation of starting materials, Mrs. Helga Albrecht for infrared spectra, and Mr. David Schlesinger for amino acid analyses.

Sulfur-Containing Polypeptides. X. A Study of β Elimination of Mercaptides from Cysteine Peptides[1-3]

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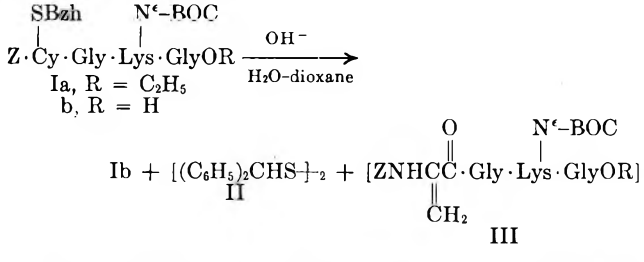
Received August 25, 1969

During the attempted saponification of ethyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysylglycinate (Ia) using 1 equiv of sodium hydroxide in aqueous dioxane, a mixture of products was obtained. In addition to some of the desired acid, Ib, the presence of several substances of higher mobility was indicated by tlc of the reaction mixture. Subsequently, one of these components was isolated and identified by melting point and mass spectral fragmentation pattern as dibenzhydryl disulfide (II). Presumably, benzhydryl mercaptide and the corresponding dehydroalanine peptide, III, were initially produced by a β-elimination[5-7] reaction; air oxidation of the mercaptide would yield II.



In order to obtain a quantitative evaluation of the extent of β elimination, a procedure devised by Patchornik and Sokolovsky[8] and Gawron and Odstrchel[9] was utilized. These workers have described an analytical method for the acid-catalyzed conversion of peptide-bound dehydroalanine to pyruvic acid and the subsequent determination of the pyruvic acid present using lactic dehydrogenase and reduced diphosphopyridine nucleotide. The amount of pyruvic acid present is assumed to represent the extent of β elimination in the original alkaline reaction. Several S-alkyl-L-cysteine esters were studied using this procedure; the substrates (Table I) included Ia, ethyl N-carbobenzoxy-S-benzyl-L-cysteinylglycinate (IV), ethyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycinate (V), and ethyl N-carbobenzoxy-S-trityl-L-cysteinylglycinate (VI). In these experiments the substrate was allowed to stand with 1.1 equiv of 1.0 *N* sodium hydroxide for 5 hr, the solvent was evaporated, and the residue was treated with 6 *N* hydrochloric acid solution at 110° for 5 hr. The amount of pyruvic acid was then determined spectrophotometrically. It is apparent from these results that the amount of β elimination is small using hydroxide ion despite the intensity of the dibenzhydryl disulfide spot on the thin layer chromatograms. The amount of pyruvic acid present was not significantly affected by solvent or the nature of the S-alkyl substituent.

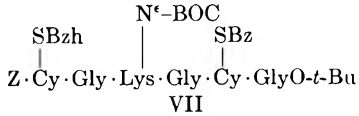
TABLE I

β ELIMINATION OF MERCAPTIDES FROM S-ALKYLCYSTEINE ESTERS DURING ESTER HYDROLYSIS

Peptide	Solvent[a]	Concn of peptide, *M*	β elimination,[b] %
Ia	EtOH	0.01	4.4, 5.0, 5.1, 5.4
Ia	DMF	0.01	4.8
IV	EtOH	0.04	4.8, 5.0, 5.3
V	EtOH	0.04	2.0, 2.3
V	DMF	0.04	2.4, 2.7
VI	EtOH	0.04	1.8
VI	DMF	0.03	1.9

[a] Solutions contain 1.1 equiv of 1.0 *N* sodium hydroxide. [b] Percentage of β elimination is equated to the percentage of pyruvic acid found in the reaction mixture after 5 hr at 25°. Pyruvic acid was determined by the procedure of A. Patchornik and M. Sokolovsky (ref 9).

The amount of β elimination accompanying the removal of an S-benzoyl group from peptides containing both S-benzhydryl- and S-benzoyl-protected L-cysteine residues was then investigated. As expected, methanolysis of *t*-butyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^{\epsilon}$-*t*-butyloxycarbonyl-L-lysylglycyl-S-benzoyl-L-cysteinylglycinate (VII), using dilute sodium methoxide in methanol solution (0.077 *M*), produced low levels of pyruvic acid (Table II). The hexapeptide, VII, was readily soluble in methanol, and methanolysis of the S-benzoyl group on a preparative scale proceeded rapidly and cleanly, as described by Zervas, *et al.*[10] It was noted, however, that, when the methoxide concentration was increased from 0.001 to 0.02 *M*, a spot corresponding to II appeared on the tlc of the reaction mixture. In contrast to VII, the hexapeptide, *t*-butyl N-carbobenzoxy-S-benzhydryl-



(1) Part IX of this series: R. G. Hiskey and J. T. Sparrow, *J. Org. Chem.*, **35**, 215 (1970).

(2) Supported in part by Grant A-3416 from the National Institute of Arthritis and Metabolic Diseases of the National Institutes of Health, U. S. Public Health Service.

(3) The following abbreviations have been incorporated in the text; Z = carbobenzoxy; BOC = *t*-butyloxycarbonyl; Bzh = benzhydryl; Tr = trityl; Bz = benzoyl; *t*-Bu = *t*-butyl; Cy = cysteinyl; Gly = glycyl; Lys = lysyl.

(4) Abstracted in part from a dissertation by R. A. Upham submitted to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. degree, Aug 1968.

(5) (a) J. A. MacLaren, W. E. Savige, and J. M. Swan, *Aust. J. Chem.*, **11**, 345 (1958); (b) J. A. Maclaren, *ibid.*, **11**, 360 (1958).

(6) L. Zervas, I. Photaki, A. Cosmatos, and N. Ghelis, *Peptides, Proc. Eur. Symp., 5th, 1962*, 27 (1963).

(7) I. Photaki, *J. Amer. Chem. Soc.*, **85**, 1123 (1963).

(8) A. Patchornik and M. Sokolovsky, *ibid.*, **86**, 1206 (1964).

(9) O. Gawron and G. Odstrchel, *ibid.*, **89**, 3263 (1967).

(10) L. Zervas, I. Photaki, and N. Ghelis, *ibid.*, **85**, 1337 (1963).

TABLE II

β ELIMINATION OF MERCAPTIDES FROM S-BENZHYDRYL- AND S-BENZOYL-L-CYSTEINE PEPTIDES DURING METHANOLYSIS

Peptide	Solvent[a]	Concn of peptide, M	β elimination,[b] %
VII	MeOH	0.013	0.24
VII	MeOH	0.0015	0.4
VIII	DMAc	0.026	23.4, 26.3
VIII	DMAc	0.022	21.5
VIII	MeOH–DMAc (1:3)	0.021	16.5
VIII	MeOH–DCAc (1:1)	0.021	10.0
VIII	MeOH–DMAc (3:1)	0.021	7.4, 7.8

[a] Solutions contain 1 equiv of 0.077 *N* sodium methoxide in methanol. [b] Percentage of β elimination is equated to the percentage of pyruvic acid found in the reaction mixture after 5 hr at 25°.

VIII

L-cysteinylglycylglycylglycyl-S-benzoyl-L-cysteinylglycinate[11] (VIII), was only slightly soluble in methanol and dissolved readily in only N,N-dimethylacetamide; therefore, the methanolysis of the S-benzoyl group was conducted with 1 equiv of sodium methoxide in N,N-dimethylacetamide. Under these conditions a substantial amount of β elimination occurred, as evidenced by the formation of *ca.* 20% of pyruvic acid upon acid hydrolysis of the reaction mixture. Although the site of β elimination (cysteine 1 or 5) was not established, the amount of β elimination occurring in VIII during removal of the S-benzoyl group was clearly related to the polarity of the solvent. When the methanolysis reaction was carried out in various mixtures of methanol and N,N-dimethylacetamide, the amount of pyruvic acid detected in the reaction mixture after hydrolysis decreased. From these data it appears that the utility of base-labile protective groups in peptides containing cysteine will depend on the base strength of the particular system employed for removal of the protective group. With larger peptides which require highly polar solvents for solution, β elimination of alkyl mercaptides from S-alkylcysteine residues may become an important and serious side reaction.

Experimental Section[12]

Ethyl N-carbobenzoxy-*S*-benzyl-l-cysteinylglycinate (IV),[5a] ethyl N-carbobenzoxy-*S*-benzhydryl-L-cysteinylglycine (V),[13] and ethyl N-carbobenzoxy-*S*-trityl-L-cysteinylglycinate[13] were prepared by the reported procedures.

Preparation of N-Carbobenzoxy-S-benzhydryl-L-cysteine N-Hydroxysuccimide Ester.—A solution containing 7.41 g (0.0176 mol) of N-carbobenzoxy-S-benzhydryl-L-cysteine[13] and 2.2 g (0.0176 mol) of N-hydroxysuccinimide in 12 ml of 1,2-dimethoxyethane was cooled to 0° and treated with 3.7 g (0.018 mol) of N,N-dicyclohexylcarbodiimide. The solution was stirred for 2 hr at 0° and 20 hr at 25°. The precipitated DCU was washed with 15 ml of 1,2-dimethoxyethane and the filtrate was evaporated *in vacuo*. The resulting solid was recrystallized from 250 ml of hot 2-propanol to provide 7.06 g (77.4%) of the ester, mp 131.5–132.5°.

Anal. Calcd for $C_{28}H_{26}N_2O_6S$: C, 64.85; H, 5.05; N, 5.40; S, 6.18. Found: C, 65.17; H, 5.23; N, 5.46; S, 6.45.

Preparation of N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycine.—To a solution containing 2.59 g (0.005 mol) of N-carbobenzoxy-S-benzhydryl-L-cysteine N-hydroxysuccinimide ester in 15 ml of 1,2-dimethoxyethane was added a solution containing 0.38 g (0.005 mol) of glycine and 0.84 g (0.010 mol) of sodium bicarbonate in 13 ml of water. The solution was stirred for 5 hr at 25°, diluted with 75 ml of water, and acidified to pH 2 with 6 *N* hydrochloric acid. The solution was saturated with sodium chloride and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, dried, and evaporated *in vacuo* to a solid. Recrystallization from a 1:10 mixture of ethyl acetate–petroleum ether (bp 30–60°) provided 1.99 g (83%) of the peptide, mp 114–117.5°, $[\alpha]^{28}D$ −0.8° (c 0.5, $CHCl_3$).

Anal. Calcd for $C_{25}H_{26}N_2O_5S$: C, 65.25; H, 5.48; N, 5.85; S, 6.70. Found: C, 65.36; H, 5.53; N, 5.83; S, 6.92.

The same material, mp 111–116°, was obtained in 83% yield by hydrolysis of *t*-butyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycinate with boron trifluoride diethyl etherate in glacial acetic acid.

Ethyl N^{α}-Carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyl-L-lysylglycinate.—A solution containing 2.79 g (0.02 mol) of ethyl glycinate hydrochloride and 11.23 g (0.02 mol) of N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyl-L-lysine N,N-dicyclohexylammonium salt[14] in 20 ml of methylene chloride and 2 ml of chloroform was cooled to 0° and treated with 4.21 g (0.022 mol) of 1-ethyl-3-(N,N-dimethylaminopropyl)carbodiimide hydrochloride. The reaction mixture was stirred at 0° for 1.5 hr and at 25° for 11 hr. The solution was filtered and washed with 50 ml of ethyl acetate, and the filtrate was evaporated to an oil. The oil was dissolved in 150 ml of ethyl acetate and washed with 1 *N* sulfuric acid, water, 5% potassium bicarbonate, water, and saturated brine. The dried ethyl acetate solution was concentrated *in vacuo* to 100 ml, cooled, and filtered. The product, yield 8.1 g (87%), appeared as a white solid, mp 110.5–112°, homogeneous by tlc (system A).

Anal. Calcd for $C_{23}H_{35}N_3O_7$: C, 59.34; H, 7.58; N, 9.03. Found: C, 59.58; H, 7.60; N, 9.21.

Preparation of Ethyl N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysylglycinate (Ia).—A solution of 11.62 g (0.025 mol) ethyl N^{α}-carbobenzoxy-N^{ϵ}-*t*-butyloxycarbonyl-L-lysylglycinate in 250 ml of absolute ethanol containing 1.2 g of 10% palladium-on-charcoal catalyst was treated with a stream of hydrogen. After 0.5 hr, tlc (system C) indicated one spot and the suspension was filtered with the aid of diatomaceous earth. The filtrate was concentrated to 50 ml and treated with 250 ml of dry ether and 17.5 ml (0.245 mol) of 1.4 *M* hydrogen chloride in 2-propanol. The dried hydrochloride salt, yield 8.42 g (91.2%), mp 109–116°, was homogeneous by tlc (system C) and was used without further purification.

A solution containing 2.47 g (0.005 mol) of N-carbobenzoxy-S-benzhydryl-L-cysteinylglycine and 1.89 g (0.005 mol) of the crude hydrochloride in 11 ml of dry chloroform was cooled to −10° and treated with 0.69 ml (0.05 mol) of triethylamine. The resulting slurry was treated with 1.05 g (0.0055 mol) of 1-ethyl-3-(N,N-dimethylaminopropyl)carbodiimide hydrochloride and stirred at −10° for 1 hr and at 25° for 12 hr. The solution was evaporated *in vacuo* to provide a solid, which was dissolved in 300 ml of chloroform and washed with 100 ml of 1 *N* sulfuric acid and four 100-ml portions of water. The dried organic layer was concentrated to 50 ml and the peptide was precipitated by the addition of 700 ml of ether. Recrystallization of the resulting solid from dioxane–water gave 3.56 g (90%) of white solid, mp 162–164°, homogeneous by tlc (system A).

Anal. Calcd for $C_{41}H_{53}N_5O_9S$: C, 62.18; H, 6.75; N, 8.84; S, 4.05. Found: C, 62.33; H, 6.74; N, 9.03; S, 4.07.

Preparation of N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N^{ϵ}-*t*-butyloxycarbonyl-L-lysylglycine (Ib). Method A.—Attempts to saponify the ester Ia using alkaline conditions consistently resulted in the formation of a mixture of products, as shown by tlc (systems A and B). Saponification of 0.8 g (1.01 mmol) of Ia with 1 equiv of 0.95 *N* sodium hydroxide solution in dioxane at 25° was stopped after 3.5 hr by the addition of 1.5 equiv of cold 0.25 *N* hydrochloric acid solution. The solution was

(11) The synthesis of VIII will be reported in a separate paper.

(12) Melting points are uncorrected and were taken in unsealed capillary tubes or on a Kofler hot stage. Elemental analyses were performed by Microtech Laboratories, Skokie, Ill. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Mass spectral studies were conducted with a Hitachi Perkin-Elmer Model RMU-6E instrument.

The following solvent systems were employed for thin layer chromatograms: system A, chloroform–methanol (9:1); system B, chloroform–methanol–acetic acid (8.5:1:0.5); system C, chloroform (saturated with ammonia)–methanol (9:1); system D, benzene–ethyl acetate (8:2); system E, chloroform–methanol (19:1).

(13) L. Zervas and I. Photaki, *J. Amer. Chem. Soc.*, **84**, 3887 (1962).

(14) L. Zervas and C. Hamalidis, *ibid.*, **87**, 99 (1965).

extracted with ethyl acetate; evaporation of the organic extract yielded an oil which crystallized upon addition of methanol to provide 0.01 g (2.5%) of needles, mp 149–151° (lit.[15] mp 151–152°), homogeneous by tlc (R_f 0.95, systems A, B, and D). The mass spectrum (direct probe at 260°, 2.6 kV dynode, 0.5 slit width) exhibited peaks at *m/e* (rel intensity) 199 (6.3) attributed to $(C_6H_5)_2CHS^+$ and a pattern from 167 (100) down consistent with $(C_6H_5)_2CH^+$. These data are consistent with the structure of benzhydryl disulfide.

Method B.—A solution of 0.323 g (0.0011 mol) of N$^\epsilon$-*t*-butyloxycarbonyl-L-lysylglycine and 0.170 g (0.002 mol) of sodium bicarbonate in 3 ml of water was treated with a solution containing 0.576 g (0.001 mol) of N-carbobenzoxy-S-benzhydryl-L-cysteinylglycine N-hydroxysuccinimide ester in 5 ml of dimethoxyethane. The reaction mixture was stirred for 18 hr at room temperature, diluted with 100 ml of water, and acidified to pH 3 with 1 *N* sulfuric acid. The precipitate was filtered, washed with 50 ml of water, and dried *in vacuo* to yield 0.71 g of crude product. The substance was washed with ethyl acetate and ether and recrystallized from chloroform–hexane to provide 0.62 g (82%) of white solid, mp 134–139°, $[\alpha]^{28}D$ −22.6° (*c* 0.53, DMF).

Anal. Calcd for $C_{39}H_{49}N_5O_9S \cdot 0.5H_2O$: C, 60.60; H, 6.52; N, 9.06; S, 4.15. Found: C, 60.59; H, 6.45; N, 9.07; S, 4.08.

Preparation of *t*-Butyl N-*o*-Nitrophenylsulfenyl-S-benzoyl-L-cysteinylglycinate.—A solution of 5.60 g (0.01 mol) of N-*o*-nitrophenylsulfenyl-S-benzoyl-L-cysteine N,N-dicyclohexylamine salt[16] in 20 ml of chloroform at −10° was treated with 1.30 ml (0.01 mol) of isobutyl chloroformate and stirred at −10° for 10 min. The solution was then treated with 1.68 g (0.01 mol) of *t*-butyl glycinate hydrochloride and 1.01 g (0.01 mol) of N-methylmorpholine in 10 ml of chloroform. The reaction mixture was stirred for 2 hr at 0° and 5 hr at 25°. The solution was evaporated *in vacuo* and the residue was suspended in an ether ethyl acetate mixture. The suspension was filtered and the filtrate was washed with 0.5 *N* sulfuric acid, water, 10% potassium bicarbonate, water, and saturated brine. The dried extract was evaporated *in vacuo* to a yellow oil which was dissolved in chloroform, slurried with 5 g of silica gel, and filtered. The resulting solution was evaporated *in vacuo* to give 4.48 g (91%) of a yellow foam, homogeneous by tlc (system A). An analytical sample was prepared by crystallization from benzene–ether–hexane, mp 81–83°, $[\alpha]^{27}D$ −10.6° (c 1.37, $CHCl_3$).

Anal. Calcd for $C_{22}H_{25}N_3O_6S_2$: C, 53.75; H, 5.13; N, 8.55; S, 13.08. Found: C, 53.29; H, 5.15; N, 8.75; S, 13.29.

Preparation of *t*-Butyl N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^\epsilon$-*t*-butyoxycarbonyl-L-lysylglycyl-S-benzoyl-L-cysteinylglycinate (VII).—To a solution of 4.48 g (0.091 mol) of *t*-butyl N-*o*-nitrophenylsulfenyl-S-benzoyl-L-cysteinylglycinate in 300 ml of dry ether was added 18 ml of 2.2 *N* hydrogen chloride in ether. An oil formed after 2 hr at 25°, the supernatant was decanted, and the oil was crystallized from chloroform–ether to give 2.09 g of *t*-butyl S-benzoyl-L-cysteinylglycinate hydrochloride, homogeneous (ninhydrin, iodine vapor) by tlc (system A).

A solution of 1.553 g (2.04 mmol) of IIb and 0.283 ml (2.04 mmol) of triethylamine in 15 ml of N,N-dimethylacetamide was treated with 0.25 ml (2.08 mmol) of pivaloyl chloride at −10°. After 10 min, 0.763 g (2.04 mmol) of crude *t*-butyl S-benzoyl-L-cysteinylglycinate hydrochloride and 0.283 ml (2.04 mmol) of triethylamine in 5 ml of N,N-dimethylacetamide was added to the reaction mixture. The solution was stirred at −10° for 1 hr and at 25° for 6.5 hr. The suspension was filtered and washed with ether and ethyl acetate, and the filtrate was added to 400 ml of ether. The supernatant was decanted and the gum was triturated with ether to give 1.91 g of solid. The material was filtered through silica gel G with 2% methanol in chloroform (v/v). The effluent was evaporated *in vacuo* and the solid was recrystallized from hot 95% ethanol–water (40:30, v/v) to give 1.616 g (73%) of VII: mp 174–180°; $[\alpha]^{26}D$ −23.0° (*c* 0.50, DMAc); homogeneous by tlc (system A, E).

Anal. Calcd for $C_{55}H_{69}N_7O_{12}S_2$: C, 60.92; H, 6.41; N, 9.04; S, 5.91. Found: C, 60.91; H, 6.29; N, 9.08; S, 5.98.

Preparation of *t*-Butyl N-Carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^\epsilon$-*t*-butyloxycarbonyl-L-lysylglycyl-L-cysteinylglycinate.—To a cooled solution of 324.5 mg (0.3 mmol) of VII in 300 ml of dry methanol was added 6 ml (0.33 mmol) of an 0.055 *N* solution of sodium methoxide in methanol. The reaction, followed on tlc with system E, required 2.5 hr for completion. The solution was acidified with 0.5 ml of glacial acetic acid, concentrated *in vacuo* to 50 ml, and poured into 700 ml of water. The washed precipitate was dried *in vacuo* to yield 283.8 mg (96.5%) of thiol: mp 185–188°; $[\alpha]^{28}D$ −10.8° (*c* 0.250, DMAc); homogeneous by tlc (system E).

Anal. Calcd for $C_{48}H_{65}N_7O_{11}S_2$: C, 58.82; H, 6.68; N, 10.00; S, 6.54. Found: C, 58.80; H, 6.63; N, 9.86; S, 6.57.

When the methanolysis of VII was carried out in more concentrated solution (0.02 *M* rather than 0.001 *M*), a spot corresponding to II appeared on the tlc of the reaction mixture.

Pyruvate Analyses. A. Saponification Reactions.—The substrate (*ca.* 0.02 mmol) was accurately weighed into a hydrolysis tube and dissolved in sufficient solvent (ethanol or N,N-dimethylformamide) to give the desired substrate concentration. The solution was treated with 1.1 equiv of 1.0 *N* sodium hydroxide solution, and the reaction mixture was left at room temperature for 5 hr. Solvent was then evaporated *in vacuo*, and 1 ml of constant-boiling 6 *N* hydrochloric acid solution was added. The tube was sealed and heated at 110° for 5 hr to liberate, by hydrolysis,[8] pyruvic acid from the dehydroalanine peptide present in the reaction mixture. The contents of the tube were carefully washed into a 5-ml volumetric flask with 1.1 *M* potassium hydrogen phosphate, the pH was brought to 7.5 with 50% sodium hydroxide, and the solution was diluted to volume with phosphate buffer. Aliquots of this solution were then analyzed for pyruvic acid with reduced diphosphopyridine nucleotide and lactic dehydrogenase as previously described.[8]

B. Methanolysis Reactions.—The substrate (*ca.* 0.01 mmol) was accurately weighed into a hydrolysis tube and dissolved in sufficient solvent (methanol, N,N-dimethylacetamide, or a mixture of both) to give the desired substrate concentration. One equivalent of 0.074 *N* sodium methoxide in methanol was then added, and the reaction mixture was allowed to stand at room temperature for 5 hr. The reaction mixture was then treated as described above. In all saponification and methanolysis reactions, the presence of unreacted starting material was observed by tlc (system A).

Registry No.—Ia, 22423-71-8; Ib, 22423-72-9; VII, 22423-77-4; N-carbobenzoxy-S-benzhydryl-L-cysteine N-hydroxysuccinimide ester, 22423-73-0; N-carbobenzoxy-S-benzhydryl-L-cysteinylglycine, 22423-74-1; ethyl N-carbobenzoxy-N$^\epsilon$-*t*-butyloxycarbonyl-L-lysylglycinate, 21869-27-2; *t*-butyl N-*o*-nitrophenylsulfenyl-S-benzoyl-L-cysteinylglycinate, 22423-76-3; *t*-butyl N-carbobenzoxy-S-benzhydryl-L-cysteinylglycyl-N$^\epsilon$-*t*-butyloxycarbonyl-L-lysylglycyl-L-cysteinylglycinate, 22423-78-5.

(15) A. Schonberg, E. Singer, E. Frese, and K. Praefcke, *Chem. Ber.*, **98**, 3311 (1965).

(16) L. Zervas, D. Borovas, and E. Gazis, *J. Amer. Chem. Soc.*, **85**, 3660 (1963).

Synthesis of Lamprolobine

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Received July 7, 1969

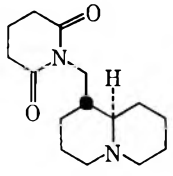
The two-step reaction sequence of partial hydrogenation of 1-alkyl-3-acylpyridinium salts and acid-catalyzed cyclization of the resultant 1-alkyl-3-acyl-2-piperideines has formed the basis of general synthesis of quinolizidines[2] and alkaloids based on this ring system.[3] Heretofore only methyl nicotinate, nicotin-

(1) Public Health Service Predoctoral Fellow, 1966–1969.

(2) E. Wenkert, K. G. Dave, and R. V. Stevens, *J. Amer. Chem. Soc.*, **90**, 6177 (1968), and references cited therein.

(3) E. Wenkert, *Accounts Chem. Res.*, **1**, 78 (1968).

aldehyde, and β-acetylpyridine have served as starting materials. Nicotinonitrile, in the form of its N_a-methyl derivative, has been shown to be susceptible to partial reduction,[4] but has not been tested in the second step of the aforementioned reaction sequence. Since it appeared to be an ideal starting compound for the construction of dinitrogenous natural bases, an investigation of the synthesis of such a product—lamprolobine (**1**), the major alkaloidal constituent of the leaves of *Lamprolobium fructicosum* Benth.[5]—from nicotinonitrile was undertaken.



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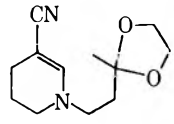
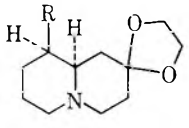


2

Alkylation of nicotinonitrile with 4-bromo-2-butanone ethylene ketal[6] and hydrogenation of the salt yielded the 2-piperideine **2**, whose treatment with *p*-toluenesulfonic acid in benzene solution afforded the pair of isomeric cyanoquinolizidone ketals **3a** and **4a**. Their reduction with lithium aluminum hydride gave the labile, liquid diamines **3b** and **4b**, which were characterized as phthalimides **3c** and **4c**, respectively.



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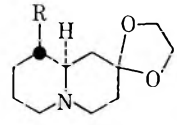

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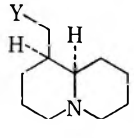
a, R = CN
b, R = CH_2NH_2
c, R = $CH_2N(CO)_2C_6H_4$

Hydrolysis of the ketals **3b** and **4b** with aqueous acid and Wolff–Kishner reduction of the resultant ketones produced diamines **5b**[7] and **6b**, respectively, whose stereochemistry was determined in the following manner. *dl*-Lupimine (**5a**)[2] and *dl*-epilupinine (**6a**)[2]



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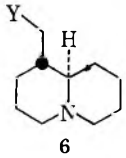
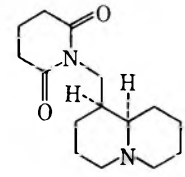


6

a, Y = OH
b, Y = NH_2
c, Y = Br
d, Y = $N(CO)_2C_6H_4$

were converted into bromides[8-10] **5c** and **6c**, respectively. Interaction of the bromides with potassium phthalimide[11] led to the crystalline imides **5d** and **6d**, respectively, the latter of which proved identical with the product of phthalation of **6b**. Furthermore, interaction of bromide **5c** with sodium glutarimide yielded isolamprolobine (**7**), identical with the imide derived from amine **5b** and glutaric anhydride.



7

Treatment of the amine **6b** with glutaric anhydride led to *dl*-lamprolobine (**1**), spectrally identical with the natural alkaloid.[5]

Experimental Section

Melting points were determined on a Reichert micro hot stage and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 137 and 621 spectrophotometers. Unless otherwise stated, proton magnetic resonance spectra of deuteriochloroform solutions containing tetramethylsilane as internal standard were determined on Varian A-60 and HA-100 spectrometers.

1-(3-Ketobutyl)-3-cyanopyridinium Bromide Ethylene Ketal.—A mixture of 6.24 g of nicotinonitrile and 12.4 g of 4-bromo-2-butanone ethylene ketal[6] was stirred at 60°. When, after 2 days, the mixture had set into a paste, 25 ml of ether was added and the solid was filtered and washed with ether. The filtrate and washings were combined, the solvent was evaporated, and the residue was left standing for 24 hr. Filtration of the resultant precipitate, washing as before, and combination with the previous solid yielded 17.0 g of salt which was sufficiently pure to be used in the next reaction. Its crystallization from a mixture of methanol and acetone ethylene ketal gave pure pyridinium salt: mp 151–153° dec; ir (KBr) 4.50 (w, C≡N) and 6.13 μ (m, C=C); pmr (dideuteriomethyl sulfoxide) δ 1.35 (s, 3, methyl), 2.4–2.6 (m, 2, methylene), 3.87 (s, 4, oxymethylenes), 4.81 (t, 2, J = 7.0 cps, aminomethylene), and 8.2–9.7 (m, 4, pyridine H).

Anal. Calcd for $C_{12}H_{15}O_2N_2Br$: C, 48.17; H, 5.06; N, 9.36. Found: C, 48.33; H, 5.29; N, 9.62.

1-(3-Ketobutyl)-1,4,5,6-tetrahydronicotinonitrile Ethylene Ketal (2).—A mixture of 10.0 g of the above salt, 1.0 g of 10% palladium on charcoal, and 10 ml of triethylamine in 50 ml of methanol was hydrogenated at room temperature under a pressure of 40 psi for 12 hr. It was filtered and the filtrate was evaporated. The residue from the filtrate was extracted with ether and the extract was evaporated. An ether solution of the residue was passed through a short alumina (activity IV) column and evaporated. Chromatography of the residual oil, 4.70 g, on silica yielded liquid **2**: ir (neat) 4.62 (m, C≡N) and 6.18 μ (m, C=C); pmr δ 1.27 (s, 3, methyl), 3.92 (s, 4, oxymethylenes), and 6.79 (s, 1, olefinic H).

Anal. Calcd for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.01; H, 8.38; N, 12.60.

9-Cyano-2-quinolizidone Ethylene Ketals 3a and 4a.—A solution of 7.4 g of **2** in 200 ml of dry benzene was added over a 30-min period to a solution of 8.0 g of *p*-toluenesulfonic acid (from which water had been removed by azeotropic distillation from benzene) in 200 ml of dry benzene and the mixture was refluxed under nitrogen for 8 hr. The cooled solution was poured onto a suspension of an excess of sodium bicarbonate in 1 l. of methylene chloride, stirred for some time, and filtered. The filtrate was evaporated and the residue was extracted with ether. The extract was dried over sodium sulfate and evaporated. Silica chromatography of the residual oil, 3.9 g, and elution with 24:1 chloroform–methanol yielded three sets of fractions whose thin layer chromatography revealed the first to contain one isomer, the second a mixture, and the third the second isomer of the desired product. Rechromatography of the second group of fractions, 1.0 g, on silica separated them into the two isomers. Distillation of the first fractions yielded 1.1 g of a crystalline solid whose crystallization from ether–hexane or sublimation gave colorless crystals of **3a**: mp 78–79.5°; ir (KBr) 4.45 μ (w, C≡N); pmr δ 3.96 (s, 4, oxymethylenes).

(4) E. Wenkert, K. G. Dave, F. Haglid, R. G. Lewis, T. Oishi, R. V. Stevens, and M. Terashima, *J. Org. Chem.*, **33**, 747 (1968).

(5) N. K. Hart, S. R. Johns, and J. A. Lamberton, *Aust. J. Chem.*, **21**, 1619 (1968).

(6) L. Williman and H. Schinz, *Helv. Chim. Acta*, **32**, 2151 (1949).

(7) F. Bohlmann, D. Schumann, U. Friese, and E. Poetsch, *Chem. Ber.*, **99**, 3358 (1966).

(8) G. R. Clemo and J. Rudinger, *J. Chem. Soc.*, 2714 (1951).

(9) F. Bohlmann, E. Winterfeldt, and U. Friese, *Chem. Ber.*, **96**, 2251 (1963).

(10) G. Fodor, *J. Amer. Chem. Soc.*, **88**, 1040 (1966).

(11) *Cf.* S. Okuda, H. Katoaka, and S. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **13**, 491 (1965).

Anal. Calcd for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.59; H, 8.29; N, 12.37.

Distillation of the last fractions yielded 1.2 g of a solid whose crystallization from ether–hexane or sublimation afforded colorless crystals of **4a**: mp 71–72.5°; ir (KBr) 4.45 μ (w, C≡N); pmr δ 3.96 (s, 4, oxymethylenes).

Anal. Calcd for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.82; H, 8.02; N, 12.77.

Phthalimides 3c and 4c.—A solution of 500 mg of **3a** in 50 ml of dry ether was added over a 1-hr period to a stirring solution of 500 mg of lithium aluminum hydride in 50 ml of ether at room temperature and the mixture was stirred for 3 hr. Sodium sulfate decahydrate was added and the mixture was shaken and filtered. The salts were washed with methylene chloride and the combined filtrate and washings were evaporated. The residual liquid amine **3b**, 440 mg, had to be used for further reactions immediately, since it formed readily a carbon dioxide addition product. A solution of 45 mg of **3b** and 50 mg of phthalic anhydride in 3 ml of chloroform was refluxed for 30 min and then evaporated. The residue was heated at 220° (0.001 Torr) and sublimed in a fractional sublimator. Crystallization of the product, 50 mg, from ether–hexane yielded colorless crystals of **3c**: mp 166–168°; ir (KBr) 5.67 (m, C=O), 5.87 (s, C=O), and 6.20 μ (w, C=C).

Anal. Calcd for $C_{20}H_{24}O_4N_2$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.20; H, 6.64; N, 7.68.

The identical procedure was applied to **4a**. Crystallization of its imide from ether–hexane gave crystals of **4c**: mp 137–138°; ir (KBr) 5.65 (w, C=O), 5.86 (s, C=O), and 6.18 μ (w, C=C).

Anal. Calcd for $C_{20}H_{24}O_4N_2$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.67; H, 6.59; N, 7.82.

Diamines 5b and 6b and Their Derivatives.—A solution of 1.5 g of diamino ketal **4b** in 10 ml of 50% sulfuric acid was kept at room temperature for 18 hr. The solution was cooled, made alkaline with 5 *N* potassium hydroxide, and extracted exhaustively with methylene chloride. The extract was dried and concentrated to a 10-ml volume. Ethylene glycol, 25 ml, was added and the remaining methylene chloride was removed by distillation. Potassium hydroxide, 4.0 g, and 10 ml of 98% hydrazine were added and the mixture was heated at 190° for *ca.* 3 hr and subsequently refluxed under nitrogen for 12 hr. It was then cooled, acidified with 6 *N* hydrochloric acid, and evaporated under vacuum. The residue was dissolved in a minimum amount of 1 *N* potassium hydroxide and the alkaline solution was extracted with methylene chloride. The extract was dried and evaporated. Distillation of the residue gave 135 mg of **6b**, which had to be used immediately in the next reactions in view of its ready air oxidation and formation of a carbon dioxide adduct.

A solution of 50 mg of **6b** and 50 mg of phthalic anhydride in 1 ml of chloroform was refluxed in a sublimation tube for 30 min. It was evaporated and the tube was heated at 250° (0.005 Torr) in a fractional sublimator. Collection of a band of crystals gave 10 mg of solid whose crystallization from ether–hexane yielded colorless crystals of **6d**: mp 128–129°; mmp (with **6d** below) 127–128.5°; mmp (with **5d** below) 108–117°; ir (KBr) 5.66 (m, C=O), 5.85 (s, C=O), and 6.20 μ (w, C=C).

Anal. Calcd for $C_{18}H_{22}O_2N_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.63; H, 7.53; N, 9.37.

The preparation of the 1-bromomethylquinolizidines **5c** and **6c** followed the procedure for the conversion of lupmine (**5a**) into optically active **5c**.[8] Epilupinine (**6a**), 330 mg, gave 410 mg of **6c**.

A solution of 100 mg of **5c** and 100 mg of potassium phthalimide in 4 ml of dry dimethylformamide was heated at 130° for 4 hr.[11] The mixture was cooled and evaporated. The residue was extracted with methylene chloride and chromatographed on 3 g of alumina (activity II). Elution with 50:1 ether–methanol gave 65 mg of a solid whose crystallization from ether–hexane yielded crystals of **5d**: mp 135–136°; ir (KBr) 5.66 (m, C=O), 5.87 (s, C=O), and 6.19 μ (w, C=C).

Anal. Calcd for $C_{18}H_{22}O_2N_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.21; H, 7.62; N, 9.27.

A similar reaction with 40 mg of **6c** and 40 mg of potassium phthalimide gave 29 mg of **6d**: mp 127.5–129°; ir (KBr) identical with that of **6d** above.

Diamine **5b**, 1.4 g, was prepared from **3b**, 90 mg, by the procedure outlined above for the conversion of **4b** into **6b**. A solution of 35 mg of diamine **5b** and 35 mg of glutaric anhydride in 4 ml of chloroform was kept at room temperature for 2 hr. Evaporation of the solution and high vacuum distillation (bath temperature 250°) of the residue yielded 10 mg of liquid isolamprolobine (**7**): ir (CCl_4) 5.78 (m, C=O) and 5.95 μ (s, C=O).

A suspension of 232 mg of bromide **5c** and 135 mg of sodium glutarimide in 4 ml of dimethylformamide was refluxed for 2 hr. The mixture was cooled and filtered and the filtrate was evaporated. The residue was chromatographed on alumina (activity IV). Distillation of the 50:1 ether–methanol eluates yielded 40 mg of liquid **7** whose ir and pmr spectra and thin layer chromatographic behavior were identical with those of **7** above.

Lamprolobine (1).—The above procedure of conversion of **5b** into **7** was applied to 100 mg of **6b** and 100 mg of glutaric anhydride. It led to 30 mg of liquid *dl*-lamprolobine (**1**), ir (CCl_4) 5.78 (m, C=O) and 5.95 μ (s, C=O), identical in all respects with the spectrum of natural lamprolobine (**1**). Crystallization of its picrate from methanol gave yellow plates, mp 190–192°.

Anal. Calcd for $C_{21}H_{27}O_9N_5$: C, 51.11; H, 5.51; N, 14.19. Found: C, 51.45; H, 5.80; N, 14.12.

Registry No.—**1**, 22142-02-5; **2**, 22423-62-7; **3a**, 22423-63-8; **3c**, 22423-64-9; **4a**, 22423-65-0; **4c**, 22423-67-2; **5d**, 10248-22-3; **6d**, 22423-69-4; **1** picrate, 22142-03-6; 1-(3-ketobutyl)-3-cyanopyridinium bromide ethylene ketal, 22423-66-1.

Acknowledgments.—The authors are indebted to Dr. J. A. Lamberton for a gift of a sample of natural lamprolobine and to the U. S. Department of Health, Education and Welfare (Grant GM-11571) for partial support of this work.

The Stereochemistry of (−)-Deoxynupharidine.[1] The Synthesis of (−)-(*R*)-α-Methyladipic Acid

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Received May 22, 1969

A recent publication[2] dealing with the synthesis of (+)-(*S*)-α-methyladipic acid has prompted us to disclose our synthesis of (−)-(*R*)-α-methyladipic acid, a synthesis carried out in an attempt to clarify the absolute configuration of (−)-deoxynupharidine and related Nuphar alkaloids.[3] Also reported here are nuclear magnetic resonance results which support the relative configuration of deoxynupharidine proposed earlier.

Originally, the absolute configuration of (−)-deoxynupharidine (**1**) was proposed on the basis that the (−)-α-methyladipic acid obtained on degradation (Scheme I) possessed the *S* configuration.[4] The configurational assignment of this acid was made on the basis of its synthesis from (−)-α-methyl-γ-butyrolactone, which in turn was correlated with (−)-(*S*)-methylsuccinic acid.[5] However, Turner[6] questioned

(1) Support of this work by the U. S. Department of Interior, Federal Water Pollution Control Administration and the McIntire–Stennis Cooperative Forestry Research Program of the U. S. Department of Agriculture is gratefully acknowledged.

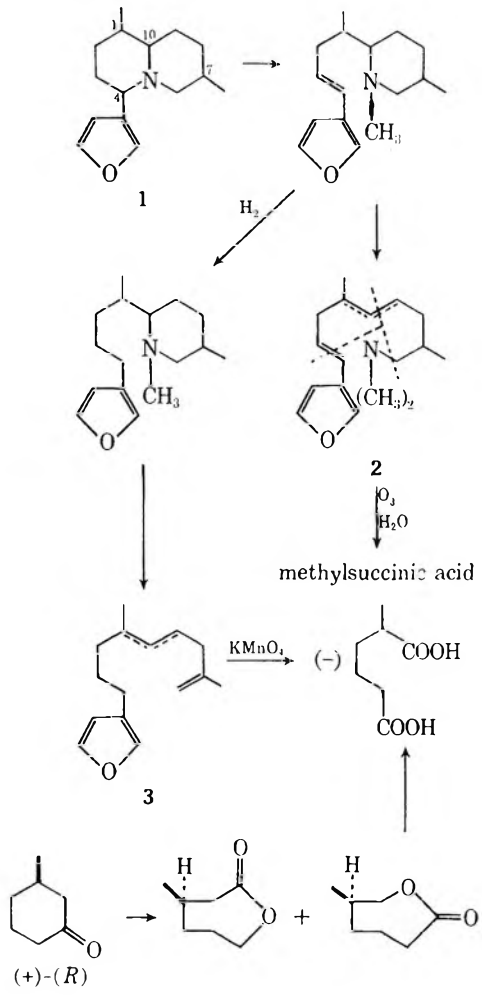
(2) I. Kawasaki and T. Kaneko, *Bull. Chem. Soc. Jap.*, **41**, 1482 (1968).

(3) These include nupharidine, Δ^3-dehydrodeoxynupharidine, nupharamine, anhydronupharamine, nuphamine, and castoramine.

(4) (a) M. Kotake, I. Kawasaki, T. Okamoto, S. Matustani, S. Kusumoto, and T. Kaneko, *ibid.*, **35**, 1335 (1962); (b) Y. Arata and T. Iwai, *Kanazawa Daigaku Yakugakuba Kenkyu Nempo*, **12**, 39 (1962).

(5) T. Kaneko, K. Wakabayashi, and H. Katsura, *Bull. Chem. Soc. Jap.*, **35**, 1149 (1962).

(6) D. C. Aldridge, J. J. Armstrong, R. N. Speake, and W. B. Turner, *J. Chem. Soc.*, 1667 (1967).



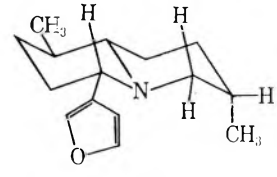
the assignment of the *S* configuration to (−)-α-methyladipic acid since (−)-(*R*)-α-methylglutaric acid, (+)-(*R*)-β-methyladipic acid, as well as (−)-α-methyladipic acid all were produced in the oxidative degradation of the cytochalasins A and B. Furthermore, Turner suggested that the proposed absolute configuration of (−)-deoxynupharidine should be reversed. Later, the formation of (−)-(*R*)-methylsuccinic acid by ozonolysis of the tertiary aminodiene **2** was offered[7] as experimental evidence to confirm Turner's suggestion.

We viewed an assignment of the absolute configuration of (−)-deoxynupharidine as ambiguous when based on a correlation with optically active methylsuccinic acid. The optically active acid possibly could have originated from C_{10}, C_1, C_2, and C_3, by ozonolysis of two carbon–carbon double bonds in **2**, or its antipode could have arisen from C_6, C_7, C_8, and C_9, by ozonolysis of a double bond and a carbon–nitrogen bond. There is precedent for the formation of aldehydes on ozonolysis of tertiary amines,[8] and oxidative conditions such as those used in the degradation of **2** would suffice to oxidize an aldehyde to a carboxylic acid. On the other hand, the origin of the (−)-α-methyladipic acid produced from **3** in the degradation is unequivocal and, therefore, a synthesis of (*R*)-α-methyladipic acid was justified for the purpose of correlation.

According to a known procedure,[9] (−)-(*R*)-δ-methyl-ε-caprolactone was obtained by repeated low-temperature fractional crystallization of the mixture of δ- and β-methyl-ε-caprolactones resulting from the Baeyer–Villiger oxidation of (+)-(*R*)-3-methylcyclohexanone (optical purity, 100%). Careful alkaline hydrolysis of the (−)-(*R*)-δ-methyl-ε-caprolactone and subsequent oxidation with an excess of potassium permanganate produced (−)-(*R*)-α-methyladipic acid which agreed in sign and magnitude of rotation with the (−) acid of degradation.

A convincing assignment of the relative configuration and conformation of (−)-deoxynupharidine has been made on the basis of synthetic methods and infrared studies.[10,11] Supporting evidence for the presence of one axial and one equatorial methyl group was furnished by an early nmr study,[4a] and a specific stereochemical assignment of methyl groups was made possible later by the transformation of nupharamine to deoxynupharidine and 7-epideoxynupharidine.[12] Since the 7 epimer was shown by nmr to have two equatorial methyl groups, deoxynupharidine must have C_1 equatorial and C_7 axial methyl groups. This stereochemistry is also demonstrated through examination of the C_6 protons in the 100 MHz nmr of deoxynupharidine. Both $H_{6\alpha}$ (7.30 τ) and $H_{6\beta}$ (8.12 τ) signals are identical quartets. The $H_{6\alpha}$ quartet arises from geminal (12.5 Hz) and equatorial–equatorial (6α–7β) coupling ($J_{e,e}$ = 2.5 Hz), while the $H_{6\beta}$ quartet arises from geminal (12.5 Hz) and axial–equatorial (6β–7β) coupling ($J_{a,e}$ = 2.5 Hz). These results are consistent with a structure having a C_7 axial methyl group. Therefore the C_1 methyl must be equatorial. Had the C_7 methyl been equatorial, a diaxial (6β–7α) coupling ($J \simeq 10$ Hz) would have resulted, in which case low- and high-field quartets would not be identical.

On the basis of the correlation of (−)-deoxynupharidine with (−)-(*R*)-α-methyladipic acid and the studies of relative stereochemistry, the absolute stereochemistry can be given as depicted in **4**.



4

Experimental Section

Spectra were obtained as follows: nmr in solution as indicated, 2% TMS (10 τ), Varian A-60A and Joelco HNM-4H-100, and determined by Mrs. D. Lee and Mrs. H. Jennison; ir in solution as indicated, Perkin-Elmer 137. Melting points were determined on a Kofler micro hot stage and are uncorrected; optical rotations, on a Perkin-Elmer 141 polarimeter. The elemental analysis was performed by Galbraith Laboratories.

(−)-(*R*)-α-Methyladipic Acid.—According to the method of Overberger and Kaye,[9] 10.3 g (0.0916 mol) of (+)-(*R*)-3-methyl-

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(9) C. G. Overberger and H. Kaye, *J. Amer. Chem. Soc.* **89**, 5640 (1967).

(10) F. Bohlmann, E. Winterfeldt, P. Studt, H. Laurent, G. Boroschewski, and K. Kleine, *Chem. Ber.*, **94**, 3151 (1961).

(11) Y. Arata, N. Hazama, and Y. Kojima, *J. Pharm. Soc. Jap.*, **82**, 326 (1962).

(12) I. Kawasaki, S. Matsutani, and T. Kaneko, *Bull. Chem. Soc. Jap.*, **36**, 1474 (1963).

cyclohexanone,[13] $[\alpha]^{25}D$ +12.3° (1 dm, neat) [lit.[9] $[\alpha]^{27}D$ +12.01 (1 dm, neat)], was treated with a mixture of 26.5 g (0.126 mol) of trifluoroacetic anhydride and 3.63 g of 90% hydrogen peroxide to yield 9.4 g of colorless liquid (bp 83° at 2.5 mm) containing a mixture of δ-methyl-ε-caprolactone and β-methyl-ε-caprolactone. The nmr spectrum (CCl_4) of this mixture showed the low-field methylene signals at 5.84 (t, J = 4 Hz) and 6.0 (m, 4.5 Hz), which were assigned to the chemical shifts of the $-CH_2O-$ groups of β- and δ-methyl-ε-caprolactone, respectively. The δ-methyl-ε-caprolactone was isolated from the mixture by fractional crystallization at 0°, yielding 0.944 g of needles: mp 35.5–36.0°; $[\alpha]^{25}D$ −37.4° (c 0.855, $CHCl_3$) [lit.[9] $[\alpha]^{25}D$ −36.11 (c 0.46, $CHCl_3$)]; ir (CCl_4) 5.78 and 8.59 μ; nmr (CCl_4) τ 6.0 (m, 2 H, $-CH_2O-$), 7.47 (m, 2 H, $-CH_2C{=}O$), 8.20 (broad m, 5 H), and 9.08 (d, J = 6.8 Hz, 3 H).

A mixture of (−)-(*R*)-δ-methyl-ε-caprolactone (415 mg, 3.24 mmol), sodium hydroxide (372 mg), and 5 ml of aqueous ethanol was heated to reflux for 2 hr. Ethanol was removed by vacuum evaporation and the residue was treated with an excess of saturated potassium permanganate (about 1 g) until the pink coloration persisted. The mixture, after storing at room temperature overnight, was treated with a few crystals of sodium bisulfite until the decantation was colorless. The brown precipitate was removed by filtration and the filtrate was extracted twice with 50 ml of methylene chloride. The aqueous layer was separated and adjusted to pH 1 by adding concentrated hydrochloric acid. Continuous extraction with ether yielded 472 mg of crystals, mp 75–78°. Fractional crystallization (thrice) from a mixture of ether and petroleum ether afforded 246 mg of crystals: mp 81–82°; $[\alpha]^{25}D$ −13.4° (c 2.15 EtOH); ir ($CHCl_3$) 3.80 (br) and 5.85 μ (s) (COOH); nmr ($CDCl_3$) τ −1.6 (s, 2 H, COOH), 7.62 (m, 3 H), 8.33 (m, 4 H), and 8.78 (d, J = 7 Hz, 3 H).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.47; H, 7.55. Found: C, 52.39; H, 7.50.

(+)-S-α-Methyladipic acid had lit.[2] mp 81–83°, $[\alpha]^{25}D$ +13.8° (c, 1.91 in EtOH). (−)-α-Methyladipic acid had lit.[4b,6] mp 82–83°, $[\alpha]^{28}D$ −18°.

(−)-Deoxynupharidine.—A 200-mg sample of nupharidine ($[\alpha]D$ +14.8° mp 218–224°, hydrochloride mp 228°; lit.[14] $[\alpha]D$ +13.0, mp 212°, hydrochloride mp 196°) was dissolved in 100 mg of absolute ethanol, and 100 mg of 10% palladized charcoal was added. The mixture was shaken under 1 atm of hydrogen at room temperature. After 0.5 hr, consumption of hydrogen was complete. The catalyst was filtered and the filtrate evaporated. Chromatography of the 190 mg of oily residue on neutral alumina (activity II), using hexane (95%)–ether (5%) gave 178 mg of deoxynupharidine: $[\alpha]^{25}D$ −105° (48.6 mg in 2 ml of MeOH), mp (hydrochloride salt) 268°; lit.[15] $[\alpha]^{25}D$ −112.5°, mp (hydrochloride salt) 262°. The key features of the 100-MHz nmr ($CDCl_3$) spectrum are given in Table I.

TABLE I

100-MHz NMR SPECTRUM OF DEOXYNUPHARIDINE

Chemical shift rel to TMS, (τ 10)	No. of protons	Splitting pattern, J, Hz	Assignment[b]
9.01	6	Doublet, 7.0	C_7 CH_3 (ax)
9.08		Doublet, 5.6	C_1 CH_3 (eq)
8.12	1/2[a]	Quartet, 12.5, 2.5	$C_{6\beta}$ H (ax)
7.30	1	Quartet, 12.5, 2.5	$C_{6\alpha}$ H (eq)
7.12	1	Quartet, 8.0, 6.2	$C_{4\beta}$ H (ax)

[a] Only the lower field half of the 8.12 quartet is clearly observed. The high-field portion is superimposed on the envelope of the remaining methinyl and methylene protons. [b] ax = axial, eq = equatorial.

Registry No.—4, 1143-54-0; (−)-(*R*)-α-methyladipic acid, 16200-25-2.

(13) Purchased from the Aldrich Chemical Co.

(14) M. Kotake, I. Kawasaki, S. Matsutani, S. Kusumoto, and T. Kaneko, *Bull. Chem. Soc. Jap.*, **35**, 698 (1962).

(15) Y. Arata, *J. Pharm. Soc. Jap.*, **66**, 138 (1946).

Anomeric Methyl 4-Thio-D-arabinofuranosides[1]

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Received July 7, 1969

Since some nucleosides of D-arabinose possess antitumor activity,[3] and a number of thio and amino sugars and their derivatives have been shown to have biological activity, it is of interest to prepare nucleosides of 4-thio-D-arabinose. The conversion of 9-(4′-thio-β-D-xylofuranosyl)adenine into 9-(4′-thio-β-D-arabinofuranosyl)adenine has been reported,[4] but the synthesis is not applicable to other nucleosides. This paper describes the synthesis of the anomeric methyl 4-thio-D-arabinofuranosides, making the sugar analog available for incorporation into a variety of nucleosides.

The starting material used in the synthesis is 5-*S*-acetyl-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose,[5] an intermediate prepared earlier in this laboratory for the synthesis of 5-thio-D-glucopyranose. Selective hydrolysis of the isopropylidene group in the presence of the thiolacetate group of 5-*S*-acetyl-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (I) in 50% aqueous acetic acid at 70° gives a 78% yield of crystalline 5-*S*-acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (II) and a 16.2% yield of 3,6-di-*O*-benzyl-5-thio-D-glucopyranose (III) Scheme (I).

The structure of compound III is confirmed by the absence of absorptions at 1685 (*S*-acetyl) and 2550 cm^{-1} (SH). Also, the absence of resonance signals at τ 7–7.2 (SH), 7.76 (*S*-acetyl), and 8.5–8.7 (isopropylidene) indicates that in compound III sulfur has replaced oxygen as the heteroatom in a stable pyranose ring. The strong dextrorotation of compound III (+97.5°) compared with the dextrorotations of compounds I and II (−64.3[5] and −40°) having furanose structures suggests that compound III has a stable pyranose structure in which sulfur has entered the ring. The presence of the *S*-acetyl group in compound II is confirmed by an absorption at 1685 cm^{-1} and by a resonance signal in the nmr spectrum at τ 7.76. The absence of a signal in the region of τ 8.5–8.7 confirms the absence of the isopropylidene group. Compound II is further characterized by acetylation to obtain 1,2-di-*O*-acetyl-5-*S*-acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (IX) for which both the ir and nmr spectra showed the presence of *S*-acetyl and *O*-acetyl groups.

The structure of compound III is confirmed by the absence of an absorption at 1685 cm^{-1}. Also, the absence of a resonance signal at τ 7.76 (*S*-acetyl protons) and τ 8.5–8.7 (isopropylidene protons) further indicates that in compound III sulfur has replaced the oxygen as the heteroatom in a stable pyranose ring.

(1) This work was supported by the National Institutes of Health, Department of Health, Education and Welfare, Grant No. 1 RO1 Am 11463; Journal Paper No. 3734 of the Purdue Agricultural Experiment Station, Lafayette, Ind. 47907.

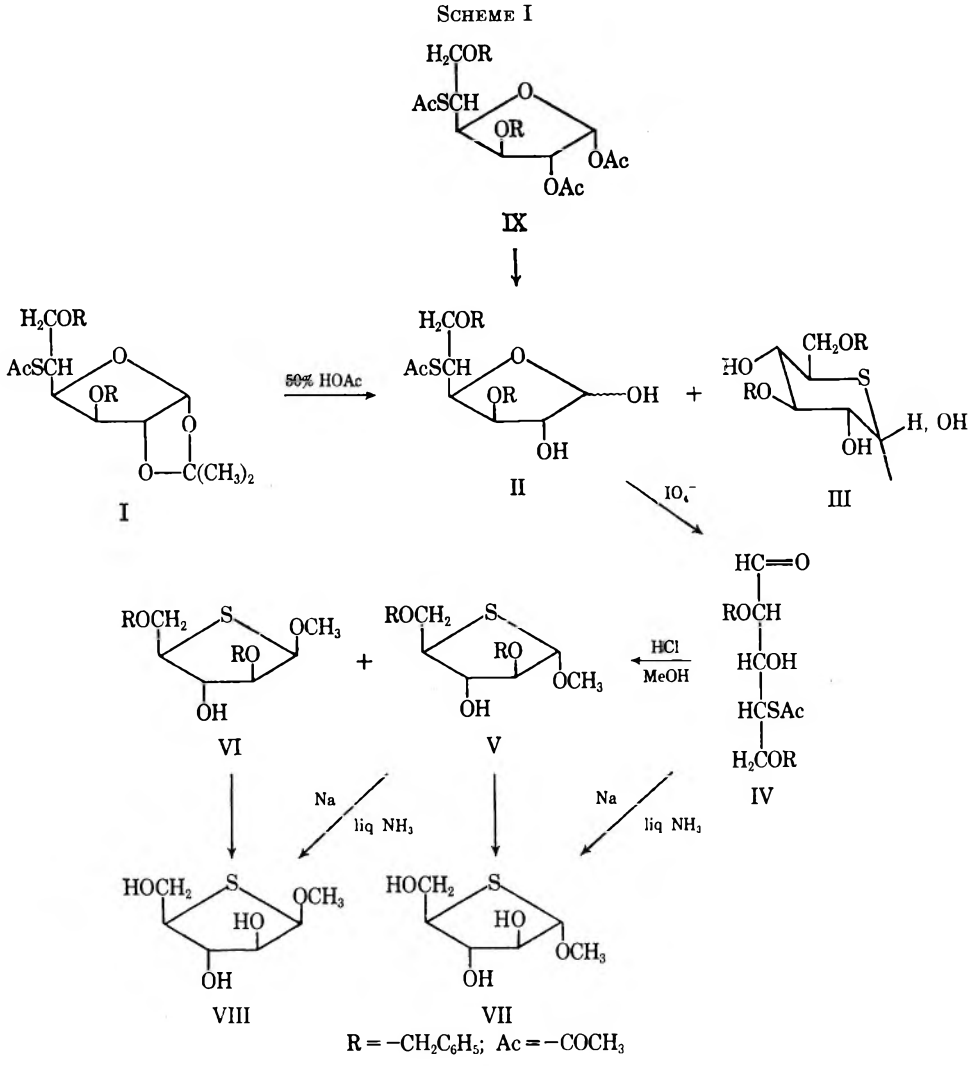
(2) National Institutes of Health predoctoral fellow, 1965–1968.

(3) For a review see S. S. Cohen in "Progress in Nucleic Acid Research and Molecular Biology," Vol. 5, J. N. Davidson and W. E. Cohn Ed., Academic Press Inc., New York, N. Y., 1965, p 1.

(4) E. J. Reist, L. V. Fisher, and L. Goodman, *J. Org. Chem.*, **33**, 189 (1968).

(5) U. G. Nayak and R. L. Whistler, *ibid.*, **34**, 97 (1969).

SCHEME I



Oxidation of sulfides to sulfoxides by metaperiodate has been described[6] as a rather general reaction and has been applied to the synthesis of sulfoxides of thio sugars.[7,8] However, the divalent sulfur of compound II is resistant to oxidation by neutral sodium metaperiodate, possibly owing to the inductive effect of the acetyl substituent. Thus, oxidation of compound II with neutral sodium metaperiodate in 50% aqueous ethanol gives a rapid and quantitative yield of 4-*S*-acetyl-2,5-di-*O*-benzyl-4-thio-*aldehydo*-D-arabinose (IV), which exhibits absorptions at 1730 (aldehyde) and 1685 cm^{-1} (*S*-acetyl). Compound IV is directly converted to the anomeric 2,5-di-*O*-benzyl-4-thio-D-arabinofuranosides (V and VI) by refluxing in 0.5% methanolic hydrogen chloride. The anomers V and VI are separated readily on a silica gel column to give pure, crystalline compounds.

The nmr spectra of both compounds V and VI integrated for 24 protons. The absence of a resonance signal in the τ 7.6–7.8 region and that of an absorption in the region of 1690 cm^{-1} confirms the absence of the *S*-acetyl group in both V and VI. The presence of a resonance signal at τ 2.7 integrating for 10 aromatic protons substantiates that both the benzyl groups are intact.

Debenzylation of V and VI with sodium in liquid ammonia separately has afforded crystalline methyl 4-thio-α-D-arabinofuranoside (VII) and methyl 4-thio-β-D-arabinofuranoside (VIII), respectively. Assignment of the anomeric configurations have been made by analogy to the known methyl D-arabinofuranoside.[9] The nmr spectra of compounds VII and VIII in D_2O show the anomeric proton as a doublet centered at τ 5.01 ($J_{1,2}$ = 4.5 Hz) and 5.3 ($J_{1,2}$ = 3.8 Hz), respectively. In compound VII the H-1 and H-2 protons are *trans* to each other and hence will have a larger coupling constant, thus confirming VII as the α anomer and VIII as the β anomer.

Experimental Section

Analytical Methods.—Purity of products was determined by thin layer chromatography (tlc) with silica gel G[10] coated on 5.0 × 12.5 cm glass slides according to published procedure.[11] Components were located by spraying with 5% sulfuric acid in ethanol and heating until permanent char spots were visible. Column chromatography was carried out on silica gel.[12] Solvents (in parts by volume) were A, chloroform–acetone (9:1); B, hexane–ethyl acetate (6:1); C, benzene–ethyl acetate (10:1); D, chloroform–methanol (10:1); and E, chloroform–methanol (6:1). Melting points are corrected and were determined with a calibrated Fisher-Johns apparatus. Nuclear Magnetic resonance (nmr) spectra were obtained with a Varian Associates A-60

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(9) I. Augestad and E. Berner, *Acta Chem. Scand.*, **8**, 251 (1954).
(10) Brinkmann Instruments, Inc., Westbury, Long Island, N. Y.
(11) R. L. Whistler, M. Lamchen, and R. M. Rowell, *J. Chem. Educ.*, **43**, 28 (1966).
(12) J. T. Baker Chemical Co., Phillipsburg, N. J.

instrument. Infrared (ir) spectra were obtained with a Perkin-Elmer Model 337 spectrophotometer. Evaporations were done under reduced pressure with a bath temperature below 40°. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter.

5-*S*-Acetyl-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-thio-α-D-glucofuranose (I).—Compound I was prepared according to published directions.[5]

5-*S*-Acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (II).—Compound I (30 g) was dissolved in 750 ml of glacial acetic acid at 25° and to this solution 750 ml of water was added with stirring. The stirred mixture was heated at 70° under nitrogen for 36 hr. The reaction mixture was concentrated on a rotatory evaporator to a solid mass which was taken in 750 ml of chloroform. The chloroform solution was washed sequentially with 10% aqueous sodium chloride, dilute aqueous sodium bicarbonate, and water until the washings were neutral. The washed chloroform solution was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to dryness, whereupon the residue solidified. The solid was recrystallized by dissolving it in 100 ml of ether. To this was added 300 ml of hexane and the solution was set aside at 25° to obtain compound II as flocculent needles: yield 20 g; mp 104–105°; $[\alpha]^{25}D$ −40° (*c* 1.2, $CHCl_3$). The supernatant from the recrystallization, on being examined by tlc in solvent A, showed the presence of some more of compound II (R_f 0.34) and compound III (major component having R_f 0.24); and hence was concentrated and chromatographed over a silica gel column using solvent A as eluent, to give an additional 1.25 g of compound II. Total yield of compound II was 21.25 g (78%): ir λ_{max} (Nujol) 3450 (OH) and 1685 (S-acetyl); nmr ($CDCl_3$) τ 2.71 (s, 10, aromatic) and 7.76 (s, 3, *S*-acetyl). The nmr spectrum of compound II in $CDCl_3$ integrated for 26 protons with assignable resonances at τ 2.71 (10 H, aromatic) and 7.76 (3 H, S-acetyl), and none for the isopropylidene protons in the region of 8.5–8.7.

Anal. Calcd for $C_{22}H_{26}O_6S$: C, 63.14; H, 6.26; S, 7.65. Found: C, 62.95; H, 6.42; S, 7.45.

The fractions having R_f 0.24 were combined and concentrated to give 4 g (16.2%) of pure compound III. An analytical sample prepared by recrystallization from ether–hexane, had mp 102–103°; $[\alpha]^{25}D$ +97.5° (*c* 1, $CHCl_3$); ir λ_{max} (Nujol) 3500 (OH); nmr ($CDCl_3$) τ 2.71 (s, 10, aromatic), 5.26 and 5.56 (2 s, 4, CH_2 of benzyl).

Anal. Calcd for $C_{20}H_{24}O_5S$: C, 63.8; H, 6.4; S, 8.52. Found: C, 64.0; H, 6.30; S, 8.41.

1,2-Di-*O*-acetyl-5-*S*-acetyl-3,6-di-*O*-benzyl-5-thio-D-glucofuranose (IX).—Compound II (1.046 g) was acetylated using pyridine and acetic anhydride and the reaction mixture was worked up in the usual manner. Compound IX was recrystallized from ether–hexane as needles: mp 85–86°; $[\alpha]^{25}D$ +1.2° (*c* 1.07, $CHCl_3$); ir λ_{max} (Nujol) 1740 (O-acetyl) and 1685 (S-acetyl).

Anal. Calcd for $C_{26}H_{30}O_8S$: C, 62.13; H, 6.02; S, 6.38. Found: C, 61.96; H, 6.16; S, 6.54.

Methyl 2,5-Di-*O*-benzyl-4-thio-α- and -β-D-arabinofuranoside (V and VI).—To a stirred solution of compound II (24.4 g, 0.058 mol) in 300 ml of ethanol was added a solution of neutral sodium metaperiodate (13.65 g, 0.0638 mol) in 300 ml of water. The mixture was stirred below 30° for 30–40 min, then filtered, using a little ethanol to wash the precipitate. The filtrate was concentrated under diminished pressure at a bath temperature below 30° to remove ethanol and water. The oily residue was then taken in 500 ml of chloroform and washed twice with water to remove the inorganic salts. The washed chloroform solution was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give an almost quantitative yield of 4-*S*-acetyl-2,5-di-*O*-benzyl-4-thio-*aldehydro*-D-arabinose (IV) (22 g) which crystallized on standing. Compound IV exhibited λ_{max} (Nujol) 1730 (aldehyde) and 1685 (*S*-acetyl).

Compound IV thus obtained, was dissolved in 400 ml of 0.5% solution of hydrogen chloride in methanol. The solution was refluxed for 3 hr, after which time it was cooled in ice water and neutralized with silver carbonate. The mixture was filtered and the filtrate was concentrated. The syrupy mixture of the anomeric glycosides were readily separated by column chromatography over silica gel using solvent C as eluent. The pure components were crystallized from ether–hexane to give 9.5 g (40.7%) of methyl 2,5-di-*O*-benzyl-4-thio-α-D-arabinofuranoside (V): mp 43–45°, $[\alpha]^{25}D$ +112° (*c* 1.4, $CHCl_3$), and 11 g (52.2%) of methyl 2,5-di-*O*-benzyl-4-thio-β-D-arabinofuranoside (VI), mp 74–75°, $[\alpha]^{25}D$ −139° (*c* 1.26, $CHCl_3$). In subsequent preparations, it was possible to achieve fractional crystallization of VI by seeding a solution of the mixture in ether–hexane. The nmr ($CDCl_3$) of compound V was suggestive of α configuration: τ 2.69 (s, 10, aromatic), 5.36 and 5.50 (2 s, 4, CH_2 of benzyl), 6.72 (s, 3, CH_3O–), and 4.93 (broad s, 1, H-1).

Anal. Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.71; S, 8.90. Found: C, 66.38; H, 7.00; S, 8.84.

The nmr ($CDCl_3$) for compound VI showed τ 2.7 (s, 10 H, aromatic), 5.35 and 5.48 (2 s, H, CH_2 of benzyl), and 6.76 (s, 3, CH_3O–).

Anal. Found: C, 66.83; H, 6.86; S, 9.12.

Methyl 4-Thio-α-D-arabinofuranoside (VII).—To a stirred solution of compound V (21.6 g, 0.06 mol) in liquid ammonia (500 ml) contained in a 1-l.. three-necked flask, fitted with mechanical stirrer and Dry Ice–acetone condenser, was added 100 ml of dry 1,2-dimethoxyethane to assist the solubility of V during reduction. Freshly cut sodium was added in small pieces (about 200-mg size), one at a time, until the blue color of the solution persisted for 15 min or more. The reaction mixture was then carefully decomposed with excess solid ammonium chloride and ammonia was allowed to evaporate overnight in a current of nitrogen. Chloroform (500 ml) was added and the solution warmed to 40° to drive off the trace of dissolved ammonia, with a current of nitrogen bubbling through the solution. The reaction mixture was filtered to separate the inorganic salts and the filtrate concentrated under reduced pressure to a yellowish syrup which was chromatographically homogeneous in solvent D but contained some bibenzyl, which was removed by silica gel chromatography using solvent D as eluent. The product (10.6 g, ~100%) crystallized spontaneously upon removal of the solvent and was recrystallized from either chloroform or ethyl acetate as small needles: mp 71–72°; $[\alpha]^{25}D$ +299° (*c* 1, CH_3OH). The nmr spectrum of VII in D_2O showed the complete absence of the benzyl groups and showed the anomeric proton as a doublet centered at τ 5.01 ($J_{1,2}$ = 4.5 Hz); the methoxyl resonance occurred at τ 6.80.

Anal. Calcd for $C_6H_{12}O_4S$: C, 39.99; H, 6.71; S, 17.79. Found: C, 39.73; H, 6.88; S, 17.65.

Methyl 4-Thio-β-D-arabinofuranoside (VIII).—In a similar manner described above for the α anomer, compound VI (21.6 g, 0.06 mol) was debenzylated. The resultant syrup was chromatographed using solvent E as eluent. Pure compound VIII (10.5 g, ~100%) so obtained was recrystallized from hotc hloroform as long needles: mp 98°; $[\alpha]^{25}D$ −156° (c 1.25, CH_3OH). Again, the nmr spectrum of compound VIII in D_2O showed the absence of benzyl groups. Assignable resonance signals for the anomeric proton occurred at τ 5.3 ($J_{1,2}$ = 3.8 Hz), and for the methoxyl protons at τ 6.38.

Anal. Found: S, 17.53.

Registry No.—II, 22538-35-8; III, 22538-36-9; V, 22377-93-1; VI, 22377-94-2; VII, 22377-95-3; VIII, 22377-96-4; IX, 22554-94-5.

The Structure and Conformation of the *cis* and *trans* Isomers of 1-(*p*-Chlorobenzylidene)-2-methyl-5-methoxyindenylacetic Acid

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Received March 20, 1969

During the course of a research program on anti-inflammatory agents, 1-(*p*-chlorobenzylidene)-2-methyl-5-methoxyindenylacetic acid was synthesized in a study of indomethacin analogs.[1] The presence of

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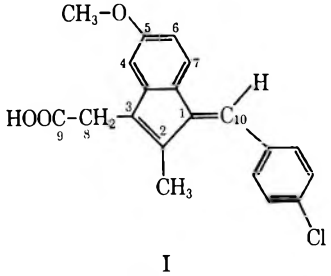
TABLE I

NUCLEAR MAGNETIC RESONANCE DATA FOR COMPOUNDS I AND II[a]

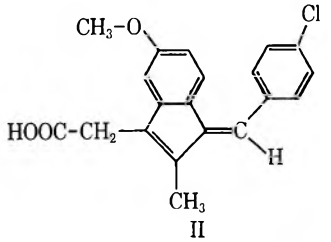
	Solvent	Protons of *p*-chlorophenyl ring	H-10	H-7, *ortho* only, J_{ortho}	H-4, *meta* only, J_{meta}	H-6, *ortho–meta*, $J_{ortho-meta}$	CH_3O	CH_2COOH	CH_3
I	$CDCl_3$	2.68	2.59	2.49 (s)	3.25 (d)	3.29 (d)	6.16	6.45	8.19
				2.63 (s)		3.43 (d)			
		UF[b]	DF[b]	DF	DF	DF	DF	UF	UF
	Acetone-d_6	2.58	2.53[c]	2.40[c] (s)	3.13	3.31 (d)	6.21	6.44	8.17
				2.48 (s)		3.43 (d)			
II	$CDCl_3$	2.60	3.00	2.71 (s)	3.27 (d)	3.55 (d)	6.22	6.42	7.85
				2.87 (s)		3.68 (d)			
	Acetone-d_6	2.52	2.93	2.78 (s)	3.20 (d)	3.56 (d)	6.26	6.43	7.83
				2.90 (s)		3.70 (d)			
Δ, chemical-shift differences, I − II	$CDCl_3$	+0.08	−0.41	0.22	−0.02	−0.26	−0.06	+0.03	+0.34
	Acetone-d_6	+0.06	−0.40	−0.38	−0.07	−0.25	−0.05	+0.01	+0.34

[a] J_{ortho} = 0.10 = 6 cps; J_{meta} = 2.4 cps. [b] UF, upfield; DF, downfield. [c] H-7 and =CH proton resonances overlapped.

a double bond between the atoms C-1 and C-10 gives rise to two isomers, one with the C-2 atom *cis* (I) and one with the C-2 atom *trans* (II) with respect to the *p*-chlorophenyl substituent.



I



II

Fractional crystallization of the final crude product synthesized according to Shen, *et al.*,[1] from a benzene solution gives crystalline material with the following physical properties: mp 168–169°; uv λ_{max} 339 mμ (ε 14,300), 288 (14,900), and 238 (21,900). On examination of the nuclear magnetic resonance spectrum of imcompletely purified material, a number of small satellite bands near the main resonances were observed, suggesting the presence of an isomeric compound. This isomer was isolated with the procedure mentioned in the Experimental Section and possessed the following physical properties: mp 186–188°; uv λ_{max} 343 mμ (ε 15,000) and 286 (25,200). The results, discussed below, obtained by nuclear magnetic resonance spectroscopy and single-crystal X-ray structure determination, show that the lower melting compound (mp 168–169°) can be identified as the *trans* isomer (II) and that the *cis* isomer (I) is the compound with the higher melting point (186–188°). The biological activity is associated with compound II, whereas compound I only shows marginal anti-inflammatory activity.

Results

The nuclear magnetic resonance data in the two solvents chloroform and acetone are presented in Table I. The assignment of the spectrum could be made on the basis of the observed chemical shifts, the relative integrated band areas, and the typical *ortho*, *ortho–meta*, and *meta* aromatic coupling patterns given by the protons at C-4, C-6, and C-7 of the indenyl substituent, while those of the *p*-chlorophenyl substituent occur as a singlet band. Compound I has protons identical in type with II and is isomerically related to it. This is supported by its elemental composition (see Experimental Section).

The magnetic anisotropy caused by the electrons in the benzene ring makes it possible to describe the relative proximity and orientation of the planes of the aromatic rings in the two isomers I and II. Protons situated in the plane of an aromatic ring are subject to paramagnetic or downfield frequency shifts, whereas protons located over the aromatic ring plane are subject to diamagnetic or upfield frequency shifts.

With these anisotropy rules in mind, it will be observed that the chemical-shift differences Δ presented in Table I are consistent with the structural and conformational assignments made in this paper for isomers I and II. Protons on the C-6, C-7, and C-10 atoms and the C-2 methyl are especially dominant in these considerations. Isomer I thus must have the *cis* configuration with its C-2 methyl over the plane of the aromatic ring of the indene system.

Since I and II are geometrical isomers, it was thought to be of interest to see if thermal and photochemical isomerization could be induced here as, for example, in the case of maleic and fumaric acids. Heating the isomer I in a *p*-dioxane solution containing some concentrated hydrochloric acid at 100° showed, on examination by uv spectroscopy at 238 and 288 mμ, that an equilibrium of *ca.* 96% II and 4% I is established in *ca.* 3–4 hr. Under these conditions, compound II reaches the same equilibrium. In methanol solution to which a small amount of iodine has been added, both I and II are isomerized to a similar equilibrium when exposed for 24 hr in quartz vessels to a quartz GE-AH5 high-pressure mercury arc lamp. Thus, II is thermodynamically the more stable isomer, and this accounts for the

fact that only a few per cent of I is formed during the synthesis of II.

An independent confirmation of the structural assignment, based on nuclear magnetic resonance data, was obtained with a single-crystal structure determination. The methyl ester of the biologically active, low-melting isomer II could be crystallized and the structure was determined with the isomorphous replacement method. Crystal data and other details are summarized in the Experimental Section.

Figure 1 shows the electron-density map representing the projection of the crystal structure along the *c* axis. All atoms are resolved and it is clear that the C-2 atoms occupy the *trans* configuration with respect to the *p*-chlorophenyl ring. Also, the molecular conformation in the crystalline state, as viewed along the axis of projection, is consistent with the nmr results in solution; the plane of the *p*-chlorophenyl ring appears approximately normal to the plane of the indene ring.

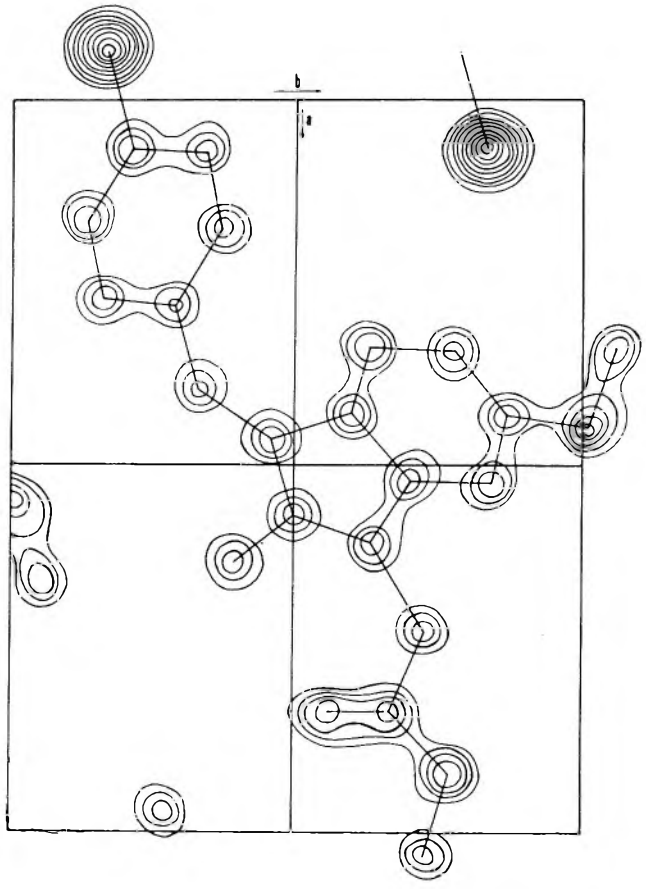


Figure 1.—Fourier synthesis of the electron-density projection along the direction of the *c* axis.

Experimental Section

All nmr data reported here were obtained with a Varian Associates Model 4300B high-resolution spectrometer equipped with a superstabilizer and a phase detector and operating at 60 Mcps. All spectra were obtained with 5–10% (w/v) solutions in deuteriochloroform or deuterioacetone placed in a spinning Wilmad precision-bore tube. The resonance positions were determined relative to benzene as an external reference and scaled by the use of side bands[2] generated by a frequency counter calibrated Hewlett–Packard audio oscillator, Model 2000 CD. The chemical shifts were calculated with the equation $t = \Delta\nu/\nu^\circ + 3.50$,[3] where $\Delta\nu$ is the observed resonance displacement from benzene in cycles per second and ν° is the spectrometer frequency in megacycles. All data in Table I are converted to internal TMS as a reference.

Isolation of I from the original mother liquor solids of II was carried out as follows. Ten grams of the total mother liquor was dissolved in 100 ml of boiling absolute ethanol, and 50 ml of hot water was added until a slight turbidity occurred. When the solution was cooled slowly to 60–70°, 320 mg of crystals were separated by hot filtration. These crystals were recrystallized in 5 ml of boiling absolute ethanol, and 2 ml of hot water was added. When the solution was cooled slowly to *ca.* 50°, 190 mg of pure I was obtained. The purity of this material was determined by uv and nmr spectroscopy and by solubility analysis, which demonstrated it to be better than 99% pure.

Anal. Calcd for $C_{20}H_{17}O_3Cl$ (mol wt 340.81): C, 70.6; H, 5.0; Cl, 10.4. Found: C, 70.72; H, 5.11; Cl, 9.93.

Initial separation of the isomers I and II from a slightly impure (*ca.* 5%) sample of II was obtained by reverse-phase partition column chromatography. The column consisted of dichlorodimethylsilane (GE Dri-Film) treated silicic acid powder as carrier containing a 1:1 chloroform–isooctane stationary phase, through which flowed a mobile phase consisting of 65:35 methanol–water. The ratio of carrier to stationary phase was 0.5 ml/g. The column bed was 25 ml in diameter and *ca.* 0.5 m long. The sample was charged by dissolving 0.06 g in 2 ml of the stationary phase and letting this flow into the top of the column bed. Isomer I occurs first behind the liquid front followed by II. The effluent is easily monitored by uv spectroscopy and observation of the ratio of the 286- to 238-mμ absorptions. Although the chromatographic bands of I and II from the above column are not widely separated, fractionation of I and II is good enough for subsequent purification of the eluted material by simple crystallization from chloroform–petroleum ether. This method is slow and tedious but seems to be the only one which works with samples of II containing only small amounts (<10%) of I.

Single crystals of the methyl ester of low-melting form II, grown from methanol, are orthorhombic, with $a = 22.12$ Å, $b = 17.36$ Å, $c = 4.71$ Å; $d_{obsd} = 1.26$ g/cm³, $d_{calcd} = 1.30$ g/cm³; space group $P_{2_12_12_1}$ (from systematic absences), four molecules of $C_{21}H_{19}O_3Cl$ per unit cell. The structure is isomorphous with the corresponding bromo derivatives. The intensities of the hko reflections, necessary for the *c*-axis projection, were determined from Weissenberg photographs by visual estimation.

After the positions of the heavy atoms were determined with Patterson syntheses, the structure was solved in the usual way and refined by difference Fourier syntheses. The final Fourier synthesis is shown in Figure 1, and the final *R* factor is 0.145. A list of coordinates and structure factors is available from the authors on request.

Registry No.—I, 22287-03-2; II, 20754-69-2.

(2) J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951).
(3) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

A New Synthetic Route to Dibenzo[*b*,*h*]biphenylene and Its 5,6,11,12-Tetramethyl and -Tetraphenyl Derivatives

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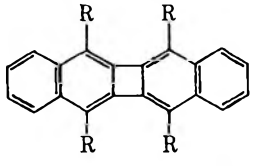
Received May 19, 1969

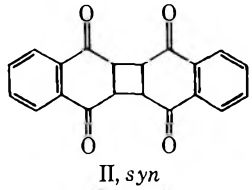
Since the first[1] successful synthesis of I (R = H) was achieved, several alternative routes[2-4] to I (R = H) and

(1) R. F. Curtiss and G. Viswanath, *Chem. Ind.* (London), 1174 (1954); *J. Chem. Soc.*, 1670 (1959).
(2) E. R. Ward and B. D. Pearson, *ibid.*, 1676 (1959).
(3) E. R. Ward and B. D. Pearson, *ibid.*, 515 (1961).
(4) J. W. Barton and S. A. Jones, *ibid.*, 1276 (1967).

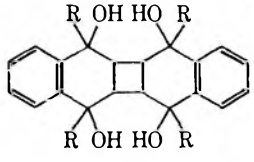
some of its derivatives[5,6] have been developed. These methods are, however, fairly laborious and mostly characterized by low overall yields.[1-3] The *syn* and *anti* photodimers[7] of 1,4-naphthoquinone, namely II and III, which are readily available and easily converted[6,7] into *lin*-binaphthylene derivatives I (R = OH, OCH_3, or $OCOCH_3$), contain carbon skeletons identical with that of I. Reduction with suitable reagents should furnish tetrahydroxy derivatives (IV, R = H, alkyl, or aryl), which should be convertible into I (R = H, alkyl, or aryl).



I



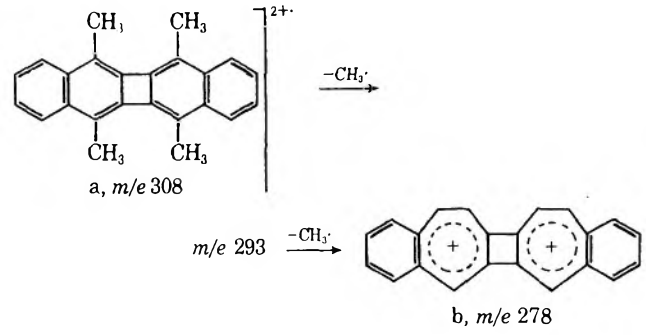
II, *syn*
III, *anti*



IV

The reaction of III with lithium aluminum hydride in tetrahydrofuran led in high yield to an amorphous, colorless product (IV, R = H) which contains no carbonilic groups and shows typical hydroxylic absorption in its infrared spectrum. Dehydration of IV (R = H), however, proceeded only under drastic conditions, leading mainly to undesired and unidentified products. Thus, with phosphoryl chloride in pyridine, the optimum yield of I (R = H) was 5%.

The reaction of III with methylmagnesium iodide, which was carried out according to a recently developed method[8] for highly insoluble substrates, proceeded smoothly, yielding crystalline IV (R = CH_3) practically quantitatively. The dehydration of IV (R = CH_3) is facilitated by the tertiary nature of the hydroxylic groups. Only one product, I (R = CH_3), which crystallized as golden yellow needles from benzene and analyzed for $C_{24}H_{20}$, was isolated in 40% yield from the reaction mixture. The relatively simple infrared spectrum displays the presence of methyl groups (2985, 2910,[9] and 1443 cm^{-1}). The characteristic olefinic absorption at 1612 cm^{-1} is probably due to the C=C stretching vibration of the localized double bonds, adjacent to the strained four-membered ring.[10,11] The ultraviolet spectrum of I (R = CH_3) corresponds to that of I (R = H),[1,2] differing only in position of the maxima, owing to a bathocromic shift caused by the methyl substituents. The mass spectrum of I (R = CH_3) is quite simple and shows, apart from the molecular ion (a, *m/e* 308), which is also the base peak, two prominent peaks at *m/e* 293 and 278, accompanied by two corresponding metastable peaks at *m/e* 279 and 264. The consecutive loss of two methyl radicals in the mass spectrometer most probably results in the formation of the dipositive ion b. To show[12] that the *m/e* 278 ion was probable di-



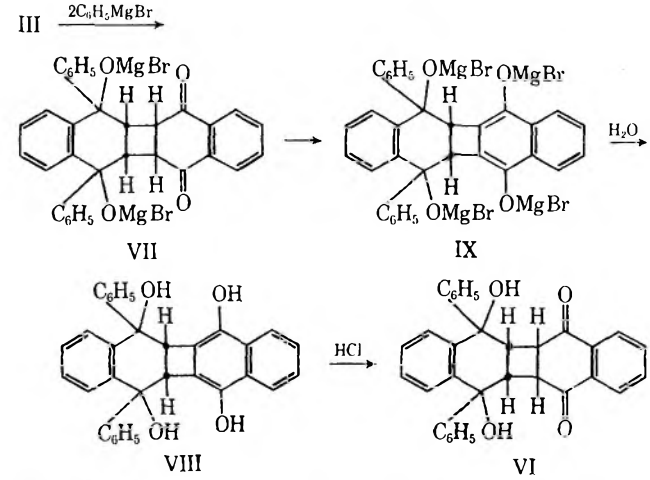
a, *m/e* 308

m/e 293

b, *m/e* 278

positive ion b, the mass spectra of 1,2-, 2,3-, and 1,4-dimethylnaphthalene were investigated. In all cases a stable benzotropilium ion (*m/e* 141) was formed, confirming the correctness of the proposed fragmentation a → b. Treatment of I (R = CH_3) with 2,4,7-trinitro-9-fluorenone led to a deep red 1:2 adduct (V), which, when chromatographed in benzene solution over alumina, afforded I (R = CH_3).

When III was treated with an excess of phenylmagnesium bromide and the reaction mixture was treated with dilute hydrochloric acid, a colorless, crystalline product, which appeared to be VI, was obtained in 61% yield, showing that two carbonyl groups of III were retained. Compound VI was recovered after further treatment with phenylmagnesium bromide. Since steric shielding of the two "unchanged" carbonyl groups in the intermediate adduct VII seemed doubtful, the above reaction was repeated, and the reaction mixture was carefully decomposed with a quantity of hydrochloric acid equivalent to the amount of Grignard reagent used. In this case a tetrahydroxylated compound, VIII, was isolated, showing that enolization of VII, followed by proton exchange, probably led to the formation of IX. The ketonization of VIII to VI,



VII IX

VIII VI

which is effected by dilute hydrochloric acid, is ascribed to the high s character of the two π bonds adjacent to

(5) C. D. Nenitzescu, M. Avram, I. G. Dinulescu, and G. Mateescu, *Ann.*, **653**, 79 (1962).

(6) J. M. Bruce, *J. Chem. Soc.*, 2782 (1962).

(7) J. Dekker, P. J. van Vuuren, and D. P. Venter, *J. Org. Chem.*, **33**, 464 (1968).

(8) J. Dekker and T. G. Dekker, *ibid.*, **33**, 2604 (1968).

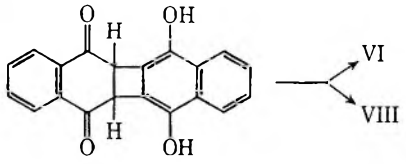
(9) The relatively high frequency of the C-H stretching vibration is ascribed to the high s character of the adjacent π bonds. This phenomenon is also encountered in the case of XV.

(10) D. P. Venter and J. Dekker, *J. Org. Chem.*, **34**, 2224 (1969).

(11) A. Streitwieser, Jr., G. R. Ziegler, P. C. Mowery, A. Lewis, and R. G. Lawler, *J. Amer. Chem. Soc.*, **90**, 1357 (1968).

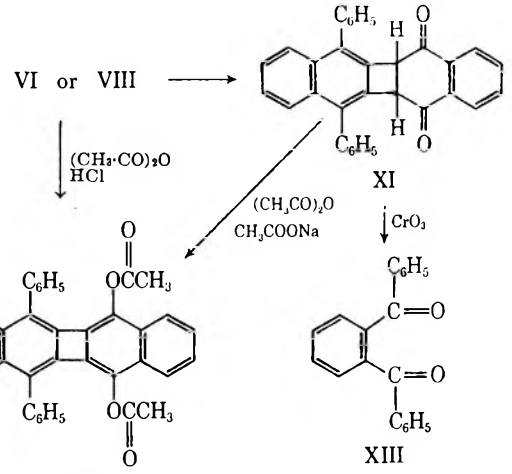
(12) P. N. Rylander, S. Meyerson, and H. M. Grubb, *ibid.*, **79**, 842 (1957); K. Biemann, "Mass Spectrometry," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 84.

the strained four-membered ring.[10,11] Compounds VI and VIII were additionally synthesized by treatment of X,[10] the partially enolized derivative of II and III, with phenylmagnesium bromide.



X

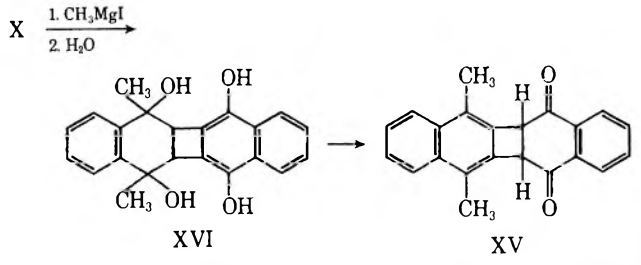
Both VI and VIII are readily dehydrated to XI. The infrared spectrum of XI illustrates typical, carbonilic absorption at 1685 cm^{-1}. The presence and position of the two carbonilic groups in XI was evidenced by the formation of the corresponding dihydrazone (XII) and oxidative degradation to *o*-dibenzoylbenzene (XIII). Acetylation of XI led to 1,4-diacetoxy-5,8-diphenyldibenzo[*b*,*h*]biphenylene (XIV). On the other hand, XIV was obtained directly simply by refluxing either VI or VIII in acetic anhydride containing a small amount of concentrated hydrochloric acid. The infrared spectrum of XIV shows strong absorption at 1205 and 1177 cm^{-1}, which is typical for phenolic acetates.[13] The spectral data obtained were consistent with the structure.



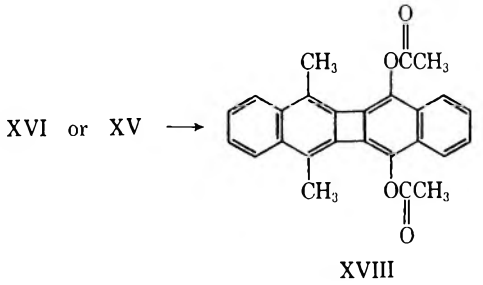
The reaction of III with phenyllithium led to an amorphous product. The latter was refluxed with acetic anhydride, whereupon three crystalline compounds, namely XIV (47% yield), 2,2′-di-1,4-naphthoquinonyl (5% yield), and an unidentified product, were obtained.

In order to obtain I (R = C_6H_5), the diketone XI was treated with excess phenylmagnesium bromide. The reaction mixture was decomposed with dilute hydrochloric acid and extracted with ether. The ether-soluble product was subsequently refluxed in a mixture of acetic anhydride and acetyl chloride, whereby orange-yellow needles of I (R = C_6H_5) were obtained in 28% yield.

The synthesis of the diketone XV was accomplished simply by treating X with methylmagnesium iodide, whereby a colorless crystalline product—which, by virtue of its typical hydroxylic absorption and the absence of carbonilic absorption in its infrared spectrum, was characterized as XVI—was obtained in 70% yield. Dehydration of XVI produced XV in 66% yield. The spectral data obtained were consistent with the structure. The ultraviolet spectrum closely resembles that of XI, showing broad maxima at 230 and 305 mμ. Further characterization was done by conversion of XV into its dihydrazone (XVII).

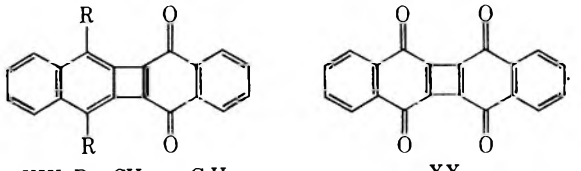


Acetylation of XV led to the formation of golden yellow needles of XVIII. The ultraviolet spectrum of XVIII resembles that of XIV, showing a small hypsochromic effect. Compound XVIII was additionally obtained by refluxing XVI in acetic anhydride containing hydrochloric acid. Furthermore, the reaction of XV with methylmagnesium iodide, followed by dehydration, led in good yield (35%) to the formation of I (R = CH_3).



XVIII

The conversion of the diketones XI and XV into the naphtho[*b*]cyclobutadiene derivatives XIX (R = CH_3 or C_6H_5) is presently being investigated in order to obtain information regarding the stabilization of the cyclobutadiene derivative XX, which we aim to synthesize eventually.



XIX, R = CH_3 or C_6H_5 XX

Experimental Section

The following instruments were used for the recording of physical properties: a Perkin-Elmer Model 221 spectrophotometer, an Unicam SP 800 spectrophotometer, a M.S.9 mass spectrometer, and a Gallenkamp (design no. 889339) melting point apparatus. Melting points are uncorrected. Owing to the low solubilities of the various compounds, no nmr spectra could be obtained.[14]

(13) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1959, p 152.

(14) After 400 scans on a saturated DMSO-d_6 solution of I (R = CH_3), weak aromatic signals (τ 2.62) were observed. The methyl bands could not be recorded because of the H_2O and d_5 impurity in the solvent. The CH_3 absorption was, however, recorded as a singlet (τ 7.38) in a single scan with CS_2 as solvent. This indicates that the methyl protons are benzylic. These spectra were recorded on a Varian HA-100 spectrometer and interpreted by Dr. Jim Feeney (Varian A. G., Klausstrasse 43, Zürich 8, Switzerland).

Dibenzo[*b*,*h*]biphenylene (I, R = H).—A suspension of III[7] (0.24 g) and $LiAlH_4$ (0.6 g) in sodium-dried THF (45 ml) was refluxed for 24 hr. The reaction mixture was concentrated to 15 ml and decomposed with 0.5 *N* hydrochloric acid. The insoluble product (IV, R = H) was filtered off and washed with water. A solution of the crude IV (R = H, 0.187 g) in pyridine (4 ml) and phosphoryl chloride (2 ml) was refluxed for 3 hr. The reaction mixture was treated carefully with water and extracted with hot benzene. The extract was washed with water, dried (Na_2SO_4), and chromatographed (alumina). Evaporation of the solvent yielded crystalline I (R = H, 0.01 g, 5%) as yellow plates, which sublimed at 342–345° (lit.[1] 340–345°); the infrared and ultraviolet spectra of I (R = H) were identical with the reported[1,2] spectra.

5,6,11,12-Tetramethyldibenzo[*b*,*h*]biphenylene (I, R = CH_3).

A.—A solution of III[7] (0.5 g) in an excess of methylmagnesium iodide in ether (4.1 *M*, 16 ml) was stirred magnetically in a stoppered flask for 36 hr. The clear solution was carefully treated with excess 0.5 *N* hydrochloric acid. The reaction product (IV, R = CH_3) was filtered and washed with ether. A solution of IV (R = CH_3) in a mixture of acetic anhydride (15 ml) and acetyl chloride (2 ml) was refluxed for 5 hr and cooled. Compound I (R = CH_3) separated as yellow needles. A solution of I (R = CH_3) in hot benzene was chromatographed over alumina. Golden yellow needles of I (R = CH_3, 0.198 g, 40%) crystallized from the eluate, which sublimed at 333–340°: ν_{max}^{KBr} 3060 (w), 2986 (w), 2910 (w), 1611 (w), 1590 (w), 1512 (w), 1443 (w), 945 (w), 761 (s), and 750 cm^{-1} (s); $\lambda_{max}^{CH_2Cl\cdot CH_2Cl}$ (log ϵ) 286.5 (4.93), 299.5 (5.24), 335 (4.36), 364 (3.36), 370 (3.36), 383 (3.78), and 408 mμ (3.96); λ_{sh} (log ϵ) 315 (4.42) and 344 mμ (3.99); mass spectrum *m/e* 308 (molecular ion).

Anal. Calcd for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 93.70; H, 6.55.

A dilute solution in benzene exhibits a strong blue fluorescence.

B. The 2,4,7-Trinitro-9-fluorenone Complex (V) of I (R = CH_3).—A hot suspension of I (R = CH_3, 0.31 g) in benzene (350 ml) was treated with a solution of 2,4,7-trinitro-9-fluorenone (0.7 g) in benzene (100 ml), and the clear, deep red solution was concentrated to 75 ml and cooled. Deep red needles separated, and recrystallization from benzene yielded V (0.53 g, 54.7%), mp 250–252° dec.

Anal. Calcd for $C_{50}H_{30}O_{14}N_6$: C, 63.97; H, 3.22; N, 8.95. Found: C, 63.75; H, 3.11; N, 9.01.

A solution of V (0.2 g) in benzene was chromatographed over alumina. The yellow eluate was concentrated and cooled, and yellow needles (0.045 g, 69.2%) of I (R = CH_3) separated.

5b,6,11,11a-Tetrahydro-5,6,11,12-tetrahydroxy-6,11-diphenyldibenzo[*b*,*h*]biphenylene (VIII). A. From the *anti* Dimer III.—A solution of III[7] (4 g) in an excess of phenylmagnesium bromide in ether (2.5 *M*, 80 ml) was stirred magnetically in a stoppered flask for 36 hr. The reaction mixture was treated with 0.05 *N* hydrochloric acid (100 ml). The amorphous product was filtered off, washed with ether, and recrystallized from acetone, yielding colorless crystals (VIII, 4.18 g, 70%): mp 289–291°; ν_{max}^{KBr} 3540 (s), 3380–3350 (broad, s), 1382 (m), 1310 (s), 1170 (w), 1150 (w), 1110 (ms), 1001 (ms), 998 (ms), 863 (s), 769 (sh), 760 (s), 743 (w), 729 (ms), and 708 cm^{-1} (w); mass spectrum *m/e* 472 (molecular ion).

Anal. Calcd for $C_{32}H_{24}O_4$: C, 81.33; H, 5.11. Found: C, 81.14; H, 5.03.

B. From the Diol X.—A solution of X[10] (2 g) in sodium-dried THF (200 ml) was introduced dropwise (2 hr) to a solution of phenylmagnesium bromide in ether (2.5 *M*, 40 ml). The reaction mixture was refluxed (24 hr), concentrated (50 ml), and treated with ether (20 ml) and 0.06 *N* hydrochloric acid (50 ml). The water layer was separated and extracted twice with ether (100 ml). The combined organic extract was washed successively with 5% $NaHCO_3$ and 5% $Na_2S_2O_3$ and dried (Na_2SO_4). Evaporation to dryness afforded a solid, which was triturated with ether (10 ml) and filtered off. Recrystallization from acetone yielded VIII (1.79 g, 60%), and the product was identified by ir spectroscopy and melting point.

5,12-Diketo-5,5a,5b,6,11,11a,11b,12-octahydro-6,11-dihydroxy-6,11-diphenyldibenzo[*b*,*h*]biphenylene (VI). A. From the *anti* Dimer III.—A solution of III[7] (0.3 g) in an excess of phenylmagnesium bromide in ether (2.5 *M*, 9 ml) was stirred magnetically in a stoppered flask for 24 hr. The reaction mixture was decomposed as in procedure A for I (R = CH_3). The amorphous product was recrystallized from acetone, yielding colorless crystals of VI (0.34 g, 7.54%): mp 301.5–303° (blackening commencing at 247°); ν_{max}^{KBr} 3430–3400 (broad, s), 1678 (s), 1665 (s), 1599 (s), 1443 (ms), 1325 (s), 1298 (ms), 1262 (s), 1077 (m), 1061 (ms), 1031 (ms), 800 (w), 764 (s), 752 (ms), 746 (ms), and 722 cm^{-1} (ms).

Anal. Calcd for $C_{32}H_{24}O_4$: C, 81.33; H, 5.11. Found: C, 81.74; H, 5.06.

B. From the Diol X.[10]—The reaction was carried out as in procedure B for VIII. The reaction mixture was decomposed with 0.5 *N* hydrochloric acid instead of 0.06 *N* hydrochloric acid. Recrystallization of the crude product from acetone yielded VI (2.75 g, 75.3%). The product was identified by ir spectroscopy and melting point.

C. From the Adduct VIII.—A suspension of VIII (2 g) in ether (45 ml) was treated with 0.5 *N* hydrochloric acid (40 ml), and the mixture was shaken for 20 min. The insoluble product was filtered off and recrystallized from acetone, yielding VI (1.63 g, 81.5%), and the product was identified by ir spectroscopy and melting point.

5,12-Diketo-5,5a-11b,12-tetrahydro-6,11-diphenyldibenzo[*b*,*h*]-biphenylene (XI).—Concentrated hydrochloric acid (10 ml) was added to a boiling suspension of VI or VIII (0.5 g) in ethanol (70 ml). The reaction mixture was refluxed in the dark for 5 hr and cooled. Colorless needles of XI (0.14 g, 30.5%), which was recrystallized from ethanol, separated: mp 238.5–239.5°; ν_{max}^{KBr} 1685 (s), 1593 (m), 1291 (s), 798 (w), 788 (w), 774 (s), 770 (sh), 751 (s), 731 (m), and 697 cm^{-1} (s); λ_{max}^{EtOH} (log ϵ) 229 (4.75), 236 (4.75), and 305 mμ (4.13); λ_{sh} (log ϵ) 378 mμ (2.91); mass spectrum *m/e* 436 (molecular ion).

Anal. Calcd for $C_{32}H_{20}O_2$: C, 88.05; H, 4.62. Found: C, 88.15; H, 4.66.

5,12-Diketo-5,5a,11b,12-tetrahydro-6,11-diphenyldibenzo[*b*,*h*]-biphenylenedihydrazone (XII).—A boiling solution of XI (0.2 g) in ethanol (40 ml) was treated with 80% hydrazine hydrate (2 ml). After 1 hr, colorless needles of the dihydrazone (XII, 0.178 g, 83.6%) separated. The product was filtered off and recrystallized from ethanol: mp 252–254° dec (darkening commencing at 225°); ν_{max}^{KBr} 3380 (m), 3215 (m), 1625 (w), 1584 (m), 1488 (w), 760 (sh), 750 (s), and 697 cm^{-1} (s); mass spectrum *m/e* 464 (molecular ion).

Anal. Calcd for $C_{32}H_{24}N_4$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.87; H, 5.24; N, 12.02.

Oxidative Degradation of XI to *o*-Dibenzoylbenzene (XIII).—A solution of chromium trioxide (0.5 g) in 50% acetic acid (3 ml) was added to a solution of XI (0.2 g) in acetic acid (3 ml). The reaction mixture was refluxed (5 hr), cooled, and treated with excess water (200 ml). The precipitate was filtered off, washed with water, and recrystallized from ether, yielding XIII (0.11 g, 90%): mp 148° (lit.[15] mp 148°). The infrared spectrum was identical with that of an authentic sample of XIII.

5,12-Diacetoxy-6,11-diphenyldibenzo[*b*,*h*]biphenylene (XIV). A. From the Adducts VI and VIII.—A solution of VI or VIII (0.234 g) in acetic anhydride (5 ml) and concentrated hydrochloric acid (0.5 ml) was refluxed for 3 hr. The solution was concentrated (2 ml), whereupon yellow needles separated. Recrystallization from benzene yielded bright yellow needles of XIV (0.18 g, 83.3%): mp 318.5–321° (darkening commencing at 270°); ν_{max}^{KBr} 1784 (s), 1628 (w), 1514 (m), 1491 (m), 1382 (m), 1355 (s), 1205 (s), 1175 (s), 1100 (m), 783 (sh), 773 (s), 761 (sh), 751 (s), 748 (sh), and 717 cm^{-1} (m); $\lambda_{max}^{CH_2Cl\cdot CH_2Cl}$ (log ϵ) 302.5 (5.06), 338 (4.28), 385 (3.60), and 409 mμ (3.75); λ_{sh} (log ϵ) 290 (4.79), 364 (3.49), 370 (3.35), and 400 mμ (2.95); mass spectrum *m/e* 520 (molecular ion).

Anal. Calcd for $C_{36}H_{24}O_4$: C, 83.06; H, 4.65. Found: C, 83.15; H, 4.69.

B. From the Diketone XI.—A mixture of XI (0.3 g), acetic anhydride (15 ml), and anhydrous sodium acetate (0.3 g) was refluxed for 8 hr and cooled. The crystalline product was filtered off, washed successively with acetic acid and water, dried, and recrystallized from benzene, yielding XIV (0.29 g, 81.3%), and the product was identified by ir spectroscopy and melting point.

The Reaction of the *anti* Dimer III with Phenyllithium.—A solution of III[7] (0.5 g) in an excess of phenyllithium in ether (1.7 *M*, 18 ml) was stirred magnetically in a stoppered flask for 36 hr. The reaction mixture was carefully treated with 0.5 *N* hydrochloric acid (40 ml), and the precipitate was filtered off and washed with water. A solution of the crude product (0.33 g) in acetic anhydride (15 ml) was refluxed for 3 hr and cooled. From the cooled solution two crystalline products, namely 2,2′-

(15) H. Simonis and P. Remmert, *Chem. Ber.*, **48**, 208 (1915).

di-1,4-naphthoquinonyl (0.025 g, 5%) and an unidentified, colorless product (0.026 g, mp >350°), which was separated by fractional crystallization from benzene, were obtained. The mother liquor was concentrated to 5 ml, whereupon yellow needles of XIV (0.163 g, 47.2%) were obtained. Products were identified by ir spectroscopy and melting point.

5,6,11,12-Tetraphenyldibenzo[*b*,*h*]biphenylene (I, R = C_6H_5).—A solution of XI (0.5 g) in an excess of phenylmagnesium bromide in ether (2.5 *M*, 20 ml) was stirred magnetically in a stoppered flask for 24 hr. The reaction mixture was decomposed with 0.5 *N* hydrochloric acid (60 ml) and extracted with ether (50 ml). The extract was washed successively with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated to 2 ml. Acetic anhydride was added and the solution was concentrated to 5 ml. Phosphoryl chloride (0.5 ml) was added and the reaction mixture was refluxed for 4 hr and cooled. Orange-yellow crystals of I (R = C_6H_5, 0.19 g, 29.8%) separated: mp >350° (lit.[5] mp >350°); the ir and uv spectra are identical with the reported[5] spectra.

The Reaction of the Diol X with Methylmagnesium Iodide.—A solution of X[10] (2.047 g) in sodium-dried THF (200 ml) was added over a period of 2 hr to a solution of methylmagnesium iodide in ether (4.1 *M*, 40 ml). The reaction mixture was treated as in procedure B for VIII. Recrystallization of the crude product from ether yielded XVI (1.58 g, 70.1%): mp 298–301° (darkening commencing at 260°); ν_{max}^{KBr} 3450–3350 (s), 1654 (m), 1646 (m), 1387 (ms), 1310 (s), 1173 (s), 1090 (ms), 1049 (ms), 1025 (ms), 993 (s), 950 (ms), 765 (s), 760 (s), 755 (s), 740 (ms), and 702 cm^{-1} (m).

5,12-Diketo-5,5a,11b,12-tetrahydro-6,11-dimethyldibenzo[*b*,*h*]biphenylene (XV).—Concentrated hydrochloric acid (15 ml) was added to a boiling solution of XVI (1.05 g) in ethanol (100 ml). The reaction mixture was refluxed for 3 hr. Yellow crystals started separating after 20 min. Recrystallization from ethanol yielded XV (0.63 g, 66.6%): mp 221–223°; ν_{max}^{KBr} 1685 (sh), 1679 (s), 1625 (w), 1590 (m), 1292 (s), 1230 (s), 920 (s), 790 (ms), 768 (sh), 753 (s), 722 (s), and 705 cm^{-1} (w); λ_{max}^{EtOH} (log ϵ) 237.5 (4.67), 281 (3.89), and 292 mμ (3.89); mass spectrum *m/e* 312 (molecular ion).

Anal. Calcd for $C_{22}H_{16}O_2$: C, 84.59; H, 5.16. Found: C, 84.75; H, 5.13.

5,12-Diketo-5,5a,11b,12-tetrahydro-6,11-dimethyldibenzo[*b*,*h*]biphenylenedihydrazone (XVII).—A mixture of XV (0.066 g), ethanol (70 ml), and 80% hydrazine hydrate (1 ml) was treated as in the procedure for XII. The colorless product was recrystallized from ethanol, yielding XVII (0.066 g, 92.3%): mp 286–287° (darkening commencing at 275°); ν_{max}^{KBr} 3325 (s), 3192 (ms), 1625 (w), 1391 (w), 791 (m), 770 (s), 748 (s), 730 (m), 720 (m), and 708 cm^{-1} (m); mass spectrum *m/e* 340 (molecular ion).

Anal. Calcd for $C_{22}H_{20}N_4$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.32; H, 5.85; N, 16.36.

5,12-Diacetoxy-6,11-dimethyldibenzo[*b*,*h*]biphenylene (XVIII).

A. From the Diketone XV.—A mixture of XV (0.5 g), acetic anhydride (15 ml), and anhydrous sodium acetate (0.2 g) was treated as in procedure B for XIV. The golden yellow needles were recrystallized from benzene, yielding XVIII (0.51 g, 81.5%): sublimed with melting at 302–305°; ν_{max}^{KBr} 1755 (s), 1383 (m), 1346 (m), 1215 (s), 1188 (m), 1159 (ms), 1090 (m), 1059 (m), 792 (w), 760 (s), 755 (s), and 727 cm^{-1} (w); $\lambda_{max}^{CH_2Cl-CH_2Cl}$ (log ϵ) 264 (4.14), 286 (4.88), 298.5 (5.22), 334 (4.38), 364 (3.37), 283 (3.62), and 408 mμ (3.80); λ_{sh} (log ϵ) 316 mμ (4.39); mass spectrum *m/e* 396 (molecular ion).

Anal. Calcd for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09. Found: C, 78.86; H, 5.16.

B. From the Adduct XVI.—A solution of XVI (0.5 g) in acetic anhydride (15 ml) and concentrated hydrochloric acid (2 ml) was treated as in procedure A for XIV. The golden yellow crystals were recrystallized from benzene, yielding XVIII (0.21 g, 36.6%), and the product was identified by ir spectroscopy and melting point.

5,6,11,12-Tetramethyldibenzo[*b*,*h*]biphenylene (I, R = CH_3) from the Diketone XV.—A solution of XV (0.5 g) in an excess of methylmagnesium iodide in ether (4.1 *M*, 12 ml) was treated as in procedure A for I (R = CH_3). A solution of the resulting product in acetic anhydride (5 ml) and acetyl chloride (0.5 ml) was refluxed for 5 hr and cooled. Compound I (R = CH_3, 0.173 g, 35%) separated as yellow needles, and the product was identified by ir spectroscopy and melting point.

Registry No.—I (R = H), 258-47-9; I (R = CH_3), 22286-70-0; V, 22319-39-7; VI, 22286-71-1; VIII, 22286-72-2; XI, 22286-73-3; XII, 22286-65-3; XIV, 22319-40-0; XV, 22319-41-1; XVI, 22286-66-4; XVII, 22286-67-5; XVIII, 22286-68-6.

Acknowledgment.—The authors are indebted to the Council for Scientific and Industrial Research of South Africa for financial support and for a postgraduate grant to N. P. du P. A grant by the Industrial Development Corporation of South Africa Ltd., to N. P. du P. is gratefully acknowledged.

Oxidative Acylation. A New Reaction of Primary Nitro Compounds

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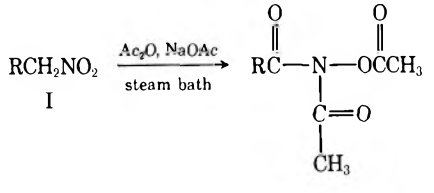
Received June 3, 1969

In the course of structure proof of miserotoxin,[2] we discovered a new reaction of primary nitro compounds which is exemplified by the following reaction scheme.



II

a, R = CH_2CH_3
b, R = CH_3

Thus, to 100 ml of acetic anhydride was added 22.3 g of Ia and 10.0 g of fused sodium acetate. The mixture was heated on a steam bath for 8 hr, during which time it became emerald green in color. The solution was then shaken with a chloroform–water mixture, sodium carbonate was carefully added to the aqueous layer, the mixture was again shaken, and the layers were separated. The chloroform layer was washed with water and dried over sodium sulfate, and the chloroform was removed by distillation. The remaining oil was distilled *in vacuo* and 29.8 g (70%) of IIa (bp 64–65° at 1 mm) was collected. The structure of IIa was chiefly assigned by the data below and also in analogy with the preparation of IIb, a previously known compound whose structure was proven[3] chemically.

Anal. Calcd for $C_7H_{11}NO_4$ (IIa): C, 48.55; H, 6.36; N, 8.08. Found: C, 48.53; H, 6.63; N, 7.90. The following spectral data were obtained: ir 1800 (strong, –CONOCO–), 1720–1710 cm^{-1} (strong, broad, –CONRCO–); nmr (parts per million from TMS) 1.11 (triplet, 3 H, CH_3CH_2), 2.68 (quartet, 2 H, CH_3CH_2), 2.28 (singlet, 3 H, $CH_3C{=}O$), 2.38 (singlet, 3 H, $CH_3C{=}$

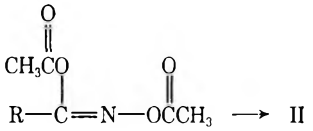
(1) National Aeronautics and Space Administration Predoctoral Fellow.
(2) F. R. Stermitz, F. A. Norris, and M. C. Williams, *J. Amer. Chem. Soc.*, **91**, 4599 (1969).
(3) T. Urbanski, *J. Chem. Soc.*, 3374 (1949).

O); mass spectrum (*m/e*, rel intensity) 173, 1 (M^+), 57, 60 ($CH_3CH_2CO^+$), 43, 100 (CH_3CO^+), no other peaks above 2% relative intensity.

Treatment of Ib in the same manner yielded IIb, corresponding in properties to IIb prepared[3] by Urbanski. A similar derivative was prepared in high yield from miserotoxin.[2]

The key to high yield preparation of II compounds (which can be considered as N-acyloxyimides or triacylhydroxylamines) is the use of steam-bath heat rather than reflux, as used by Urbanski.[3] Thus, Urbanski isolated only IIb as the main product, no matter what R was present in I. Indeed, we found that, if the reaction mixture is heated to reflux, a self-sustaining exothermic reaction takes place which results in complete conversion of all II compounds into IIb. The II derivatives are excellent for mass spectral studies since the $RC{=}O^+$ fragment is readily formed and this provides a handle for interpretation.

The mechanism of this reaction is obviously complex and must involve several steps. The clearest step of the reaction is likely to be the last one, which is probably a 1,3-acyl migration from III. At the present



III

there is no way of choosing between several ways[3] of arriving at III. However, elucidation of the mechanism may well have a bearing on a known rearrangement[4] of cyclic nitro ketones.

Registry No.—IIa, 22427-07-2.

(4) H. O. Larson and E. K. W. Wat, *J. Amer. Chem. Soc.*, **85**, 827 (1963); A. Hassner and J. Larkin, *ibid.*, **85**, 2181 (1963).

Photochemical Synthesis of Aromatic Chloro Compounds from Aromatic Iodo Compounds[1]

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Received July 7, 1969

The photodecomposition of aromatic iodo compounds has long been known, but only recently has this process been used for synthetic purposes. Thus, photolysis of aromatic iodides has led to syntheses of biphenyls, phenanthrenes, and organophosphorus and organoboron compounds, all in acceptable yields.[3]

Aromatic iodo compounds are now readily accessible from a wide variety of aromatic hydrocarbons through initial thallation with thallic trifluoroacetate followed by treatment with aqueous potassium iodide,[4] and we were therefore interested in exploring further their potential as synthetic intermediates.

We have found that irradiation of dilute solutions of aromatic iodo compounds in carbon tetrachloride with 3000-Å light leads to formation of the corresponding chloro compounds. Replacement of an iodo substituent by chlorine using iodine monochloride as the chlorine donor is known to take place on irradiation with visible light,[5] but the only reported use of carbon tetrachloride as a chlorine donor is in the formation of 4-chlorobiphenyl from 4-iodobiphenyl.[6] Exchange of chlorine for iodine takes place cleanly without contamination by positional isomers. In most cases irradiation for 5 hr was sufficient to effect a 70–75% conversion into the chloro compound, although actual yields were higher because of recovery of unchanged starting material. Longer reaction times were avoided because of possible complications involving reactions with the iodine liberated in the course of the photolysis. Within a given period of time, percentage conversion of the aromatic iodide into the corresponding chloride was (compared with iodobenzene) greater for compounds with electron-donating substituents; the electron-withdrawing carboxyl group, for example, considerably slowed the reaction[7] and substantial amounts of unreacted *o*-iodobenzoic acid could be recovered.

Representative results are summarized in Table I.

TABLE I
PHOTOLYSIS OF AROMATIC IODO COMPOUNDS IN CARBON TETRACHLORIDE

Substrate	% yield of corresponding chloro compound[a]
Iodobenzene	76[b]
2-Iodotoluene	60
2-Iodoanisole	78
4-Iodoanisole	96
2-Iodophenol	80
1,4-Dimethyl-2-iodobenzene	75
2-Iodophenylacetic acid	81
3-(4-Iodophenyl)butanoic acid	78
4-(4-Iodophenyl)butanoic acid	87
3-(4-Iodophenyl)propanoic acid	76
2-Iodobenzoic acid	51

[a] Based on recovered starting material and determined by glpc. Identity of products was confirmed by melting point, spectral analysis, and/or chromatographic means. [b] Irradiated for 8 hr.

In accordance with the generally accepted mechanism for photodecomposition of iodo compounds, we suggest the following reaction scheme to account for our results.

$$ArI \longrightarrow Ar\cdot + I\cdot$$
$$Ar\cdot + CCl_4 \longrightarrow ArCl + \cdot CCl_3$$
$$2I\cdot \longrightarrow I_2$$
$$2\cdot CCl_3 \longrightarrow C_2Cl_6$$

Hexachloroethane could be isolated from the photolyses in yields up to 5%, in agreement with the above suggested reaction pathway.

Irradiation of 2-iodotoluene and 1,4-dimethyl-2-iodobenzene gave, in addition to the product of halogen

(1) We gratefully acknowledge partial financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.

(2) NRCC Postdoctoral Fellow, 1968–1970.

(3) For a review, see R. K. Sharma and N. Kharasch, *Angew. Chem.*, **80**, 69 (1968); *Angew. Chem. Intern. Ed. Engl.*, **7**, 36 (1968).

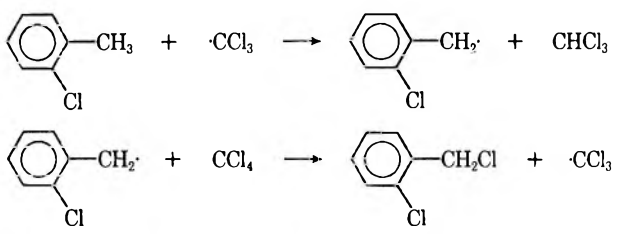
(4) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2427 (1969).

(5) B. Milligan, R. L. Bradow, J. E. Rose, H. E. Hubbert, and A. Roe, *J. Amer. Chem. Soc.*, **84**, 158 (1962).

(6) N. Kharasch, R. K. Sharma, and M. Hussain, unpublished results; see ref 60 in ref 3.

(7) W. Wolf and N. Kharasch, *J. Org. Chem.*, **30**, 2493 (1965).

exchange, α,2-dichlorotoluene (7.5%) and α,2-dichloro-1,4-dimethylbenzene (10%), respectively. These latter compounds must arise by a secondary process which is depicted below.



Irradiation of 4-iodoaniline in carbon tetrachloride gave only traces of the corresponding chloro compound; the nature of the dark, insoluble material which was formed was not investigated further.

We suggest that this photochemical conversion of aromatic iodo into aromatic chloro compounds may prove to be of synthetic value because of the mild reaction conditions employed and the effectiveness of the halogen exchange.

Experimental Section

Photochemical Reactor.—A Rayonet photochemical reactor (The Southern New England Ultraviolet Co.) equipped with 16 3000-Å lamps was used. The reactions were carried out in a 30 × 5 cm quartz tube at room temperature (the temperature rose slowly during the time of reaction to 45°).

Gas Chromatography.—An Aerograph A90-P3 instrument with a 30 ft × 3/8 in. column with 30% QF-1 on 45–60 Chrom W was employed.

General Procedure.—The iodo compound (1 g) was dissolved in 500 ml of carbon tetrachloride and the solution irradiated for 5 hr. The violet solution was then evaporated *in vacuo*, the residue dissolved in ether (100 ml), and the ether solution extracted once with 20 ml of a 5% sodium bisulfite solution. The ether layer was dried over anhydrous sodium sulfate and evaporated. The chloro compounds were isolated by crystallization from hexane (in the case of solids), or their presence and purity quantitatively determined by gas chromatography (in the case of liquids). The crude acids (see Table I) obtained after evaporation of the ether solution were methylated with diazomethane prior to gas chromatography.

Syntheses of Some Haloalkyl Methyl Ethers[1a]

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Received July 14, 1969

The absence of reports of the preparation of several simple haloalkyl methyl ethers probably stems, in part, from tendencies toward elimination and/or participation inherent in the ethers and/or in intermediates in the syntheses of these ethers. We report here syntheses of several haloalkyl methyl ethers, which were needed in our studies of halogen participation.[2] In the case of the preparations of four of the ethers, our results are reported because they differ significantly from those reported in the literature.

In our work, various attempts to prepare 2-chloro-1-propyl methyl ether by methylating 2-chloro-1-propanol failed, presumably because the nucleophilicity of the alcohol is decreased by the inductive effect of the chlorine. A yield of 53% was finally obtained from the reaction of 1-methoxy-2-propanol with thionyl chloride. The reported[3] 13% yield of 2-bromo-1-propyl methyl ether from the reaction of 1-methoxy-2-propanol with phosphorous tribromide was reproducible. Modifying the procedure by distilling the product directly as it is formed, under vacuum, improved this yield to 58%. 2-Iodo-1-propyl methyl ether was prepared (86% yield, with 14% recovery of starting material) from 2-bromo-1-propyl methyl ether and sodium iodide in refluxing acetone. Attempted preparation of the compound from the reaction of 2-tosyloxy-1-propyl methyl ether with sodium iodide in acetone unaccountably failed.

A 35% yield of 3-chloro-1-butyl methyl ether from 3-chloro-1-butanol was obtained *via* reaction of the benzenesulfonate of the alcohol with sodium methoxide in methanol. Only 4% 3-bromo-1-butyl methyl ether was formed from 1,3-dibromobutane and methanolic sodium methoxide. (A 35% yield of 3-bromo-1-butyl methyl ether from the reaction of propene with bromomethyl methyl ether has been reported.)[4]

4-Chloro-1-pentyl methyl ether was prepared without difficulty in 76% yield from 4-chloro-1-bromopentane and sodium methoxide in methanol. The analogous reaction of dibromopentane was twice[5,6] reported to proceed with about 50% yield of 4-bromo-1-pentyl methyl ether. In our hands the reaction was less successful. Five variations of conditions were tried, some more than once. In all cases a mixture of isomers, 4-bromo-1-pentyl and 5-bromo-2-pentyl methyl ethers, was obtained. Yields of this mixture ranged from 3 to 28%. The proportion of 4-bromo-1-pentyl methyl ether in the mixture also depended upon conditions, ranging from about 50 to 92%. Pure 4-bromo-1-pentyl methyl ether was obtained from the mixture by selective reaction of 5-bromo-2-pentyl methyl ether with sodium iodide in acetone.

The halogenation of 5-methoxy-1-pentene led to a mixture of dihalopentyl methyl ethers (Scheme I), which could not be separated by preparative gas chromatography because of decomposition during the runs. High-speed spinning-band distillation using a Teflon band was employed in the separation of 1,5-dichloro-2-pentyl methyl ether from its isomer, 4,5-dichloro-1-pentyl methyl ether. This procedure failed in the case of the bromine analogs because they both decomposed upon heating. Since 4,5-dibromo-1-pentyl methyl ether decomposed more slowly than the isomer, it was possible to isolate this *vic*-dibromide. The distribution of products in the two halogenations seems to indicate that participation is more important in the chlorination than in the bromination (Scheme II). The results obtained in these halogenations are similar to those reported[7] for the iodination of 4-penten-1-ol in

(1) (a) We gratefully acknowledge partial support of the research and partial support of the purchase of a Varian HA-100D nmr spectrometer by the National Science Foundation through Grants GP-6638 and GP-8510, respectively; (b) NDEA Fellow, 1966–1969.

(2) P. E. Peterson and F. J. Slama, *J. Amer. Chem. Soc.*, **90**, 6516 (1968).

(3) R. L. Jacobs and R. D. Schuetz, *J. Org. Chem.*, **26**, 3472 (1961).

(4) S. Mamedov and M. R. Kulibekov, *Zh. Obshch. Khim.*, **27**, 1499 (1957); *Chem. Abstr.*, **52**, 3750a (1958).

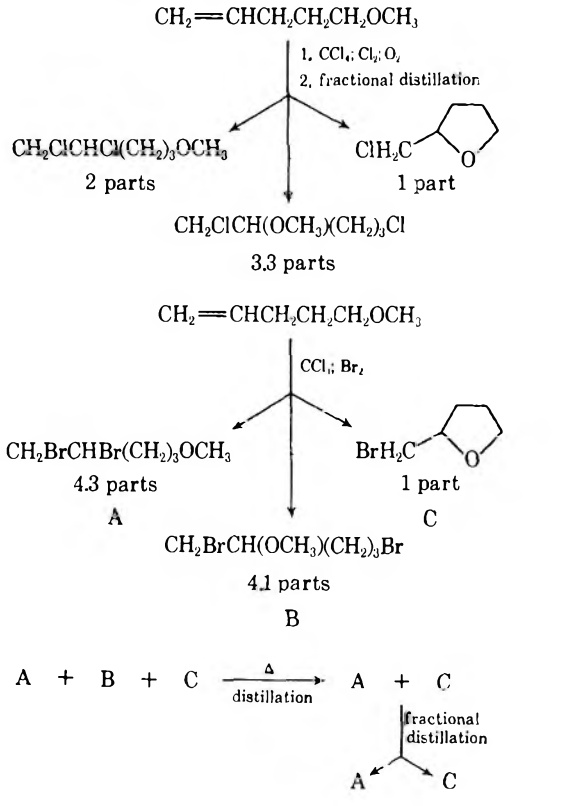
(5) S. Oae, *J. Amer. Chem. Soc.*, **78**, 4030 (1956).

(6) L. Wartski, *Bull. Soc. Chim. Fr.*, 3066 (1965); *Chem. Abstr.*, **64**, 1945c (1966).

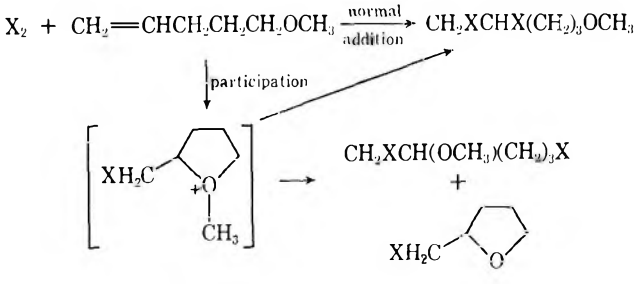
(7) D. L. H. Williams, *Tetrahedron Lett.*, 2001 (1967).

SCHEME I

SYNTHESES OF DIHALOPENTYL METHYL ETHERS



SCHEME II



aqueous acetone to produce some 2-iodomethyltetrahydrofuran. The preparation of 4,5-dibromo-1-pentyl methyl ether in 80% yield by the method of Scheme I has been reported,[8] with no mention of isomeric products. Identification of the isomers by their nmr spectra, taken in two solvents, was unequivocal.

Experimental Section

Distillations and Analyses.—Distillations were performed on platinum spinning-band columns, except as noted. Analyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark.

2-Chloro-1-propyl Methyl Ether.—Thionyl chloride (71.4 g, 0.60 mol) was added dropwise to 1-methoxy-2-propanol (54 g, 0.60 mol) and pyridine (50.4 g, 0.60 mol) in an ice-cooled flask. The flask was then heated to 120° for 1 hr. Distillation afforded 29.5 g (53%) of 2-chloro-1-propyl methyl ether: bp 98° (1 atm); nmr (CCl_4) δ 1.46 (d, 3, CCH_3), 3.32 (s, 3, OCH_3), 3.2–3.6 (m, 2, CH_2), and 3.8–4.1 (m, 1, CH).

Anal. Calcd for C_4H_9OCl: C, 44.25; H, 8.36. Found: C, 44.45; H, 8.51.

2-Bromo-1-propyl Methyl Ether.—Phosphorus tribromide (136 g, 0.5 mol) was added slowly to prechilled 1-methoxy-2-propanol (90.0 g, 1.0 mol) and kept at −10° until the initial exothermic process was completed. The flask was placed on a distilling column in a 100° bath. The distillate, collected immediately at a pressure of 62 Torr, was washed with 10% sodium bicarbonate and with saturated sodium chloride. Redistillation afforded 92 g (58%) of 2-bromo-1-propyl methyl ether: bp 62° (79 Torr); nmr (CCl_4) δ 3.3 (s, 3, CH_3O), 1.64 (d, 3, CH_3C), 3.4–3.7 (m, 2, CH_2), and 4.0–4.5 (m, 1, CH).

2-Iodo-1-propyl Methyl Ether.—Sodium iodide (40 g, 0.276 mol), reagent grade acetone (60 ml), and 2-bromo-1-propyl methyl ether (20.0 g, 0.122 mol) were refluxed for 48 hr. Solids were precipitated with ether. Distillation afforded 14% of the starting bromide and 21.1 g (86%) of 2-iodo-1-propyl methyl ether: bp 67° (54 Torr); nmr (CCl_4) δ 1.84 (d, 3, CH_3C), 3.2–3.7 (multiplet and singlet, 5, CH_2 and CH_3O), and 3.9–4.6 (m, 1, CH).

Anal. Calcd for C_4H_9OI: C, 23.91; H, 4.52. Found: C, 24.05; H, 4.54.

3-Chloro-1-butyl Methyl Ether.—Pyridine (100 ml, 1.25 mol), benzenesulfonyl chloride (49.2 g, 0.28 mol) and 3-chloro-1-butanol (21.6 g, 0.20 mol, prepared by lithium aluminum hydride reduction of 3-chlorobutyric acid) were mixed for 2 hr at −5 to −10°, and then poured into 320 ml of prechilled 6 *N* hydrochloric acid. The mixture was extracted with chloroform and dried with magnesium sulfate. Chloroform was removed in a rotary evaporator. Methanol (100 ml) containing 0.17 mol of sodium methoxide was added dropwise and refluxed for 10 min. Filtration and distillation afforded 8.62 g (35% from the alcohol) of 3-chloro-1-butyl methyl ether: bp 65° (95 Torr); ir (CCl_4) 1105 cm^{-1} (ether); nmr (CF_3COOH) δ 1.56 (d, 3, CH_3C), 3.60 (s, 3, CH_3O), 1.8–2.5 (m, 2, $CHClCH_2$), and 3.61–4.5 (m, 3, CH_2OCH_3 and CHCl).

4-Chloro-1-pentyl Methyl Ether.—4-Chloro-1-bromopentane (0.107 mol) (prepared from 2-methyl-tetrahydrofuran *via* reaction with acetyl chloride to form 4-chloro-1-pentyl acetate,[9] which was subjected to acidic methanolysis, followed by reaction of the resulting 4-chloro-1-pentanol with phosphorus tribromide) was added to methanol (50 ml) which contained sodium methoxide (0.107 mol), refluxed 1 hr, and distilled, to afford 3.04 g of starting material (4-chloro-1-bromopentane) and 10.11 g (76%) of 4-chloro-1-pentyl methyl ether: bp 65° (32 Torr); ir 1113 cm^{-1} (ether); nmr (CCl_4) δ 1.48 (d, 3, CH_3C), 3.24 (s, 3, CH_3O), 3.25–3.4 (m, 2, CH_2OCH_3), 3.8–4.2 (m, 1, CHCl), and 1.6–1.9 (m, 4, $CH_2CH_2CH_2O$).

Anal. Calcd for $C_6H_{13}OCl$: C, 52.74; H, 9.59. Found: C, 52.75; H, 9.55.

Mixture of 4-Bromo-1-pentyl and 5-Bromo-2-pentyl Methyl Ethers.—1,4-Dibromopentane (230 g, 1.0 mol) was allowed to react for 4 days at room temperature with sodium iodide (150 g, 1.0 ml) in dry acetone (450 ml). After filtration, the acetone was removed by distillation. Methanol (220 ml) was added. Sodium methoxide (0.33 mol) in methanol (220 ml) was added dropwise to the refluxing solution over 1.5 hr. Distillation afforded 20.03 g (28%) of a mixture of 4-bromo-1-pentyl and 5-bromo-2-pentyl methyl ethers bp [69–70° (22 Torr)].

Isolation of 4-Bromo-1-pentyl Methyl Ether.—A mixture (9 g, 0.05 mol) containing about 50% 4-bromo-1-pentyl methyl ether and 50% 5-bromo-2-pentyl methyl ether was dissolved in dry acetone and added to a flask containing sodium iodide (4.5 g, 0.03 mol) in acetone. After 12 hr at room temperature, filtration and distillation afforded several cuts, one of which was pure 4-bromo-1-pentyl methyl ether (1.89 g): bp 71° (22 Torr); nmr (CCl_4) δ 1.5–2.2 (7, including a doublet at 1.68), 3.1–3.5 (5, including a singlet at 3.25), and 3.8–4.4 (m, 1, CH_3CHBrC); ir 1105 cm^{-1} (ether). The ether was separable from its isomer, 5-bromo-2-pentyl methyl ether, by gas chromatography on a 150-ft DC-550 capillary column, and was shown to be 99.8 ± 0.2% isomerically pure. The highest boiling fraction (4.86 g) was impure 5-iodo-2-pentyl methyl ether: bp 78–81° (13 Torr); nmr (CCl_4) δ 1.3–2.2 (m, 4, $CH_2CH_2CH_2I$), 1.19 (d, 3, CH_3), 3.0–3.6 (6, including a singlet at 3.23).

4,5-Dichloro-1-pentyl and 1,5-Dichloro-2-pentyl Methyl Ethers.—Chlorine (17.1 g, 10.9 ml, 0.24 mol) was evaporated into a stream of oxygen and led into ice-cold carbon tetrachloride (100 ml) containing 4-methoxy-1-pentene (25.0 g, 0.25 mol). A high-speed Teflon spinning-band column was used to separate the isomers. The resulting fractions contained 17.6 g (43%) of

(8) R. Paul and O. Riobe, *C. R. Acad. Sci., Paris*, **230**, 1185 (1950); *Chem. Abstr.*, **45**, 1518*b* (1951).

(9) S. Searles, Jr., K. Pollart, and F. Block, *J. Amer. Chem. Soc.*, **79**, 952 (1957).

1,5-dichloro-2-pentyl methyl ether, 10.6 g (26%) of 4,5-dichloro-1-pentyl methyl ether, and 3.7 g (13%) of 2-chloromethyltetrahydrofuran: bp 75–77° (28 Torr) [lit.[10] 55–56° (20 Torr)]. The isomeric ethers were separable analytically on a DC-550 gas chromatographic column and were identified by their spectra.

1,5-Dichloro-2-pentyl methyl ether: bp 103° (19 Torr); nmr (CCl_4) δ 3.38 (s, 3, CH_3O), 3.2–3.6 (m, 5, $ClCH_2CH$ and $ClCH_2$), and 1.5–2.1 (m, 4, $CH_2CH_2CH_2Cl$).

Anal. Calcd for $C_6H_{12}OCl_2$: C, 42.14; H, 7.04. Found: C, 42.14; H, 7.04.

4,5-Dichloro-1-pentyl methyl ether: bp 95–100° (19 Torr); nmr (CCl_4) δ 3.27 (s, 3, CH_3O), 3.36 (t, 2, OCH_2), 1.4–2.6 (m, 4, $CH_2CH_2CH_2O$), 3.4–3.9 (m, 2, $ClCH_2$), and 3.8–4.2 (m, 1, CH).

Anal. Calcd for $C_6H_{12}OCl_2$: C, 42.14; H, 7.04. Found: C, 42.33; H, 7.05.

That 2-chloromethyltetrahydrofuran was not arising from the dichloro compounds during distillation was evidenced by its sharp disappearance from distillation fractions early in the distillation.

4,5-Dibromo-1-pentyl Methyl Ether.—5-Methoxy-1-pentene (20.0 g, 0.20 mol) and bromine (30 g, 0.187 mol) were allowed to react in carbon tetrachloride (100 ml) in subdued light. Because of the pyrolytic instability of 1,5-dibromo-2-pentyl methyl ether, the only compounds isolated in pure form by slow distillation were 2-bromomethyltetrahydrofuran, bp 60–61° (14 Torr) [lit.[10] bp 63.5–64° (17 Torr)], and 4,5-dibromo-1-pentyl methyl ether: bp 105° (7 Torr) [lit.[8,9] bp for "$CH_2BrCHBr(CH_2)_3OCH_3$," 100° (8 Torr)]; nmr (CCl_4) δ 3.9–4.3 (m, 1, CH), 3.4–3.9 (m, 2, $BrCH_2$), 3.36 (t, 2, CH_2O), 3.27 (s, 3, CH_3O), and 1.2–2.4 (m, 4, $CH_2CH_2CH_2O$).

Registry No.—2-Chloro-1-propyl methyl ether, 5390-71-6; 2-bromo-1-propyl methyl ether, 22461-48-9; 2-iodo-1-propyl methyl ether, 22461-49-0; 3-chloro-1-butyl methyl ether, 3565-66-0; 4-chloro-1-pentyl methyl ether, 22461-51-4; 4-bromo-1-pentyl methyl ether, 4457-68-5; 5-bromo-2-pentyl methyl ether, 3706-57-8; 1,5-dichloro-2-pentyl methyl ether, 22434-10-2; 4,5-dichloro-1-pentyl methyl ether, 22461-54-7.

(10) G. Eglinton, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 2873 (1952).

Stereoselective Addition of Bromine to 2-Buten-2-yl Tosylates. Formolysis of *erythro*-2,3-Dibromo-2-butyl Tosylate[1a]

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Received July 14, 1969

It is widely recognized that the electrophilic addition of bromine to olefins proceeds *via* an intermediate bromonium ion, or its equivalent, to give *trans* adducts. This cyclic intermediate was first postulated by Roberts and Kimball[2] and later observed in the nmr studies of Olah and Bollinger.[3] Olefins which can form highly stabilized cations are less prone to form bridged cations, and they may give mixtures of stereoisomeric products.[4]

Of particular interest to this study is the stereochemistry of the addition of bromine to olefins containing an sp^2-hybridized bond to an atom other than hydrogen or carbon. Lemieux has demonstrated that bromination of dihydropyran and related compounds occurs *via* a stabilized oxonium ion, and that this reaction yields significant amounts of the *cis*- as well as the *trans*-dibromide.[5] Stevens has shown that bromine-82 adds to 1-bromocyclohexene with *trans* stereospecificity.[6]

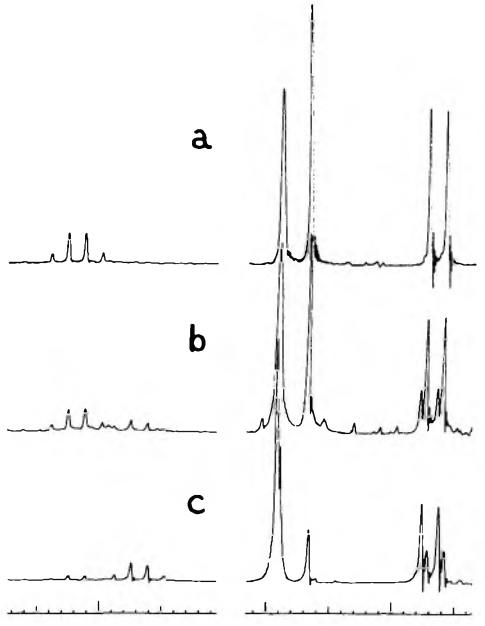


Figure 1.—Nmr spectrum (CCl_4): (a) crystallized *erythro*-2,3-dibromo-2-butyl tosylate; (b) mixture of *erythro* and *threo* diastereosmers from the addition of bromine to *trans*-2-buten-2-yl tosylate; (c) mixture of diastereosmers from the addition of bromine to the *cis* isomer.

In the present study, the stereochemistry of the addition of bromine in carbon tetrachloride to 2-buten-2-yl tosylates was determined.[7] The nmr spectra (Figure 1) of the products of the addition to the *cis* and *trans* isomers, indicate some stereoselectivity in the addition to the double bond (Scheme I). The lack of complete stereospecificity can be interpreted in terms of stabilized oxonium ions **2** and **3** which may be formed directly or from **1** and **4** in competition with attack of bromide ion. The stereochemical assignment is based on the assumption of a preponderance of *trans* addition. The products of the addition of bromine to 1-cyclohexen-1-yl tosylate proved to be so unstable that they could not be identified.

The α,β-dibromo tosylates are of some interest as solvolytic substrates which may undergo solvolysis with α- or β-bromine assistance or with both. Accordingly, the crystalline **6** was dissolved in formic acid containing sodium formate and was found to have undergone rapid formolysis to give 3-bromo-2-butanone (eq 1).

$$\mathbf{6} \xrightarrow[\text{HCOONa}]{\text{HCOOH}} CH_3CHBrC(=O)CH_3 \qquad (1)$$

Information concerning the role of β-bromine in solvolyses was available from an unpublished study of

(1) (a) We acknowledge partial support of the purchase of a Varian HA-100D nmr spectrometer through National Science Foundation Grant GP-8510. (b) NSF Graduate Trainee, 1966–1969.

(2) I. Roberts and G. E. Kimball, *J. Amer. Chem. Soc.*, **59**, 947 (1937).

(3) G. A. Olah and J. M. Bollinger, *ibid.*, **89**, 4744 (1967).

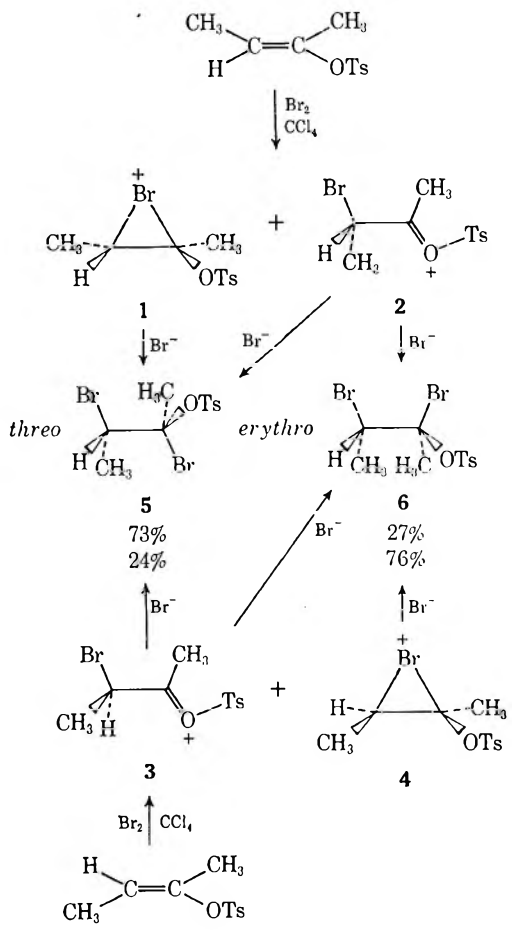
(4) (a) R. C. Fahey and H. J. Schneider, *ibid.*, **90**, 4429 (1968); (b) J. H. Rolston and K. Yates, *ibid.*, **91**, 1469 (1969); (c) J. H. Rolston and K. Yates, *ibid.*, **91**, 1477 (1969).

(5) (a) R. U. Lemieux and B. Fraser-Reid, *Can. J. Chem.*, **42**, 532 (1964); (b) R. U. Lemieux and B. Fraser-Reid, *ibid.*, **43**, 1460 (1965).

(6) C. L. Stevens and J. A. Valicenti, *J. Amer. Chem. Soc.*, **87**, 838 (1965).

(7) For the preparation and stereochemical assignments of the vinyl tosylates, see P. E. Peterson and J. M. Indelicato, *ibid.*, **90**, 6515 (1968).

SCHEME I



the formolysis of *trans*- and *cis*-2-bromocyclohexyl brosylate. In the case of the *trans* isomer where β-bromine assistance is possible, the rate of formolysis relative to that of the parent cyclohexyl brosylate was decreased by a factor of 2.8. In the case of the *cis* isomer where β-bromine assistance is impossible, the inductive effect of the bromine decreased the reaction rate by a factor of 8500.[8] On the other hand, the effect of an α-bromine in the case of the solvolysis of some benzhydryl dibromides was to speed up solvolysis.[9] Based on an estimate that the half-life for the reaction (eq 1) was less than 6 min, the solvolysis of the α,β-dibromo tosylate **6** is faster than that of 2-butyl tosylate by at least a factor of 35.[10] The cited literature suggests that both α- and β-bromine assistance occur in the formolysis of **6**.

Finally, it may be noted that the reaction of α,β-dibromo tosylates with formic acid may be of synthetic value, as it provides an alternative to a standard preparation of α-bromo ketones and aldehydes through the bromination of enol acetates.[11]

(8) (a) J. E. Duddey, Ph. D. Thesis, St. Louis University (1967). (b) These results may be compared with the acetolysis data from the literature: E. Grunwald, *J. Amer. Chem. Soc.*, **73**, 5458 (1951), and S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(9) A. Streitwieser, "Solvolytic Displacement Reactions," McGraw Hill Book Co., New York, N. Y., 1962, p 102.

(10) P. E. Peterson, R. E. Kelley Jr., R. Belloli, and K. A. Sipp, *J. Amer. Chem. Soc.*, **87**, 5169 (1965).

(11) (a) E. R. H. Jones and D. J. Wluka, *J. Chem. Soc.*, 907 (1959); (b) P. Z. Bedoukian, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 127.

Experimental Section

Infrared spectra were determined on a Beckman Model IR-5A double-beam spectrophotometer. Gas chromatographic analysis was carried out on a Hewlett–Packard Model 5750 gas chromatograph. Nmr spectra were determined on a Varian Model HA-100D spectrometer.

Addition of Bromine to 2-Buten-2-yl Tosylates.—*trans*-2-Buten-2-yl tosylate (0.0358 g, 1.585×10^{-4} mol) was dissolved in 0.5 ml of CCl_4 and cooled in an ice bath. Bromine (0.025 g, 0.1585 mmol) was added and the mixture kept cold until the nmr spectrum was taken (2–5 min; *cf.* Figure 1): nmr (CCl_4) δ 1.83 and 1.85 (2d, J = 6 Hz, $\mathbf{CH_3}$CHBr–), 2.34 and 2.46 (2s, $\mathbf{CH_3}$COTsBr–), 2.45 (s, $\mathbf{CH_3}C_6H_4$–), 4.59 and 4.34 (2q, J = 7 Hz, $CH_3\mathbf{CH}$Br–), 7.72 (m, aromatic). To show that two peaks were present at δ 4.45 and 4.46, 20% benzene was added to the solution. The $\mathbf{CH_3}C_6H_4$– peak was shifted upfield to δ 2.32 and the $\mathbf{CH_3}$COTsBr– peak shifted upfield only to δ 2.43. The spectrum remained constant in the proportions of isomers after 36 hr at room temperature, indicating no interconversion of isomers. The addition to the *cis* isomer was carried out in a similar manner. The nmr spectrum showed that the minor component from the previously described addition reaction was now the predominant isomer present.

Isolation Experiment.—The *trans* isomer (0.0026 mol) was brominated. The solution was washed with distilled water and saturated NaCl solution and dried ($MgSO_4$). Removal of the solvent on a rotary evaporator yielded 91% of a mixture of diastereomers. Several crystallizations from hexane gave *erythro*-2,3-dibromo-2-butyl tosylate: mp 77.9–79.8; nmr (CCl_4) δ 1.83 (d, 3, J = 6 Hz, $\mathbf{CH_3}$CHBr–), 2.34 (s, 3, $\mathbf{CH_3}$COTsBr–), 2.45 (s, 3, $\mathbf{CH_3}C_6H_4$–), 4.59 (q, 1, J = 7 Hz, $CH_3\mathbf{CH}$Br–), 7.52 (m, 4, aromatic).

Anal. Calcd for $C_{11}H_{14}Br_2O_3S$: C, 34.22; H, 3.65. Found: C, 34.22; H, 3.65.

Formolysis of *erythro*-2,3-Dibromo-2-butyl Tosylate.—To a weighed quantity of dibromobutyl tosylate formic acid (0.125 M in sodium formate) was added to form a solution 0.1 M in tosylate. The tosylate was slow to dissolve, but did so after 10 min. At that time, nmr indicated that no starting material was present. The solution was neutralized with $NaHCO_3$ and extracted with CCl_4. The sole product of the reaction was identified by ir and nmr to be 3-bromo-2-butanone.

In a similar experiment, glpc of the reaction mixture, employing a base forecolumn,[12] indicated quantitative conversion into the bromo ketone.

Registry No.—Bromine, 7726-95-6; **5**, 22461-42-3; **6**, 22461-43-4.

(12) P. E. Peterson and E Tao, *J. Org. Chem.*, **29**, 2322 (1964).

Quaternary Carbons by the Alkylation of Tertiary Halides with Aluminum Alkyls. A Model for Initiation and Termination in Cationic Polymerization

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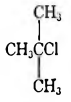
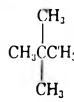
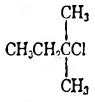
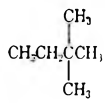
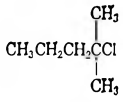
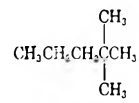
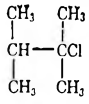
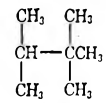
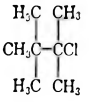
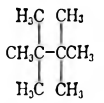
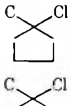
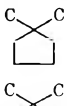
The reactions of halo hydrocarbons with aluminum alkyls have been studied previously.[1] The best report in this field is by Miller,[1] who investigated the interaction between aluminum triethyl and a variety of halogen-containing hydrocarbons in ethyl ether at room or higher temperatures. Product analysis showed medium to high conversions into a variety of products

(1) D. B. Miller, *J. Org. Chem.*, **31**, 908 (1966), and references cited therein.

TABLE I
SYNTHESIS OF QUATERNARY CARBON ATOM CONTAINING COMPOUNDS BY REACTION OF TERTIARY ALKYL CHLORIDES WITH $Al(CH_3)_3$[a]

Alkyl halide	Registry no.	Product	Solvent: Methyl chloride	Solvent: Cyclopentane
	507-20-0		*c*	No appreciable reaction for 15 min at −25°; complete reaction in less than 10 min at −21°
	594-36-5		*d*	*e*
	4325-48-8		*d*	No appreciable reaction for 4 days at −78°; complete clean reaction after 12 hr at room temperature
	4398-65-6		*d*	No appreciable reaction for 4 days at −78°; complete, clean reaction after 12 hr at room temperature
	918-07-0		*d*	Partial reaction after 24 hr at −70°
	6196-85-6		*d*	Partial reaction after 24 hr at −70°; *ca.* 1% olefin present
	931-78-2		*d*	Partial reaction after 24 hr at −70°; *ca.* 1% olefin present

[a] Molar quantities of $Al(CH_3)_3$ and RCl reacted. Product analysis by nmr. [b] Also confirmed by gc. [c] Quantative, clean reaction in less than 10 min at −78°. [d] Quantative, clean reaction at −78°. [e] Not examined.

which arose *via* a variety of reaction paths, *i.e.*, coupling, reduction, elimination (dehydrohalogenation), polymerization, etc.

In the course of our studies on the mechanism of cationic polymerizations, we carried out experiments to elucidate the polymerization–catalytic action of AlR_3–RCl initiator systems.[2,3] Aluminum trialkyls (*e.g.*, $AlMe_3$, $AlEt_3$, $AliBu_3$) in the presence of certain alkyl halides are efficient initiators for the polymerization of cationically initiable monomers, *e.g.*, isobutylene, styrene, etc.[2,3] It was observed that the introduction sequence of the reactants is of decisive importance for successful polymerization. Thus efficient polymerization commences when the introduction sequence is monomer–$AlMe_3$–RCl; however, no or very little polymer is formed when the sequence is $AlMe_3$–RCl–monomer. This initial observation was followed up experimentally to elucidate the reaction(s) between AlR_3 and various alkyl halides. This work provided important insight into the initiation and termination mechanisms of olefin polymerizations with AlR_3–RCl initiator systems and, in addition, resulted in the definition of an alkylation (coupling) reaction for the synthesis of branched hydrocarbons in general and quaternary carbon compounds in particular.

Results

Table I summarizes the results obtained with a series of tertiary chlorides and $AlMe_3$. All reactions proceeded by eq 1. Alkylation was very rapid in

$$Al(CH_3)_3 + RCl \longrightarrow Al(CH_3)_2Cl + RCH_3 \quad (1)$$

methyl chloride solvent and complete conversion into final products was obtained by the time of nmr analysis (usually less than 10 min). In cyclopentane the reactions were slower but proceeded without disturbing side reactions (*e.g.*, elimination) as well.

Table II shows the results obtained with $AlMe_3$ and various primary, secondary, allyl, and benzyl chlorides. The conversion of 1-chloroethylbenzene into cumene was complete in less than the time of nmr analysis (*ca.* 10 min). Allyl, isopropyl, and isobutyl chloride did not react at −78° during the times shown in Table II; however, the expected methylated hydrocarbons formed at a higher temperature. It should be noted that the sole product from isobutyl chloride was neopentane (*cf.* below). There was no evidence for disturbing side reactions (elimination, etc.) in any of these experiments. Benzyl chloride, which gives polybenzyl ($-C_6H_4CH_2-$) in the presence of Lewis acids,[4] gave *ca.* 20% ethylbenzene and *ca.* 80% polymer. Ethyl chloride did not react with $AlMe_3$.

Table III shows the results of a series of experiments with various aluminum trialkyls and *t*-butyl chloride. Again, the reactions proceeded rapidly and without the formation of by-products.

Experiments were also carried out to study the stoichiometry of the *t*-BuCl + $Al(CH_3)_3$ reaction by the addition of increasing amounts of *t*-BuCl to the $Al(CH_3)_3$. No complications occurred upon the addition of up to 3 mol of *t*-butyl chloride to 1 mol of $Al(CH_3)_3$ in methyl chloride solvent at −78°. Product analysis by nmr indicated the formation of stoichiometric amounts of neopentane. Further addition

(2) J. P. Kennedy in "Polymer Chemistry of Synthetic Elastomers," J. P. Kennedy and E. Tornqvist Ed., Interscience Publishers, Inc., New York, N. Y., 1968, part 1, Chapter 5A, p 291.

(3) J. P. Kennedy, Belgian Patent 663,319 (1965).

(4) J. P. Kennedy and R. B. Isaacson, *J. Macromol. Chem.*, **1**, 541 (1966).

TABLE II

SYNTHESIS OF VARIOUS HYDROCARBONS BY REACTION OF ALKYL AND ARALKYL CHLORIDES WITH $Al(CH_3)_3$ IN METHYL CHLORIDE SOLUTION[a]

Halide	Product	Remarks
$C_6H_5CH_2Cl$	$C_6H_5CH_2CH_3$[b]	*Ca.* 20% ethylbenzene formed in the temperature range of −78 to 20°; by-product polybenzyl
$C_6H_5\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCl$	$C_6H_5\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_3$[b]	Complete, clean reaction at −78°
$CH_2=CHCH_2Cl$	$CH_2=CHCH_2CH_3$	No reaction for 24 hr at −78°. Slow reaction at room temperature: *ca.* 30% conversion after 4 days, 100% conversion into 1-butene after 9 days
$(CH_3)_2CHCl$	$(CH_3)_2CHCH_3$	No reaction at −78°. Slow reaction when heated to room temperature: *ca.* 50% conversion into isobutane after 9 days
$(CH_3)_2CHCH_2Cl$	$CH_3\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_3$	No reaction for 2 hr at −78°; complete conversion into neopentane after 4 days at room temperature
CH_3CH_2Cl	...	No reaction for 2 weeks at room temperature

[a] Molar quantities reacted; product analysis by nmr. [b] Confirmed by gc.

TABLE III

SYNTHESIS OF HYDROCARBONS BY REACTION OF VARIOUS ALUMINUM TRIALKYLS WITH *t*-BUTYL CHLORIDE IN METHYL CHLORIDE SOLUTION[a]

Aluminum trialkyl	Product	Remarks
$Al(CH_3)_3$	$CH_3\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_3$	Immediate complete reaction at −78°. The $[Al(CH_3)_3]_2$/*t*-butyl chloride ratio was 0.5:1
$Al(C_2H_5)_3$	$CH_3\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2CH_3$	Immediate reaction at −78°. The $[Al(C_2H_5)_3]_2$/*t*-butyl chloride ratio was 0.5:1
$Al(i\text{-}C_4H_9)_3$	$CH_3\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_2\underset{\displaystyle CH_3}{\underset{\vert}{C}}HCH_3$	Partial reaction at −78°. The $Al(i\text{-}C_4H_9)_3$/*t*-butyl chloride ratio was 1:1

[a] Product analysis by nmr.

of *t*-butyl chloride resulted in the formation of a white precipitate, and the nmr spectra became difficult to interpret.

Discussion

The reaction represented by eq 2, where R and R′ are

$$(1/3Al)R + R^1Cl \longrightarrow RR^1 + (1/3Al)Cl \quad (2)$$

alkyl or aralkyl groups, most likely proceeds by a carbonium ion mechanism.[1] For example, the reaction between aluminum trimethyl and *t*-butyl chloride to neopentane can be visualized as follows (eq 3). The

$$AlMe_3 + t\text{-BuCl} \longrightarrow t\text{-Bu}^+ AlMe_3Cl^- \longrightarrow t\text{-BuMe} + AlMe_2Cl \quad (3)$$

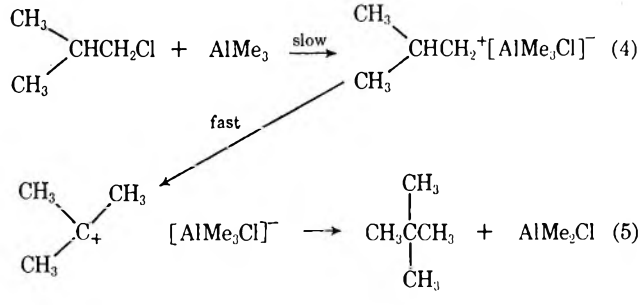
reaction is very rapid in methyl chloride solvent at −78° and it is complete before the nmr spectroscopic analysis can be performed (<10 min). The reaction in methyl chloride, the more polar solvent (ϵ *ca.* 18 at −78°), is faster than in cyclopentane. In cyclopentane the reaction is slow at −25°, but occurs rapidly at −21°. Similar observations were also made with the other tertiary chlorides, as shown in Table I.

All the reactions proceeded selectively to the quaternary carbon compound indicated. The synthesis of organic molecules with quaternary carbon atoms is quite difficult with present-day techniques. The Grignard reaction commonly used for this purpose is slow and is beset by disturbing complications, *e.g.*, elimination, reduction, etc., and therefore usually gives low yields. The reaction with aluminum alkyls and tertiary alkyl halides, particularly in inert polar solvents at low temperatures, proceeds very rapidly and selectively.

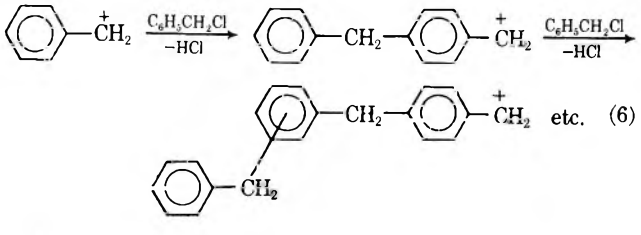
Under our conditions tertiary halides react very rapidly with aluminum trimethyl, secondary halides react much more slowly, and normal primary halides do not react at all. *E.g.*, isopropyl chloride gives

isobutane with a half-life of *ca.* 9 days at room temperature, whereas ethyl chloride remains unchanged even after 14 days at room temperature.

The isobutyl chloride experiment (*cf.* Table II) is important, as it provides insight into the reaction mechanism. Isobutyl chloride gives exclusively neopentane in a relatively slow reaction (no reaction after 2 hr at −78°, complete conversion in 4 days at room temperature). These results are interpreted by assuming a slow reaction in which the chlorine is removed by the aluminum trialkyl, followed by a fast isomerization *via* hydride shift to the more stable tertiary butyl cation, which captures a methyl group (methine anion) from the Gegen ion and gives neopentane (eq 4 and 5). Neopentane formation from isobutyl chloride strongly supports a carbonium ion mechanism.



Among the benzyl halides, 1-chloroethylbenzene gave cumene selectively and rapidly in 100% yield at −78°. Benzyl chloride produced *ca.* 20% ethylbenzene and *ca.* 80% white powdery product, polybenzyl ($-C_6H_4CH_2-$). Evidently, with benzyl chloride a competitive side reaction occurs in which benzyl cations (and/or growing benzyl cations) are consumed by ring benzylation (eq 6). The dehydrochlorination



which accompanies each benzylation step most likely gives rise to $AlMeCl_2$ (eq 7), a strong chlorine acceptor,

$$AlMe_3 \xrightarrow[-CH_4]{HCl} AlMe_2Cl \xrightarrow[-CH_4]{HCl} AlMeCl_2 \text{ etc.} \quad (7)$$

so that this reaction is probably autocatalytic for polybenzyl formation. The polyalkylation reaction of benzyl chloride to polybenzyl is a well-investigated, extremely facile reaction and proceeds with high rate even at −130°.[4,5]

With 1-chloroethylbenzene no polymer formation was observed. Apparently, in this case the repetitive alkylation of the aromatic rings with the methyl phenyl carbonium ion ($C_6H_5CH^+CH_3$) is retarded owing to steric hindrance.

Allyl chloride gave exclusively 1-butene in a relatively slow reaction. In this experiment no reaction occurred at −78°, *ca.* 30% conversion was found after 4 days at room temperature, and 100% after 9 days.

The reaction between aluminum alkyls and alkyl halides can be viewed as a model for the initiation and termination reactions in carbonium-ion polymerizations. Thus initiation of cationic polymerizations occurs by the generation of a suitable carbonium ion. The polymerization initiator is usually a Lewis acid the function of which is to help generate the first carbonium ion (or proton) by, *e.g.*, eq 8. This step is

$$RX \text{ (or HX)} + AlR_3 \rightleftharpoons R^+ \text{ (or } H^+) + AlR_3X^- \quad (8)$$

identical with the first step of the alkylation reaction discussed above. The R^+ (or H^+), in the presence of a cationically active monomer, initiates polymerization which, depending on a series of important parameters (*e.g.*, structure of the monomer, temperature, solvent, etc.), might proceed to high polymer.

In the absence of a cationically initiable monomer, the electrophile (R^+ or H^+) is stabilized by alkylation or by a variety of other processes, *e.g.*, elimination, etc. (eq 9). This reaction has been referred to in our earlier publication.[6]

$$R^+ \text{ (or } H^+) + AlR_3X^- \longrightarrow RR \text{ (or HR)} + AlR_2X \quad (9)$$

This process can be regarded as a model for the termination in carbonium-ion polymerizations initiated with AlR_3–RX systems. In these polymerizations the growing cation is converted into a high molecular weight hydrocarbon (eq 10).

$$R\sim\sim^+AlR_3X^- \longrightarrow R\sim\sim R + AlR_2X \quad (10)$$

Experimental Section

All the experiments and manipulations were performed in a stainless-steel enclosure under N_2 atmosphere (*ca.* 30 ppm moisture).[6] The aluminum alkyls (Texas Alkyls Co.) and other chemicals used were commercially available materials (K & K Laboratories or Matheson Coleman and Bell) and were freshly distilled *in vacuo* before use. 2-Chloro-2,3-dimethylbutane and 2-chloro-2,3,3-trimethylbutane were produced by hydrochlorination of the corresponding olefins by known methods. Both gas chromatography and nmr spectroscopy were used to ascertain the purity of the starting materials. Most experiments were carried out in nmr tubes. A representative experiment was performed as follows. Separate molar solutions of *t*-butyl chloride and aluminum trimethyl in methyl chloride (or cyclopentane) solvent were prepared at −78°. Into nmr tubes 2-ml aliquots of these solutions were filled and mixed at −78°. The tubes were capped, frozen in liquid N_2, and sealed. Subsequently, the temperature of the samples was brought back to −78° for nmr spectroscopy. Nmr analysis was performed as soon as feasible after sample preparation by the use of a Varian 60 nmr spectrometer. If no reaction occurred at −78°, the tubes were stored at this temperature and/or warmed to higher temperatures to effect conversion.

Selected samples were also analyzed by gas chromatography. A Perkin-Elmer 226 instrument (0.01 in. × 300 ft capillary, DC 550 silicon oil at 40°, He carries gas) and a flame ionization detector were used. In these instances the samples were prepared in test tubes, and the reactions were quenched by the introduction of an excess of cold methanol. Upon methanol treatment a voluminous while precipitate formed. Gc analysis was performed by removing aliquots of the supernatant liquid.

Registry No.—$Al(CH_3)_3$, 75-24-1; $Al(C_2H_5)_3$, 97-93-8; $Al(i\text{-}C_4H_9)_3$, 100-99-2.

(5) P. Finocciaro and R. Passerini, *Ann. Chim.* (Rome), **58**, 418 (1968).

(6) J. P. Kennedy and G. Milliman, Advances in Chemistry Series, No. 91, American Chemical Society, Washington, D. C., 1969, Chapter 18, p 287.

Acknowledgment.—The help of Dr. M. A. Melchior and F. Cassidy in the interpretation of nmr and gc spectra, respectively, is gratefully acknowledged. The advice of Dr. G. E. Milliman during the initial phase of this work was of great value. Most of the experimental operations were carried out with greatest competence by Mr. R. R. Phillips.

Direction of Cyclization of 1,2-Bis-(cyanomethyl)benzenes[1a]

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Received July 9, 1969

2-Amino-3-cyano-1H-indenes bearing a single chlorine substituent on the benzene ring were required as synthetic intermediates.[1b] A convenient route to amino nitriles of this type is the base-catalyzed Thorpe cyclization of 1,2-bis(cyanomethyl)benzenes, which has been reported for the unsubstituted parent compound, **1a**.[2] Unsymmetrically substituted dinitriles, such as 4-chloro-1,2-bis(cyanomethyl)benzene (**1b**) and 3-chloro-1,2-bis(cyanomethyl)benzene (**1c**), can each give rise to two isomeric products, depending on which cyanomethyl group undergoes anion formation most easily in the presence of base. This note describes a useful chemical method to establish the direction of cyclization of these dinitriles with complete certainty. This method, outlined in Scheme I, may be of general interest and applicability for similar systems.

Cyclization of the unsymmetrical dinitriles **1b** and **1c** afforded the corresponding cyano ketones; alkylation gave the cyano enol ethers, which were oxidized to homophthalic acids with chromic acid under mild conditions. The direction of cyclization of the dinitriles, which proved to be in accordance with predictions based on classical electronic effects, was confirmed by identification of the homophthalic acids.

Dinitriles **1b** and **1c** were prepared by bromination of 4-chloro-*o*-xylene[3] and 3-chloro-*o*-xylene, and reaction of the resulting 1,2-bis(bromomethyl) compounds with sodium cyanide in aqueous ethanol.[4] Cyclization of the dinitriles was accomplished in absolute ethanol in the presence of a catalytic amount of sodium ethoxide according to the method previously described for the cyclization of **1a**.[2] The amino group in amino nitriles **2b** and **2c** was hydrolyzed by refluxing in 6 *N* sulfuric acid for 3 hr. Treatment of the strongly enolic cyano ketones **3b** and **3c** with ethereal diazomethane yielded the corresponding enol ethers, **4b** and **4c**. All the chloro-substituted indenes prepared in this work were sharp melting and appeared to be single compounds by thin layer chromatography. Gas–liquid chromatography of the enol ethers also failed to reveal the presence of more than one component. Thus, it seemed likely that dinitriles **1b** and **1c** were both undergoing cyclization unidirectionally. Since the structures of the cyclization products could not be determined by physical methods, it was necessary to resort to chemical degradation.

Attempted ozonolysis of **3a** gave only unchanged starting material. However, gentle oxidation of ethyl enol ether **4a**[5] with 1 equiv of chromic acid gave a mixture of unreacted starting material and a product which proved to be ethyl *o*-carboxyphenylacetate (**5a**).[6] When the oxidation was carried out with 2 equiv of chromium trioxide, the product appeared to be a mixture of **5a** and another compound, which is probably the intermediate acyl cyanide shown in Scheme I. This assignment was supported by the infrared spectrum of the mixture, which contained a nitrile band at 2230 cm^{-1} and a carbonyl peak at 1780 cm^{-1}. The latter peak lies in the high wave number region characteristically ascribed to C=O functions attached directly to strong electron-attracting groups.[7] The presence of a small amount of the presumed acyl cyanide was also indicated by the nmr spectrum, which contained, in addition to the signals arising from **5a**, a minor second set of peaks displaced by only about 2 cps.

Similar oxidation of **4b** with 1 equiv of chromium trioxide, gave, in addition to some unchanged **4b**, a product whose analysis and spectra were consistent with structure **5b**. On the other hand, oxidation with 2 equiv of chromium trioxide and direct saponification of the crude product afforded a 63% yield of 4-chlorohomophthalic acid (**6b**). Since no unchanged **4b** was recovered, it was clear that the employment of 2 equiv of oxidant had resulted in a more complete reaction. The identification of **6b** was made by comparison of its infrared spectrum with that of an authentic specimen,[8] and also by mixture melting point determination. The formation of **6b** during the oxidation of **4b** established unequivocally that the Cl substituent in indenes **2b**–**4b** was attached to the 5 rather than the 6 position. Hence, the base-catalyzed cyclization of dinitrile **1b** had to proceed *via* preferential ionization of the cyanomethyl group *meta* to the Cl atom.

Oxidation of **4c** with 2 equiv of chromium trioxide gave a 48% yield of a single product identified as 6-chlorohomophthalic acid (**6c**) by comparison with an authentic sample prepared as shown in Scheme II.

(1) (a) This investigation was supported in part by Research Contract DA-49-193-MD-3008 from the U. S. Army Medical Research and Development Command, Walter Reed Army Institute of Research, and Research Career Development Award K3-CA-22,151 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. This is publication No. 656 from the Army Research Program on Malaria. (b) A. Rosowsky, A. S. Dey, J. Battaglia, and E. J. Modest, *J. Heterocycl. Chem.*, **6**, 613 (1969).

(2) (a) C. W. Moore and J. F. Thorpe, *J. Chem. Soc.*, **93**, 165 (1908); (b) W. Schroth and W. Treibs, *Ann. Chem.*, **639**, 214 (1961).

(3) D. R. Lyon, F. G. Mann, and G. H. Cookson, *J. Chem. Soc.*, 662 (1947).

(4) A. C. Cope and S. W. Fenton, *J. Amer. Chem. Soc.*, **73**, 1368 (1951).

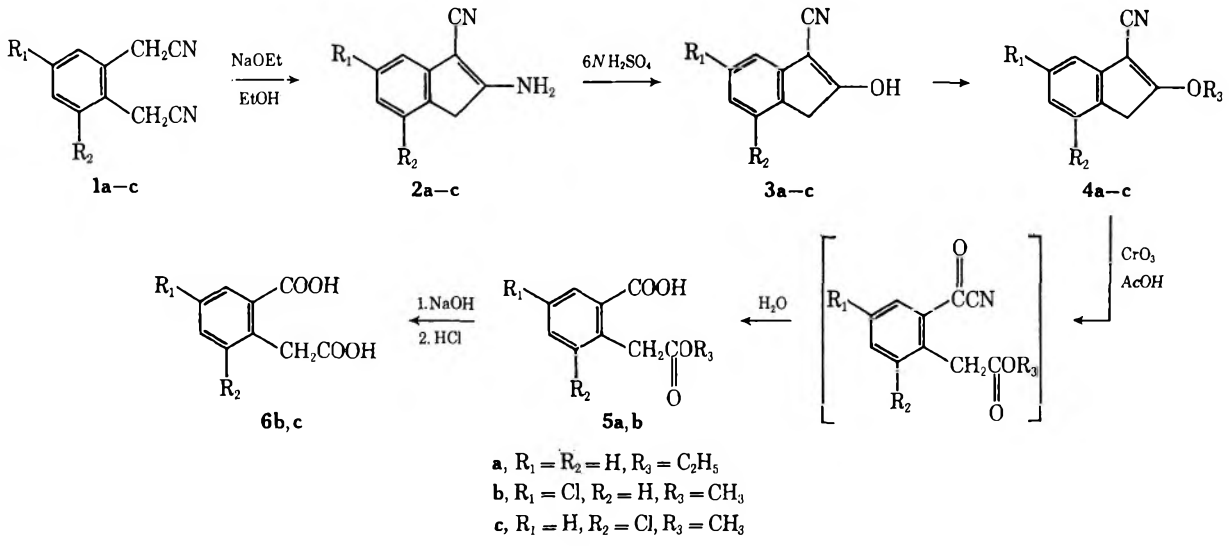
(5) Compound **4a** was prepared directly from **2a** by refluxing with ethanol in sulfuric acid as described by Moore and Thorpe.[2a]

(6) This compound has been claimed previously as the product of the reaction of *o*-carboxyphenylacetonitrile with ethanol and sulfuric acid: H. W. Johnston, C. E. Kaslow, A. Langsjoen, and R. L. Shriner, *J. Org. Chem.*, **13**, 477 (1948). The material isolated by these workers was a liquid, bp 164–169° (19 mm), whereas our product was a solid, mp 98–100° (see Experimental Section). It is probable that the material described by Johnston and coworkers was actually a mixture of at least two compounds.

(7) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958, p 125.

(8) We are very grateful to Dr. P. A. S. Smith, of the Department of Chemistry, University of Michigan, for furnishing us with a sample of 4-chlorohomophthalic acid.

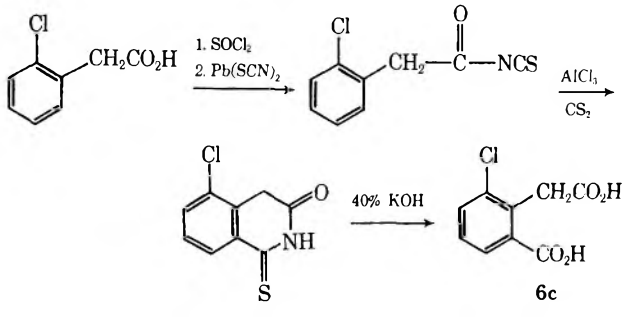
SCHEME I



a, $R_1 = R_2 = H$, $R_3 = C_2H_5$
b, $R_1 = Cl$, $R_2 = H$, $R_3 = CH_3$
c, $R_1 = H$, $R_2 = Cl$, $R_3 = CH_3$

Although several substituted homophthalic acids were prepared *via* this route by Smith and Kan,[9] **6c** was not described. The identification of **6c** as the oxidation product of **4c** proved that the cyclization of dinitrile **1c** proceeded, as in **1b**, *via* anion formation on the cyanomethyl group *meta* to the Cl atom.

SCHEME II



The present finding that dinitriles **1b** and **1c** undergo cyclization unidirectionally in the presence of base can be interpreted in terms of classical electronic effects. The Hammett constant, σ, which is considered a measure of net polar effect (inductive and resonance), is + 0.23 for *p*-Cl and +0.37 for *m*-Cl substituents.[10] Since positive σ values denote net electron withdrawal, one would predict that in **1b** the cyanomethyl group *meta* to the Cl substituent should be more acidic than the *para*-cyanomethyl group. On this basis, the expected product should be **2b**, in agreement with the experimental result. Although Hammett σ constants are not very useful in predicting the net polar effect of *ortho* substituents, the Taft σ^* constant, which is considered to reflect more accurately the combined effect of polar and steric factors, can be used for this purpose.[11] The σ^* constant for *o*-Cl (+0.20) is very similar to σ for the *p*-Cl substituent. Hence with respect to the cyclization of **1c**, one would predict that the cyanomethyl group *meta* to the Cl substituent should be more acidic than the *ortho*-cyanomethyl group and that the favored product should therefore be **2c**.

In summary, the chromic acid oxidation of enol ethers **4a–c** represents a useful method for the selective cleavage of the double bond in this type of indene derivative. The reaction is simple to perform and proceeds cleanly, gives reasonable yields of homophthalic acids, and can probably be extended successfully to other compounds of similar structure.

Experimental Section[12]

4-Chloro-1,2-bis(cyanomethyl)benzene (1b).—Bromination of 4-chloro-*o*-xylene[3] according to a standard procedure[13] gave, after repeated vacuum distillation, a 23% yield of >90% glpc-pure α,α'-dibromo-4-chloro-*o*-xylene: bp 102–106° (0.05 mm) [lit.[3] 111–127° (0.1 mm)]. The dibromide (16 g, 0.05 mol) was added fairly rapidly and with vigorous stirring to a solution of NaCN (5.9 g, 0.12 mol) in 50 ml of 50% EtOH under N_2. After being refluxed for 30 min, the mixture was cooled and poured into 300 ml of water, and the product was extracted into $CHCl_3$ (200 ml total). The combined $CHCl_3$ layers were washed with water, dried, and evaporated under reduced pressure. Crystallization of the brown residue from absolute EtOH gave 6.8 g (67%) of material melting at 77–81°. A second crystallization from aqueous ethanol gave yellow solid: mp 80–82°. Analytically pure colorless crystals were obtained upon repeated crystallization of a separate sample[14] from *i*-PrOH: mp 81°; ir (KCl) 2270 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 3.73 (singlet, $-CH_2CN$).

Anal. Calcd for $C_{10}H_7ClN_2$: C, 63.00; H, 3.70; Cl, 18.60; N, 14.70. Found: C, 62.89; H, 3.65; Cl, 18.80; N, 14.60.

(9) P. A. S. Smith and R. O. Kan, *J. Org. Chem.*, **29**, 2261 (1964).

(10) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(11) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 619.

(12) Ultraviolet spectra were measured with Cary Model 11 and Model 15 spectrophotometers. Infrared spectra were taken in potassium chloride disks with a Perkin-Elmer Model 137B double-beam recording spectrophotometer. Nmr spectra were determined in deuteriochloroform solution on a Varian A-60 instrument, with tetramethylsilane as the internal reference. Glpc analyses were performed on an F & M Model 720 instrument, using 6 ft × 1/4 in. 10% silicone rubber (SE-30) columns and helium as the carrier gas. Analytical samples were dried over Drierite at 70–100° (0.05 mm). Melting points were measured in Pyrex capillary tubes in a modified Wagner–Meyer apparatus [E. C. Wagner and J. F. Meyer, *Ind. Eng. Chem., Anal. Ed.*, **10**, 584 (1938)] at a heating rate of 2°/min, and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(13) E. F. M. Stephenson in "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, New York, N. Y., 1963, p 984.

(14) This sample of **1b** was obtained *via* an alternate, but less satisfactory, route involving ditosylation of 4-chlorobenzene-1,2-dimethanol[15,16] *via* the tosyl chloride–sodium hydride procedure,[17] and subsequent reaction of the ditosylate with sodium cyanide in dimethyl sulfoxide.

(15) J. Tirouflet, *C. R. Acad. Sci., Paris*, **238**, 2246 (1954).

(16) R. F. Bird and E. E. Turner, *J. Chem. Soc.*, 5050 (1952).

(17) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3443 (1953).

3-Chloro-1,2-bis(cyanomethyl)benzene (1c).[18]—2,3-Dimethylaniline was diazotized and treated with CuCl in the usual fashion.[3] After being heated briefly to 55°, the reaction mixture was steam distilled. The distillate, which appeared to contain a significant amount of 2,3-dimethylphenol in addition to the expected product,[19] was basified with 5% NaOH and extracted with Et_2O. The organic layer was washed several times with 5% NaOH, rinsed to neutrality, and evaporated. The combined products from two runs were purified further by repeated basic extraction and vacuum distillation until no more 2,3-dimethylphenol was detectable by glpc to yield pure 3-chloro-*o*-xylene, 51.9 g (22%), bp 93–95° (33 mm) [lit.[20] 187–190° (1 atm)]. Bromination of this material according to the procedure used with the 4-chloro isomer gave after two vacuum distillations 55.6 g (50%) of α,α'-dibromo-3-chloro-*o*-xylene, bp 105–106° (0.005 mm), mp 31.5–35° (solidifying in the receiver).

Anal. Calcd for $C_8H_7Br_2Cl$: C, 32.20; H, 2.36; Br, 53.56; Cl, 11.88. Found: C, 31.99; H, 2.36; Br, 53.83; Cl, 11.96.

The above dibromide was treated with NaCN in refluxing EtOH as described for the preparation of the 4-chloro isomer. Crystallization from EtOH afforded 18.3 g (52%) of yellow solid: mp 130–131.5°; ir (KCl) 2270 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 3.88 and 3.97 (singlets, $-CH_2CN$). The analytical sample had mp 127–129°.

Anal. Calcd for $C_{10}H_7Cl_2N$: C, 63.00; H, 3.70; Cl, 18.60; N, 14.70. Found: C, 62.91; H, 3.54; Cl, 18.62; N, 14.69.

2-Amino-5-chloro-3-cyano-1H-indene (2b).—To a solution of **1b** (9.6 g, 0.05 mol) in 30 ml of absolute EtOH at reflux was added under N_2 a solution of Na (0.1 g, 0.004 mol) in absolute EtOH (5 ml). A dense solid was formed within 2 min. After being heated an additional 5 min, the mixture was cooled and filtered, and the solid was washed with a little cold EtOH to give 5.1 g (53%) of gray-purple powder, which tended to darken upon standing. Recrystallization from 95% EtOH gave very small purplish needles: mp 250–253° dec. Further recrystallization did not improve the appearance of the product.

Anal. Calcd for $C_{10}H_7ClN_2$: C, 63.00; H, 3.70; Cl, 18.60; N, 14.70. Found: C, 63.12; H, 3.57; Cl, 18.82; N, 14.71.

2-Amino-7-chloro-3-cyano-1H-indene (2c).—A solution of **1c** (1.0 g, 0.0052 mol) in the minimum amount (9 ml) of refluxing EtOH was treated, under N_2, with a solution of Na (0.011 g, 0.00044 mol) in absolute EtOH (0.2 ml). The reaction mixture, which rapidly turned brown and then black, was refluxed for 40 min, then cooled, and filtered. Recrystallization of the crude product (0.5 g, 50%) from absolute EtOH gave small beige needles: mp 213–216° dec; ir (KCl) 2200 cm^{-1} (conjugated C≡N).

Anal. Calcd for $C_{10}H_7ClN_2$: C, 63.00; H, 3.70; Cl, 18.60; N, 14.70. Found: C, 63.30; H, 3.72; Cl, 18.75; N, 14.64.

6-Chloro-1-cyano-2-indanone (3b).—A mixture of **2b** (1.9 g, 0.01 mol), 19 ml of concentrated H_2SO_4, and 95 ml of water was refluxed with stirring for 3 hr, then cooled, diluted with 100 ml of water, and filtered. Recrystallization of the crude product (1.8 g, 94%) from aqueous EtOH gave a beige powder: mp 193–195° dec; ir (KBr) 2260 cm^{-1} (C≡N), 3500 cm^{-1} (enolic OH).

Anal. Calcd for $C_{10}H_6ClNO$: C, 62.68; H, 3.16; Cl, 18.50; N, 7.31. Found: C, 62.77; H, 3.32; Cl, 18.57; N, 7.16.

4-Chloro-1-cyano-2-indanone (3c).—A mixture of **2c** (1.6 g, 0.0082 mol), 15 ml of concentrated H_2SO_4, and 75 ml of water was stirred under reflux for 3 hr, then cooled, and filtered. Crystallization of the crude product (1.5 g, 94%) from aqueous EtOH gave a beige powder: mp 206–209° dec; ir (KCl) 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_{10}H_6ClNO$: C, 62.68; H, 3.16; Cl, 18.50; N, 7.31. Found: C, 62.51; H, 3.18; Cl, 18.34; N, 7.54.

5-Chloro-3-cyano-2-methoxy-1H-indene (4b).—A suspension of **3b** (1.9 g, 0.01 mol) in Et_2O was treated with freshly prepared ethereal CH_2N_2 until gas evolution ceased. The resulting solution was evaporated under reduced pressure, and the brown residue was crystallized from aqueous EtOH: 1.3 g (63%), mp 114–116° dec. Further recrystallization from aqueous EtOH gave yellow crystals: mp 120–122°; ir (KCl) 2240 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 4.25 (singlet, OCH_3), 3.55 (singlet, $ArCH_2$).

Anal. Calcd for $C_{11}H_8ClNO$: C, 64.24; H, 3.92; Cl, 17.24; N, 6.81. Found: C, 64.39; H, 4.05; Cl, 17.48; N, 6.54.

7-Chloro-3-cyano-2-methoxy-1H-indene (4c).—Reaction of **3c** with ethereal CH_2N_2 as described for the preparation of **4b** gave a 63% yield of beige powder. One crystallization from aqueous ethanol gave the analytical sample: mp 140–142° dec; ir (KCl) 2230 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 4.27 (singlet, OCH_3), 3.55 (singlet, $ArCH_2$).

Anal. Calcd for $C_{11}H_8ClNO$: C, 64.24; H, 3.92; Cl, 17.24; N, 6.81. Found: C, 63.91; H, 3.83; Cl, 17.33; N, 6.90.

Oxidation of 3-Cyano-2-ethoxy-1H-indene (4a). Procedure A.—To a solution of **4a**[5] (0.50 g, 0.0027 mol) in 25 ml of glacial AcOH at 50° was added a warm solution of CrO_3 (0.25 g, 0.0025 mol) in 30 ml of glacial AcOH. After being kept at 50° (internal) in a bath for 10 min and then at room temperature for 80 min, the mixture was poured into ice water. The precipitate was filtered to give 0.30 g of material, mp 72–78°, consisting mainly of starting material mixed with some oxidation product. The solid was redissolved in 25 ml of glacial AcOH and treated with additional CrO_3 (0.15 g, 0.0015 mol) in a bath at 65–70° for 1 hr. The mixture was poured into 200 ml of ice water, and a minute quantity of unchanged **4a** was filtered off. The filtrate was extracted with Et_2O, and the organic layer was washed with water, dried, and evaporated to give a yellow oil. Addition of water to the oil gave some orange solid, mp 63–69°, consisting again mainly of unchanged **4a**. However, extraction of the cloudy filtrate with Et_2O, followed by the usual work-up, gave a residue which solidified upon standing overnight at room temperature. Repeated crystallization from benzene–petroleum ether (bp 40–60°) gave yellow needles of **5a** (0.05 g, 9%): mp 98–100°; ir (KCl) 1680 cm^{-1} (acid C=O), 1730 cm^{-1} (ester C=O), 3040 cm^{-1} (associated OH); nmr ($CDCl_3$) δ 4.23 (quartet, OCH_2CH_3), 4.12 (singlet, $ArCH_2CO$), 1.27 (triplet, CH_2CH_3).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.80. Found: C, 63.68; H, 5.78.

Oxidation of 5-Chloro-3-cyano-2-methoxy-1H-indene (4b). Procedure B.—A solution of **4b** (0.5 g, 0.0024 mol) in 20 ml of glacial AcOH at 95° was treated with CrO_3 (0.25 g, 0.0025 mol). After being stirred at 95–105° (internal) for 50 min, the mixture was poured into water and extracted with Et_2O. The organic layer was washed with water, dried, and evaporated under reduced pressure to give a yellow oil which solidified under petroleum ether (bp 40–60°). The yellow, somewhat gummy solid (0.25 g), consisted of equal parts of unreacted **4b** and methyl 2-carboxy-4-chlorophenylacetate (**5b**), as shown by the nmr spectrum; pure **4b** could be recovered by recrystallization from aqueous EtOH. Dilution of the filtrate remaining after recovery of **4b** with $CHCl_3$ afforded crude **5b** and recrystallization from benzene–petroleum ether gave analytically pure orange crystals: mp 110–113°; nmr ($CDCl_3$) δ 4.10 (singlet, $ArCH_2CO$), 3.76 (singlet, OCH_3).

Anal. Calcd for $C_{10}H_9ClO_4$: C, 52.53; H, 3.96; Cl, 15.50. Found: C, 52.77; H, 3.82; Cl, 15.49.

Treatment of the original reaction product with 10% NaOH in the cold, followed by filtration to remove dark insoluble material and acidification of the filtrate with 12 *N* HCl, gave a small fraction of unreacted **4b**. However, ether extraction of the cloudy acid filtrate gave a yellow oil which crystallized slowly upon standing. The solid was suspended in $CHCl_3$ and a trace of undissolved 4-chlorohomophthalic acid (**6b**) filtered off: mp 195–198° with gas evolution (rapid heating); ir (KCl) 1710 cm^{-1} (acid C=O). The mixture melting point with authentic **6b**[8] was 196–199°.

Procedure C.—A solution of **4b** (0.56 g, 0.0027 mol) in 20 ml of glacial AcOH on the steam bath was treated with CrO_3 (0.56 g, 0.0056 mol). The mixture was kept on the steam bath, with occasional shaking, for 1 hr, then poured into 400 ml of cold water, and extracted with 100 ml of $CHCl_3$, followed by 100 ml of Et_2O. The combined organic layers were evaporated under reduced pressure, and the residue was treated with 20 ml of 10% NaOH. Some dark insoluble material was removed by filtration, and the basic filtrate was heated on the steam bath for 30 min. Acidification of the cooled solution with 12 *N* HCl gave 0.14 g (24%) of **6b**: mp 195–198° dec. Extraction of the acid filtrate with Et_2O gave an oil which crystallized partially. Washing of this solid

(18) This compound was first isolated unexpectedly when a commercial batch of "4-chloro-*o*-xylene" (K & K Laboratories, Inc., Plainview, N. Y.) was subjected to bromination and treatment with sodium cyanide in the usual manner. Fractional crystallization of the product yielded both the desired **1b** and, in addition, a substantial amount of **1c**. Analysis of the starting 4-chloro-*o*-xylene by nmr then showed clearly that this material actually contains 4-chloro- and 3-chloro-*o*-xylene in a ratio of approximately 1:1.

(19) The apparent ease of hydrolysis of this diazonium salt is noteworthy in view of the fact that the corresponding reaction of 3,4-dimethylaniline[3] proceeded without complication.

(20) A. F. Dokukina and M. M. Koton, *Zh. Obshch. Khim.*, **29**, 2201 (1959); *Chem. Abstr.*, **54**, 10905 (1960).

with $CHCl_3$ gave an additional 0.23 g (39%) of **6b**: mp 195–197° dec. The total yield obtained by this procedure was 0.37 g (63%).

Oxidation of 7-Chloro-3-cyano-2-methoxy-1H-indene (4c).—Upon being heated with CrO_3 (2 equiv) and worked up in a manner similar to the preceding experiment (procedure C), **4c** gave a 48% yield of 6-chlorohomophthalic acid (**6c**). Recrystallization from water gave colorless crystals: mp 174–176° with gas evolution; ir (KCl) 1680 cm^{-1} (aromatic COOH), 1705 cm^{-1} (aliphatic COOH). This product was identical with the authentic sample of **6c** prepared from *o*-chlorophenylacetic acid (see below) and the mixture melting point was not depressed.

Anal. Calcd for $C_9H_7ClO_4$: C, 50.36; H, 3.28. Found: C, 50.34; H, 3.01.

5-Chloro-1-thio-1,2,3,4-tetrahydro-1,3(2H,4H)-isoquinolinedione.—A mixture of *o*-chlorophenylacetyl chloride[21] (8.6 g, 0.046 mol), PbSCN (14.7 g, 0.046 mol), and 18 ml of benzene was refluxed with stirring for 5 hr, then filtered twice, and evaporated under reduced pressure. Short-path distillation of the residue gave 8.1 g (84%) of almost colorless liquid: bp 107–110° (0.25 mm); ir (KCl) 1730 cm^{-1} (C=O), 1980 cm^{-1} (broad, SC≡N). A solution of this *o*-chlorophenylacetyl isothiocyanate (8.0 g, 0.038 mol) in 10 ml of CS_2 was added dropwise to a stirred suspension of $AlCl_3$ (11.1 g, 2.2 molar equiv) in 30 ml of CS_2, while cooling in an ice bath. When addition was complete, the mixture was refluxed for 5 hr, then cooled in ice, and treated with 12 ml of 1 *N* HCl. The brown reaction product was broken up with a spatula to give a bright orange solid, which was filtered off and washed with water. Crystallization from glacial AcOH gave several crops of bright orange product (total 3.6 g, 45%): mp 247–250° dec. The analytical sample had mp 250–252° dec.

Anal. Calcd for C_9H_6ClNOS: C, 51.07; H, 2.86; N, 6.62. Found: C, 50.77; H, 2.90; N, 6.37.

6-Chlorohomophthalic Acid (6c).—5-Chloro-1-thio-1,2,3,4-tetrahydro-1,3(2H,4H)-isoquinolinedione (1.0 g, 0.0047 mol) was hydrolyzed with 40 ml of 40% KOH under reflux for 2.5 days in a flask of alkali-resistant glass. After being left at room temperature for 3 days, the mixture was refluxed an additional 6 hr, then cooled, acidified with HCl, diluted with water to dissolve the precipitated inorganic material, and extracted twice with ether. Evaporation of the dried ether extract gave 0.68 g (67%) of crude light yellow product: mp 157° with gas evolution. Crystallization from water afforded a small first crop of malodorous material probably containing sulfur. Extraction of the filtrate with ether gave light yellow material: mp 167–169° with gas evolution. Recrystallization from glacial AcOH gave pure **6c** as a white powder: mp 172–174° (gas evolution). The infrared spectra of this material and of the product obtained from the oxidation of **4c** were identical, and a mixture melting point was not depressed.

Registry No.—**1b**, 22479-38-5; **1c**, 22479-39-6; **2b**, 22479-41-0; **2c**, 22528-32-1; **3b**, 22479-42-1; **3c**, 22479-43-2; **4b**, 22479-44-3; **4c**, 22479-45-4; **5a**, 22479-46-5; **5b**, 22482-73-1; **6c**, 22482-74-2; 5-chloro-1-thio-1,2,3,4-tetrahydro-1,3(2H,4H)-isoquinolinedione, 22482-75-3; α,α'-dibromo-3-chloro-*o*-xylene, 22479-40-9.

Acknowledgments.—The laboratory assistance of Mrs. Josephine Battaglia and Mrs. Rebecca G. Stephenson is gratefully acknowledged. The authors are also indebted to Mr. Roger Cavallo and Mr. Chester Rosansky for the determination of infrared spectra.

(21) L. R. Cerecedo and C. P. Sherwin, *J. Biol. Chem.*, **58**, 215 (1923).

The Bromination of Butadiene in Methanol

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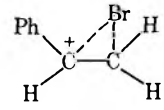
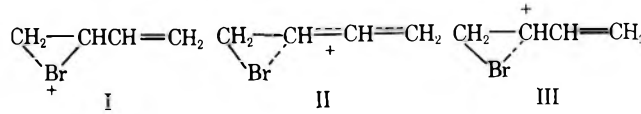
Received May 8, 1969

Recent studies[1,2] on the bromination of styrene and substituted styrenes suggest that the intermediates in these reactions are best described as unsymmetrically bridged bromonium ions with weak bonding between the bromine atom and the benzylic carbon atoms, as is illustrated below for styrene. Failure to achieve a



symmetrically bridged bromonium ion in these reactions is undoubtedly due to increased stabilization of the carbonium ion system by the phenyl ring. On the other hand, the bromonium ion involved in bromination of *cis*- and *trans*-2-butene was shown to involve symmetrical bridging.[2]

In the course of our studies on the bromination of dienes, we became interested in the nature of the bonding in the intermediates in these reactions. In the addition of bromine to butadiene, at least three charge distributions could be involved. Their structures are shown below. Intermediate I is a bromonium



ion with symmetrical bridging. Intermediate II represents the charge as highly delocalized across the bromine atom and the adjacent allylic system. Intermediate III shows the charge as essentially localized on the secondary carbonium ion. This intermediate should assume increasing importance as the polarity of the solvent becomes greater. In this regard, Rolston and Yates[2] and Buckles, Miller, and Thurmaier[3] have shown that, in the bromination of substituted styrenes and stilbenes, respectively, the charge becomes localized to form the most stable carbonium ion as the polarity of the solvent is increased.

It seemed to us that bromination in methanol might permit differentiation between these intermediates. Intermediate I should be attacked by the methanol molecule[4] at either carbon atom of the bromonium ion to give both 4-bromo-3-methoxy-1-butene (**1**) and 3-bromo-4-methoxy-1-butene (**2**). Intermediate II should lead to significant quantities of 1-bromo-4-methoxy-2-butene (**3**), presumably the *trans* isomer, by attack at the terminal carbon atom of the allylic system; **1** and perhaps some **2** would also be expected. Attack by methanol on III should give primarily **1**. All of the intermediates could give **3** by a S_N2' attack by methanol on the terminal carbon atom of the allylic system.

Formation of 3,4-dibromo-1-butene (**4**) and *trans*-1,4-dibromo-2-butene (**5**) would be expected.

Results and Discussion

The results in Table I show that, of the methoxybromides, 4-bromo-3-methoxy-1-butene (**1**) is the prin-

(1) R. C. Fahey and H. J. Schneider, *J. Amer. Chem. Soc.*, **90**, 4429 (1968).

(2) J. H. Rolston and K. Yates, *ibid.*, **91**, 1469 (1969); J. H. Rolston and K. Yates, *ibid.*, **91**, 1477 (1969); J. H. Rolston and K. Yates, *ibid.*, **91**, 1483 (1969).

(3) R. E. Buckles, J. L. Miller, and R. J. Thurmaier, *J. Org. Chem.*, **32**, 888 (1967).

(4) It is possible that the weakly nucleophilic solvent might not open this bromonium ion (*I*). In that case, the product would be exclusively the dibromides.

TABLE I
BROMINATION OF BUTADIENE IN METHANOL AT −15°

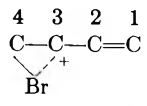
Butadiene, mole fraction	Methoxybromides, % 1	3	Ratio of 1/3	Dibromides, % 4	5	Ratio of 4/5	Yield, %
0.02	63	4.3	15	22	10	2.2	98
0.05	45	3.2	14	35	16	2.2	
0.07	34	3.9	8.7	42	20	2.1	
0.10	28	3.1	9.0	48	21	2.3	57
0.15	23	3.2	7.2	48	24	2.0	
0.20	21	2.3	9.1	51	25	2.0	
0.35	12	1.2	10	52	34	1.5	
0.50	13	1.3	10	53	33	1.6	67
0.02[a]	55	4.1	13	26	14	1.9	
0.50[a]	6.8	0.5	14	52	42	1.2	
0.02[b]	60	3.7	16	23	14	1.6	
0.50[b]	7.9	0.6	13	53	38	1.4	

[a] Oxygen was passed through the reaction solution. [b] The radical inhibitor, 2,6-di-*t*-butyl-4-methylphenol, was added to the reaction solution.

cipal product. A small amount of *trans*-1-bromo-4-methoxy-2-butene (**3**) was also formed;[5] no 3-bromo-4-methoxy-1-butene (**2**) was detected. Evidence for the absence of **2** is explained in the Experimental Section. As far as the dibromides are concerned, approximately twice as much **4** as **5** is formed under under all conditions.

Before the mechanism of these reactions can be discussed from an ionic standpoint, it is essential that the possibility of a radical pathway be eliminated. It has already been shown[6] that a 1,2 to 1,4 ratio of *ca.* 2 in the bromination and chlorination of butadiene is indicative of an ionic mechanism. From this standpoint, it seems that the addition of bromine to butadiene in methanol is following an ionic pathway at all mole fractions of butadiene. This viewpoint is supported by the fact that the radical inhibitors, oxygen and 2,6-di-*t*-butyl-4-methylphenol, did not substantially alter the ratio of **4**/**5**. However, it should be pointed out that addition of ethylbenzene, as a radical scavenger, to the reaction mixtures led to some α-bromoethylbenzene at all the mole fractions except 0.02. We have interpreted these data to mean that only at a mole fraction of 0.02 is an ionic pathway followed completely; at higher mole fractions ac ertain amount of radical reaction accompanies the principal ionic reaction. For this reason, and also because of the improved yield, all mechanistic considerations will be confined to the data which were obtained at a mole fraction of 0.02.

The almost exclusive formation of 4-bromo-3-methoxy-1-butene (**1**) over **2** or **3** seems to indicate that the intermediate involved in this reaction is best described by III, with, perhaps, slight delocalization of the charge across the allylic system. A comparison of the ratios **1**/**3** and **4**/**5** shows that the bromide ion (or tribromide ion) is much more effective at attacking position 1 (see the following structure) than is the



methanol molecule. One explanation for this observation might be that the larger bromide ion experiences severe steric hindrance when attacking at position 3 and therefore chooses position 1. Another more likely explanation involves considerations of intermediate III and the relative nucleophilic abilities of the methanol molecule and the bromide ion. In intermediate III, nucleophiles can either react with the carbonium ion at position 3 or attack position 1 by an SN2′ reaction. Since the bromide ion is a strong nucleophile, it readily reacts with position 1 by the SN2′ pathway. Methanol, on the other hand, is a weak nucleophile and reacts almost completely with the carbonium ion.

Experimental Section

Materials.—All solvents and reagents were obtained commercially in high purity unless otherwise indicated. The butadiene was Matheson Coleman and Bell instrument grade, 99.5% pure.

Bromination. General Procedure.—Liquefied butadiene was added to the determined quantity of methanol, on a balance, until the appropriate weight was obtained. The reaction solution has a magnitude of 80–100 ml. To this solution at −15°, under a nitrogen atmosphere, bromine was added dropwise until 10–20% of the butadiene had been allowed to react. The reaction product was poured into cold water (*ca.* 100 ml), sodium carbonate was added to destroy the HBr, and sufficient sodium chloride was added to saturate the solution and salt out the products. This solution was then extracted with 300–600 ml of low-boiling petroleum ether, in three portions. It was established that no rearrangement of the dibromides occurred during the reaction or isolation. It was also established that under the reaction and isolation conditions the dibromides did not solvolyze to give the methoxybromides.

All brominations were carried out in a dark room with a photographic safelight.

Procedure for Analysis of Products.—The vpc analyses of the products were accomplished with an Aerograph Model 90 P-3 chromatograph and an F & M Model 700 chromatograph. The conditions for analysis for the former instrument follow: flow rate (He), 334 ml/min; column dimensions, 6 ft × 0.25 in.; column temperature, 60°; column composition, 2.5% SE-30 on 60–80 mesh DMCS Chromosorb W. Under these conditions, the retention times of **1**, **3**, **4**, and **5** are, respectively, 45, 111, 72, and 189 sec. The conditions for analysis in the latter instrument follow: flow rate (He), 55 ml/min; column dimensions, 8 ft × 0.125 in.; column composition, identical with that given above. The retention times of **1**, **3**, **4**, and **5** are, respectively, 54, 132, 84, and 234 sec.

None of the products rearranged under the conditions of analysis. This was determined by collecting the product after it had passed through the chromatograph and observing that no change in composition had occurred on reinjection.

(5) *cis*-1-Bromo-4-methoxy-2-butene was synthesized unambiguously, and shown by vpc analysis to be absent in the bromination products.

(6) M. Poutsma [*J. Org. Chem.*, **31**, 4167 (1966)] has already discussed the variation in the ratio of 1,2 to 1,4 addition with a change in mechanism in the chlorination of butadiene. We have found that this ratio varies in nearly an identical manner in the bromination of butadiene. An article on our investigation has been accepted for publication in a forthcoming issue of this journal.

The percentages of the compounds were based on their adjusted areas in the chromatograms. The adjustments were based on the following determinations: the ratio of A_4/A_5 divided by W_4/W_5 is equal to 0.85; A_1/A_5 divided by W_1/W_5 is equal to 1.23; and A_3/A_5 divided by W_3/W_5 is equal to 1.18. The material balances were obtained by the internal-standard method using α-bromoethylbenzene. The area/weight ratio for α-bromoethylbenzene to **5** was found to be 1.30.

Identification of the Products Formed in the Bromination of Butadiene in Methanol.—The chromatogram of the product from the bromination of butadine in methanol showed four peaks. The second and fourth peaks were identified as **4** and **5**, respectively, on the basis of having retention times and ir spectra identical with those of the authentic isomers, which were synthesized according to the procedure of Hatch, *et al.*[7]

The first peak was assigned to 4-bromo-3-methoxy-1-butene (**1**) on the following basis. The bromination product was fractioned and the compound responsible for the first peak was isolated in pure form, bp 51–52° (30 mm), as indicated by vpc analysis. The compound gave the correct analysis for a bromomethoxybutene, C_5H_9BrO. *Anal.* Calcd for C_5H_9BrO: C, 36.39; H, 5.497; Br, 48.43. Found: C, 36.27; H, 5.57; Br, 48.69. The infrared spectrum[8] indicated either **1** or **2**, since it contained the hydrogen absorption band for the CH_3O group at 2810 cm^{-1} and the terminal vinyl absorption band at 928 and 985 cm^{-1}. The nmr spectrum was complex, but supported the structure of **1** or **2** by showing relative areas of three vinyl hydrogens to six methyl, methylene, and methine hydrogens. The compound was assigned the structure of 4-bromo-3-methoxy-1-butene (**1**) rather than 3-bromo-4-methoxy-1-butene (**2**) on the basis of stability. Heating the compound for 45 min at 115° gave no detectable rearrangement to *trans*-1-bromo-4-methoxy-2-butene (**3**), which would definitely be expected[9] if the compound were **2**.

trans-1-Bromo-4-methoxy-1-butene (**3**) was synthesized unambiguously, and when analyzed by vpc was found to have a retention time identical with that of the third peak. The synthesis of **3** is outlined in the following sequence.

trans-1,4-dibromo-2-butene $\xrightarrow[\text{HOAc}]{\text{KOAc}}$ *trans*-2-butene 1,4-diacetate $\xrightarrow{\text{Ba(OH)}_2}$ *trans*-2-butene 1,4-diol (bp 73–75° (0.30 mm)) $\xrightarrow{(CH_3O)_2SO_2}$ *trans*-4-methoxy-2-buten-1-ol (bp 92–97° (0.25 mm)) $\xrightarrow{PBr_3}$ *trans*-1-bromo-4-methoxy-2-butene (bp 76–79° (3.3 mm))

The infrared spectrum of each of the intermediates in the above synthetic sequence supported the proposed structure. The infrared spectrum of the synthesized **3** showed the following absorption bands:[7] 2810 (hydrogens of the CH_3O group), 965 (*trans* vinyl hydrogens, strong), and 572 and 595 cm^{-1} (CBr group). The molecular analysis corresponded to C_5H_9BrO. *Anal.* Calcd for C_5H_9BrO: C, 36.39; H, 5.497; Br, 48.43. Found: C, 36.43; H, 5.63; Br, 48.19.

(7) L. F. Hatch, P. D. Gardner, and R. E. Gilbert, *J. Amer. Chem. Soc.*, **81**, 5943 (1956).

(8) For a discussion of the position of absorption bands in the infrared, see D. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry," McGraw-Hill Publishing Co. Ltd., London, 1966.

(9) For a general discussion of the greater thermodynamic stability of 1,4- compared with 1,2-addition products from the chlorination and bromination of butadiene and isoprene, see B. T. Brooks, "The Chemistry of the Nonbenzenoid Hydrocarbons," Reinhold Publishing Corp., New York, N. Y., 1950, p 362–366. In support of our assignment of structure **1** to this compound rather than **2** on the basis of stability, we would like to indicate that, under identical conditions, **4** rearranges to **5**. Also, under nearly identical conditions, 3,4-dibromo-2-methyl-1-butene rearranges extensively. [See V. L. Heasley, C. L. Frye, R. T. Gore, Jr., and P. S. Wilday, *J. Org. Chem.*, **33**, 2342 (1968).] We also observed that, upon standing, *cis*-1-bromo-4-methoxy-2-butene slowly rearranges to *trans*-1-bromo-4-methoxy-2-butene (**3**). Only a trace of what may be 3-bromo-4-methoxy-1-butene (**2**) was detected. This definitely confirms the greater thermodynamic stability of **3** compared with **2**.

Registry No.—Butadiene, 106-99-0; *trans*-2-butene 1,4-diacetate, 1576-98-3; *trans*-2-butene-1,4-diol, 821-11-4; *trans*-4-methoxy-2-buten-1-ol, 22427-04-9; **1**, 22427-00-5; **3**, 22427-01-6.

Acknowledgment.—Acknowledgment is made to the Petroleum Research Fund, administered by the American Chemical Socieity, and to Union Oil Co., Brea, Calif., for support of this research.

Conformation of Bicyclo[3.3.1]nonane Systems. A Semiempirical Investigation

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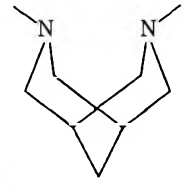
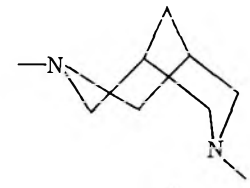
Received June 17, 1969

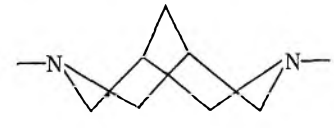
The structures of compounds belonging to the ring system bicyclo[3.3.1]nonane have been the subject of considerable interest in recent years.[1-6] Apart from various distorted structures, these species may exist in any of the following three conformations, all of which are free from bond-angle strain. In most of the cases studied thus far, the chair–chair structure with various degrees of distortion seem to be favored. Thus Brown,



chair–chair

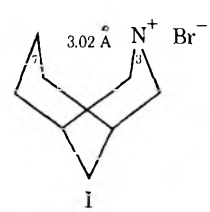


boat–chair

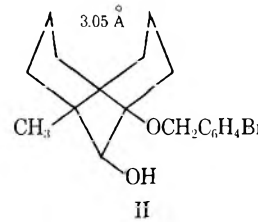


boat–boat

et al.,[2] and Dobler, *et al.*,[3] by their X-ray crystallographic studies, proved the chair–chair structures for compounds I and II with C_3–C_7 and N_3–C_7 distances of 3.05 and 3.02 Å, respectively. Douglass and Ratliff[1]



I



II

synthesized N,N′-dimethylbispidine and, based on dipole moment and nmr studies, tentatively assigned a flattened chair–chair structure for this compound.

(1) J. E. Douglass and T. B. Ratliff, *J. Org. Chem.*, **33**, 355 (1968).
(2) W. A. C. Brown, J. Martin, and G. A. Sim, *J. Chem. Soc.*, 1844 (1965).
(3) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta.*, **47**, 695 (1964).
(4) C.-Y. Chen and R. J. W. LeFevre, *J. Chem. Soc., B*, 539 (1966).
(5) H. S. Aaron, C. P. Ferguson, and C. P. Rader, *J. Amer. Chem. Soc.*, **89**, 1431 (1967).
(6) N. W. J. Pumphrey and M. J. T. Robinson, *Chem. Ind.* (London), 1903 (1963).

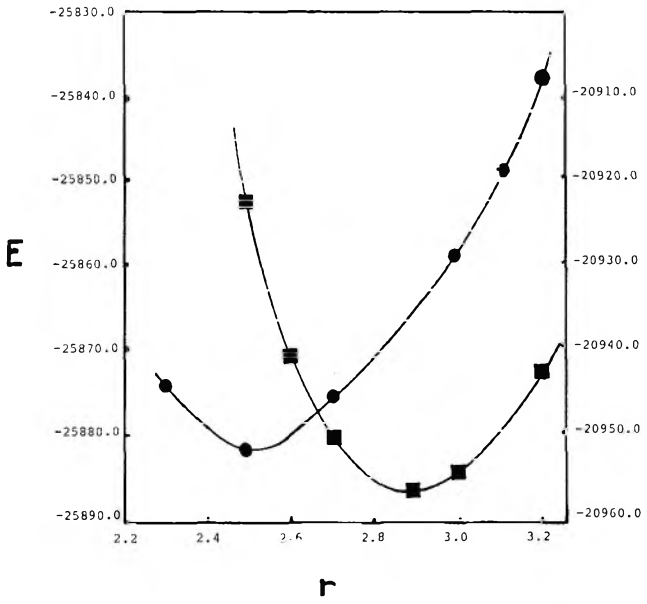


Figure 1.—Total energy calculated by the EHT method as a function of the distance between atoms in positions 3 and 7: ■, 3-azabicyclo[3.3.1]nonane; ●, N,N′-dimethylbispidine.

Unfortunately, however, the measured dipole moment does not unequivocally rule out the possibility of the chair–boat structure for this compound. We, therefore, carried out LCAO–MO calculations in order to throw some light on the structure of this compound.

Methods of Calculations. Extended Hückel MO Method.—The method is that developed by Hoffmann.[7] Calculations were made on an IBM 7040 computer using QCPE Program No. 30. Values of valence-state ionization potentials used in this calculation have been reported in the literature.[8,9]

CNDO/2 Method.—This method, developed by Pople and Segal,[10] is an LCAO–SCF method. Calculations were made on an IBM 7040 computer using QCPE Program No. 91, the output of which consists of total energy, charge densities, dipole moments calculated from charge densities, and dipole moments calculated from the effective charge densities taking into account the symmetries of the individual orbitals.

The C–C and C–H distances were assumed to be the same as those in cyclohexane and C–N distances were considered to be the same as C–C distances.

Results and Discussion

Hoffmann[7] used the extended Hückel method for obtaining the most probable conformation in several hydrocarbons. Here we applied this method for the bicyclo[3.3.1]nonane system. X-Ray data are available for compounds I and II. Of these two compounds, I has a nitrogen atom in position 3. We, therefore, decided to carry out calculations on this compound for its chair–chair conformation with various degrees of distortion. The energy values of this molecule and N,N′-dimethylbispidine for their chair–chair conformation were calculated in which the distance r between atoms in positions 3 and 7 was varied. The results are given in Figure 1. It is clear from this figure that the minimum energy value for compound I is obtained at an r value of 2.9 Å.

On the other hand, for N,N′-dimethylbispidine the minimum energy was obtained at an r value of 2.5 Å, which is the N–N distance in a normal chair–chair form. The main difference between N,N′-dimethylbispidine and compound I is the absence of *endo* hydrogen atoms in the former. It is, therefore, reasonable to expect less strain in the normal form of this compound than in the latter. Similar calculations on the chair–boat and boat–boat forms yielded higher energy values (Table I).

TABLE I
TOTAL ORBITAL ENERGY DIFFERENCES AND CALCULATED DIPOLE MOMENTS FOR VARIOUS CONFORMATIONS OF N,N′-DIMETHYLBISPIDINE

	——E, kcal——		——Dipole moment, D——	
Conformation	EHT	CNDO/2	Calcd[a]	Found
Chair–chair	0	0	2.2	...
Chair–boat	20.6	18.0	1.7	2.0 ± 0.2
Boat–boat	45.4	24.9	3.56	...

[a] Calculated complete dipole moment by CNDO/2 method. From ref 1.

The CNDO/2 method gives reliable dipole-moment data and relative conformations at fixed input bond lengths.[11–13] For large molecules, the calculations, even in a high-speed digital computer, are prohibitively time consuming. Hence we decided to carry out calculations only on the normal chair–chair, chair–boat, and boat–boat structures. The energy values and dipole moments for these structures are given in Table I. These energy values, when compared with those calculated by the EHT method, show the same trend. Energy values obtained by the SCF method seem more reasonable. To the best of our knowledge, the difference in the energy values for this type of bicyclic system have not been reported.

Cyclohexane is known to exist entirely in the chair conformation at room temperature. The energy difference between the chair and the boat forms of this molecule is still a subject of controversy. Reported values[14,15] range from 1.31 to 10.6 kcal/mol. Yousif and Roberts[16] reported the activation energy of the inversion of 4,4-difluoropiperidine to be 13.9 kcal/mol in methanol solution. The energy differences between the various conformations given in Table I are of similar magnitude. The calculated dipole moment for the chair–chair form agree with the experimental value[1] within the limit of the experimental error. We, therefore, conclude that at room temperature this molecule does exist entirely in a normal or near normal chair–chair form.

Registry No.—N,N′-Dimethylbispidine, 14789-33-4.

Acknowledgment.—Our sincere thanks are due to Dr. J. E. Douglass and Dr. A. R. Lepley for valuable discussion. One of us (M. R. C.) is grateful to the Benedum Foundation for a summer research grant.

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Lithium–Methylamine Reduction. I. Reduction of Furan, 2-Methylfuran, and Furfuryl Alcohol[1]

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Received December 30, 1968

Rosenblum[4] has reported the reduction of the furan ring of 2-furoic acid using sodium and ammonia as well as sodium, alcohol, and ammonia, but he was unable to reduce furan (**1**) by the same methods. 2-Methylfuran (**2**) also is not reducible using sodium in ammonia.[5] Furfuryl alcohol (**3**) has been converted (about 40%) into **2** with sodium in liquid ammonia, but no further reduction was observed.[6]

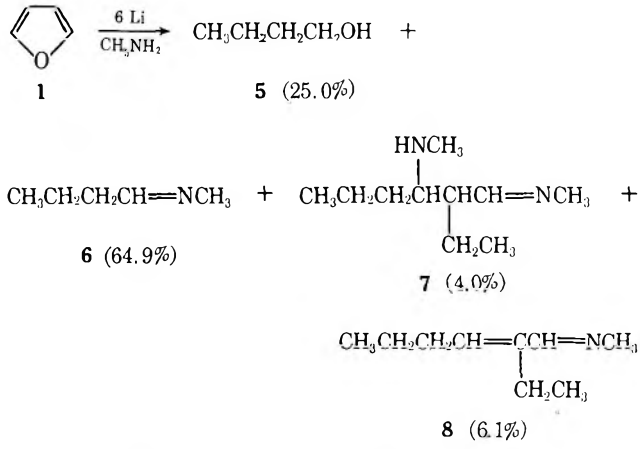
It has been shown that there are only slight differences between sodium–alcohol–ammonia reductions and those employing lithium–alcohol–methylamine.[7] However, in previous work Benkeser and coworkers[8] demonstrated that lithium–amine is a more powerful if less selective reducing system than sodium–ammonia.

On the basis of the aforementioned facts, it seemed worthwhile to attempt the reduction of **1**–**3** using lithium in methylamine.

Results

The reduction of 2-methylfuran (**2**) with lithium in methylamine produces six products (see Table I), some of which indicate that extensive ring opening has occurred. The relative amounts of these products is dependent on the amount of lithium employed. One of the products of this reaction, N-1-methylbutylidenemethylamine (**4**), was characterized by matching its infrared spectrum with that of an authentic sample prepared[9] from 2-pentanone and methylamine. The fact that **4** (very sensitive to moisture) could be reduced either catalytically or by lithium in methylamine to the known N-1-dimethylbutylamine contributed to its identification. The ethanol isolated in the reduction of **2** is unexpected and seemingly results from the rupture at −6° of a carbon–carbon as well as a carbon–oxygen bond.[10]

The reduction of **1** (*vide infra*) yielded four products, two of which (**7** and **8**) were probably the result of an aldol-type condensation of N-butylidenemethylamine (**6**). N-(2-Ethyl-2-hexenylidene)methylamine (**8**) was identified by independent synthesis,[11] comparison of ir spectra, and an nmr spectrum. Glpc collection and reinjection of the other product (**7**), probably N-(2-ethyl-3-methylaminohexylidene)methylamine, showed considerable conversion of this compound into **6** and **8**. Further substantiation of this identification was obtained from an nmr spectrum (see Experimental Section). Attempts to isolate **7** again for further study failed.



The reductions of furfuryl alcohol with lithium and methylamine are summarized in Table II.

Discussion

The present conception of the reduction of the furan ring is shown in Scheme I. No attempt was made to postulate the role of lithium in the reaction or the reducing species involved (*i.e.*, e^-, e_2^{2-}, $e^-Li^+ e^-$).[12]

The reduction of **2** (Table I) with 2 equiv of lithium apparently results from the reduction of half of **2** with 4 equiv of lithium, and half of **2** remains unreacted. The inability to account for all the starting material appears to be characteristic of this type of reduction.[4,6]

A carbinolamine species is an obvious intermediate in the conversion of 2-pentanone into **4**,[13] and by analogy with aliphatic ketals[14] one would not expect an aliphatic carbinolamine to be reduced. Thus it is believed that a carbinolamine or some ionic form thereof is an intermediate in this reduction.

The products previously discussed are predictable on the basis of metal–ammonia reduction of benzofurans,[15,16] but the isolation of ethanol is quite unexpected. Although carbon–carbon bond cleavage in metal–ammonia reductions is not unknown, those compounds in which it has been observed have one or more phenyl groups on each carbon involved in the bond cleavage[17] or contain a cyclopropyl system.[18] It is

(1) (a) This work was supported in part by funds given to the University of Southern Mississippi by the Mississippi Board of Trustees of Institutions of Higher Education for the support of basic research. (b) Portions of this work were presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, and the 20th Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968.

(2) University of Southern Mississippi Graduate Fellow.

(3) National Science Foundation Graduate Fellow.

(4) L. Rosenblum, Ph.D. Dissertation, The Ohio State University, 1952.

(5) A. P. Dunlop and F. N. Peters, "The Furans," Reinhold Publishing Corp., New York, N. Y., 1953, p 52.

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TABLE I

REDUCTION OF 2-METHYLFURAN[a]

Products from reduction with	2 Li	4 Li	6 Li	8 Li
Tetrahydro-2-methylfuran, %[b]	4.8	14.4	13.4	10.5
2-Pentanone, %	5.6	10.3	...	...
N-1-Methylbutylidenemethylamine,[c] %	80.0	47.1	33.6	37.4
2-Pentanol, %	1.0	7.2	28.6	28.6
1-Pentanol, %	3.8	16.6	12.7	15.6
Ethanol, %	4.8	4.5	13.4	8.1
Amount of reduced material recovered, g	10.6	16.3	19.1	19.7

[a] In all the reactions 20.5 g (0.250 mol) of 2-methylfuran and 500 ml of methylamine were used. [b] This is per cent of reduced material recovered. It was determined from glpc curve areas. No attempt was made to correct the peak areas for differences in thermal conductivity of the components. [c] See Experimental Section for the preparation of the authentic sample.

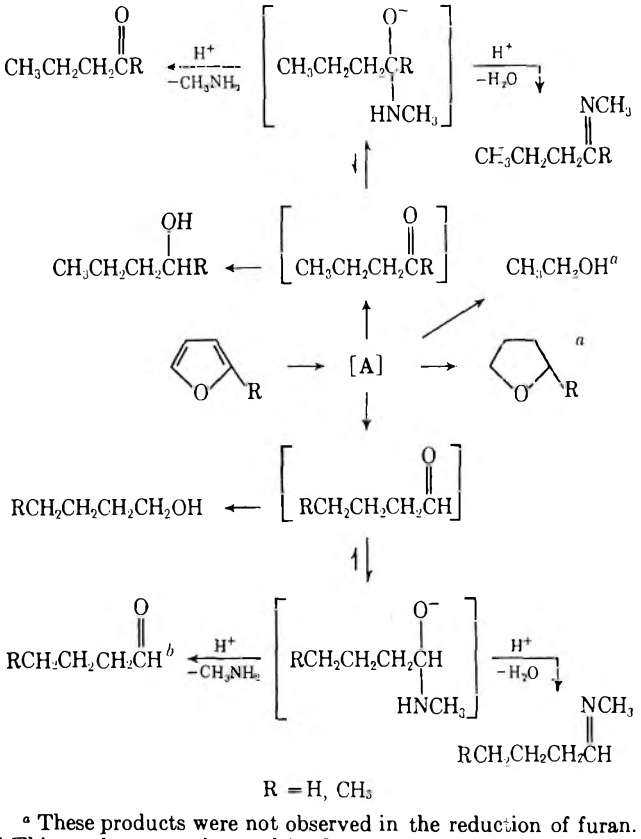
TABLE II

REDUCTION OF FURFURYL ALCOHOL[a]

Products from reduction with	2 Li	4 Li	6 Li	8 Li
Tetrahydrofurfuryl alcohol, %[b]	...	...	8.4	...
2-Methylfuran, %	51.5	12.3	...	...
Tetrahydro-2-methylfuran, %	...	...	...	2.6
2-Pentanone, %	...	26.9	9.8	3.8
N-1-Methylbutylidenemethylamine,[c] %	24.2	39.8	41.2	17.4
N-Pentylidenemethylamine, %	...	...	...	15.5
2-Pentanol, %	...	...	7.3	41.9
1-Pentanol, %	...	12.8	19.3	18.7
Ethanol, %	4.8	2.7	13.7	...
Furfuryl alcohol, %	19.9	5.4	...	...
Amount of reduced material recovered, g	15.0	19.1	17.3	14.8

[a] In each reaction 24.5 g (0.250 mol) of furfuryl alcohol and 500 ml of methylamine were used. [b] This is per cent of reduced material recovered. The percentages were determined from glpc curve areas uncorrected for differences in thermal conductivity of the components. [c] See Experimental Section for the preparation of the authentic sample.

SCHEME I



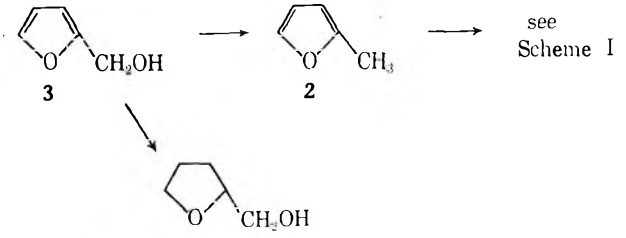
[a] These products were not observed in the reduction of furan. [b] This product was observed in the reduction of furfuryl alcohol but not in the reduction of 2-methylfuran.

presently thought that ethanol produced in the reduction arises from C_2–C_3 cleavage of a ring-intact intermediate followed by a base-catalyzed ether cleavage of the ion produced (possibly a concerted process). A study of variables in the production of ethanol is currently in progress. Initial investigations show that the amount of ethanol formed is dependent on solution conditions and ring substituents. Up to 48% ethanol can be obtained.[19]

The reduction of furan was differentiated from that of **2** by the aldol-type imine condensation, absence of ethanol, and absence of cyclic products.

The reduction of furfuryl alcohol (Scheme II) involved extensive hydrogenolysis of **3** to **2**, as Birch observed using sodium–ammonia.[6] Tetrahydrofurfuryl alcohol

SCHEME II



and N-pentylidenemethylamine were isolated in addition to the products found from the reduction of **2**. The absence of N-pentylidenemethylamine among the products of reduction of **2** and its occurrence in reduction of **3** is attributed to the more acidic conditions existing during the reduction of **3** owing to the ionizable hydroxyl hydrogen.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer Model 257 grating spectrophotometer. Nmr spectra were determined on a Varian

(19) Unpublished results from this laboratory.

Model A-60D spectrometer with tetramethylsilane as an internal reference. Glpc analyses were carried out on a Microtek Model GC-2000R linear temperature programmed gas chromatograph using 0.25 in. × 10 ft coiled stainless steel tubes packed with 20% Carbowax 20M on 60–80 mesh nonacid-washed Chromosorb W. The carrier gas in these determinations was helium, and the temperature program was 50–225° at a rate of 10 deg/min.

General Procedure.—After a three-necked Pyrex flask equipped with Dry Ice condenser and mercury trap, mechanical stirrer, and gas-inlet tube was flushed with dry nitrogen, 2-methylfuran (2) or furfuryl alcohol (3) was added. The desired amount of methylamine was then condensed in the flask, and the calculated amount of 1/8-in. lithium wire was added to the stirred mixture. The solution was decomposed with ammonium chloride in water, and the product was extracted with ether and dried (Na_2SO_4). The solvent was distilled off under vacuum without heat, the products were analyzed by glpc, and the compounds were identified by comparison of their ir and, where noted, nmr spectra with those of authentic compounds.[20] The results of the reduction of 2-methylfuran and furfuryl alcohol are summarized in Tables I and II, respectively.

Reduction of 2-Methylfuran (2).—Following the general procedure above, 20.5 g (0.250 mol) of 2 and 10.35 g (1.50 g-atoms of lithium in 500 ml of methylamine were allowed to react for 8 hr. After extraction (methyl *n*-propyl ether), 23.3 g of reduced material was recovered. The major products, in order of their elution from glpc, were tetrahydro-2-methylfuran[21] (7.1%) ethanol[21] (7.7%), 2-pentanone[21] (31.6%), N-1-methylbutylidenemethylamine[21] (29.1%), 2-pentanol[21] (17.7%), and 1-pentanol[21] (6.8%). Their relative retention times were 1:2.26:2.64:2.93:3.89:5.14.

N-1-Methylbutylidenemethylamine (4).—Using a modification of Tiollais' method[9] for preparation of N-alkylaldimines, 40.5 g (0.472 mol) of 2-pentanone was added dropwise to 150 ml of methylamine and stirred for 1.5 hr. The excess methylamine was removed by heating to 50°. Addition of potassium carbonate caused foaming and separation into two layers. The organic layer was decanted, diluted with an equal volume of ether, and dried (Na_2SO_4). A 45–50% yield of 4, bp 108–110°, was realized:[22] ir $\nu_{max}^{CCl_4}$ 2962, 2879, 1451, 1358 (CH), and 1659 cm^{-1} (C=N); nmr (CCl_4, max) τ 6.90 (s, 3, C=NCH$_3$), 7.39–8.80 (complex m, 7, CH_2 and CH_3), and 9.06 (t, 3, CH_3).

Reduction of N-1-Methylbutylidenemethylamine (4). **A. Catalytic Hydrogenation of Authentic 4.**—An 8.80-g mixture of 4 and 2-pentanone was allowed to react in a Parr hydrogenation apparatus[23] until detectable reaction ceased (5.5-psi decrease). The final product mixture, analyzed by glpc, was composed of 2-pentanone (18.2%), 2-pentanol (23.2%), and N,1-dimethylbutylamine (58.6%).

The spectral data for N,1-dimethylbutylamine follow: ir $\nu_{max}^{CCl_4}$ 2966, 2935, 2875, 2791, 1467, 1372 (CH), 3263 (NH, very weak), and 1161 cm^{-1} (CN); nmr ($CDCl_3$, max) τ 7.58 (s, 3, NCH$_3$) and 8.33–9.30 (complex m, 11, CH, CH_2, and CH_3).

Anal. Calcd for $C_6H_{15}N$: C, 71.21; H, 14.94. Found: C, 70.95; H, 14.77.

B. Catalytic Hydrogenation of 4 from the Reduction of 2-Methylfuran (2).—In a Brown[2] Micro Hydro-Analyzer[24] was placed 4.0 mg (0.0403 mmol) of 4. The reduction, which consumed 0.0400 mmol of the theoretical 0.0403 mmol of hydrogen, produced N,1-dimethylbutylamine identical with that obtained from reduction of the authentic 4.

C. Reduction of 4 with Lithium in Methylamine.—Using the general procedure (*vide supra*), an 18.5-g mixture of 0.1 mol of 2-pentanone, 0.1 mol of 4, 2.76 g (0.400 g-atom) of lithium, and 400 ml of methylamine were stirred together for 5 hr and 10 min. The 17.0-g product mixture, analyzed by glpc, was composed of N,1-dimethylbutylamine (54.7%), 2-pentanol (7.9%), 2-pentanone (13.3%), and 4 (24.2%).

Reduction of Furan (1).—After 8 hr, the reaction of 34.0 g (0.500 mol) of freshly distilled furan and 20.7 g (3.00 g-atoms) of lithium in 1000 ml of methylamine yielded 21.9 g of reduced material. This was composed of N-butylidenemethylamine[21] (64.9%), 1-butanol[21] (25.0%), N-(2-ethyl-2-hexenylidene)-methylamine[21] (6.1%), and N-(2-ethyl-3-methylaminohexylidene)methylamine (4.0%).

N-Butylidenemethylamine (6)[9] gave the following spectral data: ir $\nu_{max}^{CCl_4}$ 2969, 2878, 2846, 1457 (CH), and 1672 cm^{-1} (C=N); nmr ($CDCl_3$, max) τ 2.35 (perturbed s, 1, CH=N), 6.73 (perturbed s, 3, C=NCH$_3$), and 7.66–9.31 (complex m, 7, CH_2 and CH_3).

N-(2-Ethyl-2-hexenylidene)methylamine (8)[11] gave the following spectral data: ir $\nu_{max}^{CCl_4}$ 2972, 2945, 2882, 2849, 2777, 1463, 1456, 1402 (CH), 1644 (C=N), and 1633 cm^{-1} (C=C); nmr ($CDCl_3$, max) τ 2.28 (perturbed s, 1, CH=N), 4.25 (t, 1, CH=C), 6.64 (s, 3, C=NCH$_3$), 7.69 (perturbed quintet, 4, C=CCH_2), and 8.28–9.28 (complex m, 8, CH_2 and CH_3).

N-(2-Ethyl-3-methylaminohexylidene)methylamine (7) gave the following spectral data: nmr (CD_3COCD_3, max) τ 4.38 (perturbed s, 1, CH=N), 6.47–6.77 (complex m, 1, CHC=N), 7.52 (s, 3, C=NCH$_3$), 7.85 (s, 3, NDCH$_3$), and 8.00–9.32 (complex m, CH, CH_2, and CH_3).

N-Pentylidenemethylamine was prepared using the procedure for the preparation of N-1-methylbutylidenemethylamine, and gave the following spectral data: ir $\nu_{max}^{CCl_4}$ 2958, 2880, 2863, 2846, 2781, 1459 (CH), and 1671 cm^{-1} (C=N); nmr (CCl_4, max) τ 2.43 (br s, 1, CH=N), 6.83 (perturbed s, 3, C=NCH$_3$), and 7.37–9.31 (complex m, 9, CH_2 and CH_3).

Registry No.—1, 110-00-9; 2, 534-22-5; 3, 98-00-0; 4, 22431-09-0; 7, 22431-11-4; N-1-dimethylbutylamine, 22431-10-3; N-pentylidenemethylamine, 10599-75-4.

Acknowledgment.—The authors wish to thank the Perkin-Elmer Corp. for mass spectra of the components of some of the reduction mixtures.

(20) Unless otherwise noted, the authentic samples were obtained from commercial sources.

(21) Nmr spectra were used for identification.

(22) This yield is based on glpc analysis of the product mixture.

(23) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., New York, N. Y., 1957, p 867.

(24) C. A. Brown, *Anal. Chem.*, **39**, 1882 (1967).

Diphenylmethyl Bishydroperoxide. An Anomalous Product from the Ozonolysis of Tetraphenylethylene

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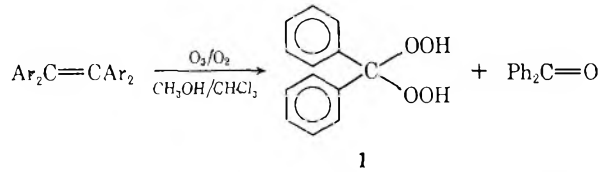
The ozonolysis of an olefin in a hydroxylic solvent is one method of synthesizing alkoxy hydroperoxides.[2-4] Tetraphenylethylene has been ozonized in the presence of methanol,[5,6] but the resultant methoxy hydroperoxide from the interception of the Criegee zwitterion (2) has never actually been isolated. We have made numerous attempts to prepare the expected methoxy hydroperoxide at temperatures ranging from −78 to 0° and have isolated only the expected benzophenone and the completely unexpected diphenylmethyl bishydroperoxide (1). A bishydroperoxide during ozonation in a hydroxylic solvent has not been previously observed.



1

(1) National Science Foundation Graduate Teaching Assistant Fellow, summers of 1968, 1969.

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(4) R. Criegee in "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Interscience Publishers, Inc., New York, N. Y., 1962, p 34.

(5) S. Fliszar, D. Gravel, and E. Cavalieri, *Can. J. Chem.*, **44**, 67 (1966).

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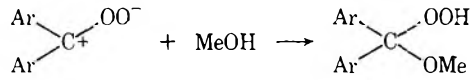
The aliphatic bishydroperoxides are usually prepared by the action of hydrogen peroxide on the ketone (acetone,[7] ethyl methyl ketone,[8] diethyl ketone,[9] and cyclohexanone[10-12]). Cadogan, *et al.*,[13] may have observed **1** from the reaction of 85% hydrogen peroxide with benzophenone. They isolated a peroxide, mp 90–92°, but did not establish the structure of the compound. Our attempts to reproduce this synthesis under a variety of conditions were unsuccessful.

Results and Discussion

Ozonolysis of tetraphenylethylene in a chloroform–alcohol solution produced, after removal of the solvent, a clear, colorless oil. Tlc analysis of this oil, on silica gel at −5° indicated the presence of only two components in the mixture. One would expect these to be, based on previously reported work,[2-6] benzophenone and diphenylmethoxy methyl hydroperoxide **3** (or the ethoxy derivative, depending on the alcohol used in the solvent system). We were able to isolate both components of the mixture and readily identified one as benzophenone. The other component, a white crystalline solid, gave ir and nmr spectra which were not compatible with **3**. The ir spectrum showed no aliphatic C–H absorptions in the 2900-cm^{-1} region while the nmr gave no indication of any aliphatic protons. A multiplet was observed at δ 7.25–7.73 and a broad singlet at 9.70 (integration ratio 5:1) which disappeared on addition of D_2O. The white solid reacted readily with starch–iodide paper, and a quantitative titration for active oxygen gave an equivalent weight of 60.8 (equivalent weight of **3** is 115). Owing to the overwhelming evidence against **3** it was rejected as the structure for the other component in the ozonolysis mixture.



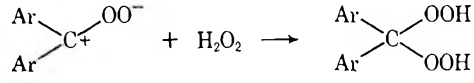
2 **3**

Structure **1** fits the experimental evidence much better than does **3**. The equivalent weight of **1** is 58, and for the nmr spectrum one would expect a multiplet due to the aromatic protons and a broad singlet downfield, integrating in the ratio of 5:1, as was observed. In addition, the ir spectrum is compatible with what would be expected for structure **1**. Confirmation for structure **1** was obtained from a low temperature mass spectrum which gave a parent ion of mass 232, the molecular weight of **1**, intensity 1%.

Chemical evidence for **1** was obtained from the thermal behavior and pyrolysis products of the white solid. Compound **1** readily converts to benzophenone and oxygen on heating. For example, a KBr pellet of **1** was prepared and the ir spectrum obtained, but after heating the pellet for 20 min at 130° a new spectrum was obtained. These two ir spectra were completely different, and the latter was superimposable on the ir spectrum of benzophenone, with the exception of a few very weak peaks due to residual **1**. In addition, when **1** was decomposed in the gas chromatograph only two peaks resulted, which by comparison with authentic samples were identified as benzophenone and oxygen. Again, these results were confirmed by mass spectrometry. A moderate temperature (source 130°) mass spectrum of **1** gave only the spectrum of benzophenone and a large oxygen 32 peak.

This thermal instability of **1**, while expected, made meaningful elemental analysis difficult and accounts for the somewhat high equivalent weight obtained. However, an acceptable analysis was obtained for the diacetyl derivative.

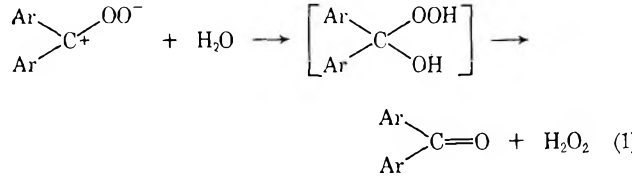
The bishydroperoxide was thought to be formed by the reaction of **2** with hydrogen peroxide. To test this



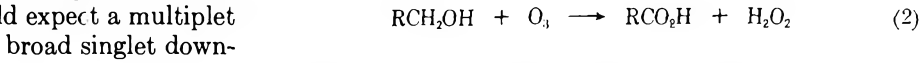
2 **1**

hypothesis 2 drops of 90% H_2O_2 was added to the reaction mixture before ozonolysis and the yield of isolatable bishydroperoxide increased from 50 to 71%. However, when the hydrogen peroxide was added to the ozonolysis product mixture after removing the solvents, no increase in the yield of **1** was observed. Apparently **1** is formed during the ozonolysis reaction and not from decomposition of some intermediate such as **3**.

There are at least two possible sources of H_2O_2 in this system, as shown by reactions 1 and 2. Reaction 1



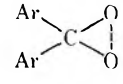
(1)



(2)

requires residual water within the system and may be the source of only a small amount of hydrogen peroxide, while reaction 2 is very likely the main source of hydrogen peroxide. Whiting and coworkers[14] indicate that this reaction occurs readily at −78°.

The results of this investigation indicate that the diphenyl-substituted Criegee zwitterion is quite stable and selective as to its requirements for reaction with a nucleophile. This stability may be due either to a large delocalization energy *via* resonance with the π system of the phenyl rings or to the formation of the dioxirane intermediate **4**. At any rate, neither the



4

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ozonide, the alkoxy hydroperoxide, nor the Criegee zwitterion dimer forms when better nucleophiles are present.

Experimental Section

Ozonolysis Procedure.—An Orec O_3V_2 ozone generator was used. The concentration of ozone was about 1% in oxygen with a flow rate of 1.5 l./hr. The O_2 was dried prior to entering the generator by passing it through concentrated sulfuric acid. The O_3–O_2 mixture was passed into the reaction system which had been previously cooled to −78° with a Dry Ice–acetone slurry.

Tetraphenylethylene (1.00 g, 3.01 mmol), mp 221–224°, was dissolved in 150 ml of chloroform (distilled) and 100 ml of methanol (distilled over magnesium) or ethanol, and treated with ozone until the appearance of blue color in the solution indicated excess ozone (*ca.* 20 min). The excess ozone was then flushed out with nitrogen. The solvent was stripped off (10–20 mm and 10–20°) leaving a clear, colorless oil. Tlc of the oil at −5° on silica gel and developed with $CHCl_3$ indicated two compounds identified as benzophenone and 1: yield 0.71 g, 3.90 mmol, of benzophenone and 0.35 g, 1.51 mmol (50%), of bishydroperoxide.

Diphenylmethyl Bishydroperoxide (1).—After recrystallization from hexane, the white needles of 1 had a melting point of 94–96°. A reaction with starch–iodide paper indicated that the compound contained active oxygen. The infrared spectrum showed no absorption in the carbonyl region but strong bands were observed at 3450, 1450, 1205, 1040, 781, 741, and 704 cm^{-1}. The nmr spectrum in acetonitrile showed two types of protons, a broad singlet at 9.70 and a multiplet at δ 7.25–7.73, which integrated 1:5, respectively. The addition of 2 drops of deuterium oxide to the nmr tube caused the singlet at δ 9.70 to disappear. A low-temperature (source at 50 ± 2°) mass spectrum established the parent ion at 232 (1% intensity) with major peaks at 77, 105, 182, and 199. Elemental analysis was not satisfactory owing to facile decomposition to benzophenone. The diacetyl derivative was formed by adding acetyl chloride to a pyridine solution of 1. The resulting diperester was recrystallized from hexane giving white needles (mp 109.5–111.0°). The nmr spectrum of the perester showed a singlet at δ 1.88 and a multiplet at 7.20–7.65 integrating 6:10, respectively. The infrared spectrum had a strong carbonyl band at 1785 cm^{-1}, characteristic of peresters.[15,16] A high resolution mass spectrum of the perester with the internal standard, heptacosafluorotributylamine, established the parent ion at 316 (0.3% intensity). *Anal.* Calcd for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10; O, 30.35. Found: C, 64.68; H, 5.23; O, 30.24.

Analysis for Active Oxygen.—An analytical technique developed at this laboratory was used to determine active oxygen content. Titrations were carried out in a 125-ml erlenmeyer flask equipped with a gas inlet stem at the bottom. During a titration nitrogen was passed into the titration vessel through a gas washing bottle filled with crushed Dry Ice. A sample (13 mg) was added to 25 ml of glacial acetic acid containing 1 g of KI. After 15 min in the dark (under carbon dioxide–nitrogen), 80 ml of water was added and the iodine titrated with 0.01 *N* sodium thiosulfate. A blank titration was unnecessary. The titrated solution remained colorless until the gas system was turned off (1 hr later). This technique was very reproducible (equiv wt: 60.41, 61.27) and, based on our results, appears superior to that used by Fliszar and Granger,[6] eliminating iodine entrapment by solid ice, air oxidation of the iodide ion, and titration at near 0°.

Registry No.—1, 22461-45-6; 1, diacetyl derivative, 22461-46-7; tetraphenylethylene, 632-51-9.

Acknowledgment.—This publication is No. 2-69 from the Chemistry Department of Colorado State University. We wish to thank this department for the support of this work.

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9H-Dibenz[c,f]imidazo[1,2-a]azepines

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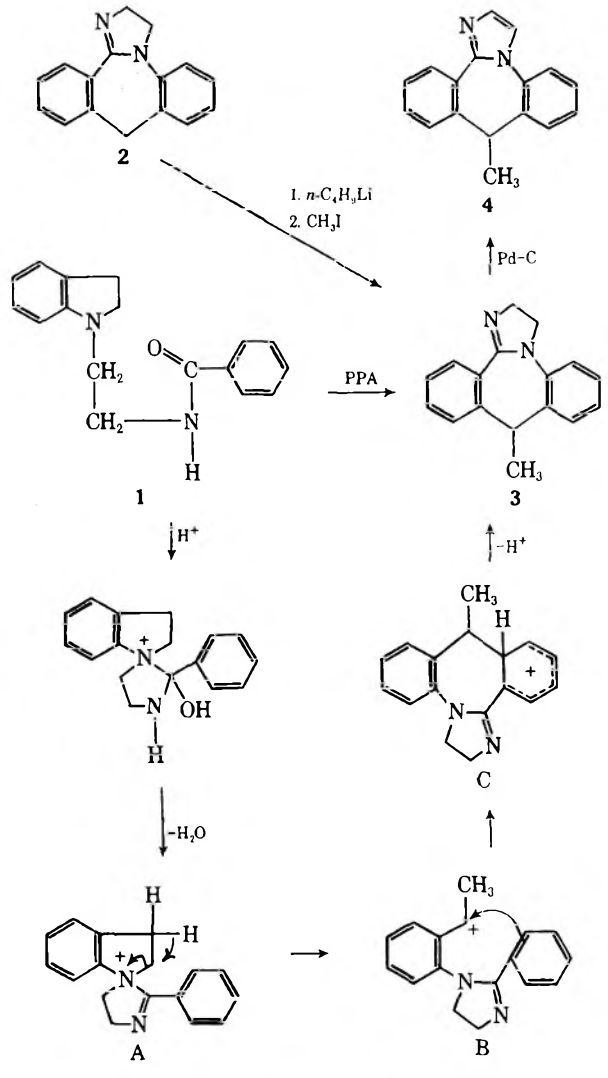
Received July 24, 1969

In connection with another investigation, we attempted to effect the cyclodehydration of the benzamide (*viz.* 1) into the 7 position of the indoline nucleus. After an initial unsuccessful attempt with phosphorus oxychloride, we investigated the reaction of 1 with polyphosphoric acid. The product obtained from this reaction in 38% yield was not the expected cyclodehydration product but an isomer thereof. Based on mechanistic considerations (*vide infra*) and the similarity of its ultraviolet spectrum to that of 2[1] [λ_{max} 256 mμ (ε 8120), 295 (6830), and 229 (inflection, 13,930)],



(1) A. E. Drukker, C. I. Judd, and D. D. Dusterhoft, *J. Heterocycl. Chem.*, **3**, 206 (1966).

we proposed structure **3** for this product. Confirmation of this structure was achieved by an independent synthesis: alkylation of **2**, which was prepared by the literature method, by successive treatment with *n*-butyllithium and methyl iodide gave a product which was identical with **3**.

A mechanistic interpretation of the reaction is shown. Initial cyclodehydration of **1** to form A might be followed by successive cleavage of the CH_2–N^+ bond and hydride migration to give the relatively stable benzylic carbonium ion (B). An electrophilic reaction of this carbonium ion with the monosubstituted benzene ring would lead, *via* C, to the observed product (**3**). A somewhat analogous reaction of N,N-dialkyl-N′-acyl-*o*-phenylenediamines with polyphosphoric acid to give benzimidazoles has been reported.[2]

Initial attempts to degrade **3** by acid (6 *N* HCl) or alkaline (20% ethanolic KOH) hydrolysis were unsuccessful; starting material was recovered in both cases. Palladium-catalyzed dehydrogenation of **3** in refluxing decalin gave **4** in 78% yield.

The nmr spectra of **3** and **4** were interesting in that the methyl group in each case was represented by a pair of doublets. This phenomenon was temperature dependent: at 120° the methyl group of **3** appeared as a doublet and at 140° the methyl group of **4** appeared as a broad singlet with a half band width of *ca.* 22 Hz. This type of behavior is characteristic of molecules which at a given temperature can assume two or more conformations which are relatively stable and slowly interconvertible.[3]

The relative intensities of the doublets for both **3** and **4** were nearly equal, which suggests that in each case the two conformations represented were approximately equally populated at ambient temperature. Molecular models of **3** and **4** show that in the two possible conformations the methyl group would be influenced differently by the electronic environment associated with the neighboring benzene rings; this is consistent with the observed results.

Experimental Section[4]

1-(2-Benzamidoethyl)indoline (1).—A solution of benzoyl chloride (63.5 g, 0.452 mol) in benzene (200 ml) was added during 20 min to a cold, stirred solution of 1-(2-aminoethyl)indoline[5] (65.8 g, 0.411 mol) and triethylamine (49.7 g) in benzene (820 ml). The resulting mixture was allowed to stand under N_2 at ambient temperature for 18 hr and poured into water (1.5 l.). This mixture was made alkaline with 50% NaOH and extracted with benzene. The benzene extract was dried (K_2CO_3) and concentrated. Crystallization of the residue from EtOAc gave 92.5 g (84.7%) of **1**, mp 99.5–103°. Data for the analytical sample follow: mp 104–104.5°; uv (EtOH) λ_{max} 250 mμ (end absorption, ϵ 13,100), 299 (2750), and 226 (inflection, 13,450); ir (Nujol) 3320 (NH) and 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.80; H, 7.02; N, 10.60.

2,3-Dihydro-9-methyl-9H-dibenz[*c,f*]imidazo[1,2-*a*]azepine (3). A.—A stirred mixture of **1** (45.0 g, 0.169 mol) and polyphosphoric acid (1.3 kg) was kept under N_2 at 150–160° for 21.5 hr and then poured into stirred ice–water (2–3 l.). The solution which resulted was made alkaline with 50% NaOH and extracted with ether. The ether extract was washed successively with water and brine, dried (K_2CO_3), and concentrated. The residue was chromatographed on silica gel (2 kg) with Et_3N–EtOAc (2:98). The first material eluted was unreacted starting material, 5.12 g, mp 103.5–105°. The product was then eluted and crystallized from EtOAc–Skellysolve B to give 14.6 g, mp 142–143°, and 1.15 g, mp 120–123° (37.6%), of **3**. That the two crops were different polymorphic crystalline forms of the same compound was demonstrated by mixture melting point and ir ($CHCl_3$) comparison. Data for the analytical sample follow: mp 128.5–129°; uv (EtOH) λ_{max} 295 mμ (end absorption, ϵ 8800), 291 (7250), and 233 (inflection, 14,600); mass spectrum *m/e* (rel intensity) 248 (100), 247 (44), 233 (96), and 204 (18); nmr ($CDCl_3$) δ 1.55, 1.73 (two d, 3, J = 7.5 Hz, CH_3CH), 4.05 (m, 5, C-2, -3, -9), 7.16 and 7.86 (two m, 7 and 1, C-5–8 and -10–13); nmr [$(CD_3)_2NCDO$, 120°] δ 1.59 (d, 3, J = 7.5 Hz, CH_3CH) and 3.96 (m, 5, C-2, -3, -9).

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.50; N, 11.28. Found: C, 82.20; H, 6.50; N, 11.51.

B.—A stirred solution of **2** (2.34 g, 0.0100 mol) in dry tetrahydrofuran (50 ml), under N_2, was treated with 10 ml (0.016 mol) of a 15.13% solution of *n*-butyllithium in hexane. The resulting dark green solution was allowed to stand at ambient temperature for 3.83 hr, cooled in an ice bath, and treated during 8 min with a solution of methyl iodide (0.935 ml, 0.015 mol) in anhydrous ether. This mixture was kept at ambient temperature for 18 hr and poured into ice–water. The resulting mixture was extracted with ether. The ether extract was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (150 g) with Et_3N–EtOAc (2:98). The product was crystallized from EtOAc–Skellysolve B to give 0.475 g, mp 119.5–122.5°, and 0.506 g, mp 117–119.5° (39.5%), of **3**. The combined product was recrystallized three times from EtOAc, mp 121–124°, identical with the cyclodehydration product (**3**) by ir, uv, and nmr comparison. The mixture melting point was undepressed.

9-Methyl-9H-dibenz[*c,f*]imidazo[1,2-*a*]azepine (4).—A mixture of **3** (1.0 g, 4.03 mmol), 10% palladium on carbon (0.5 g), and decalin (20 ml) was refluxed under N_2 for 15 hr and allowed to stand at ambient temperature for 18 hr. The solid was collected by filtration, washed with Skellysolve B, and extracted with hot MeOH. The MeOH extract was concentrated and the residue was crystallized from EtOAc to give 0.769 g (77.5%) of **4**, mp 167–168.5°. Data for the analytical sample follow: mp 166.5–167.5°; uv (EtOH) λ_{max} 271 mμ (ϵ 11,900); mass spectrum *m/e* (rel intensity) 246 (93), 231 (100), 204 (11), and 177 (9); nmr ($CDCl_3$) δ 1.12, 1.80 (two d, 3, J = 7.5 Hz, CH_3CH), 3.93, 4.09 (two, q, 1, J = 7.5 Hz, CH_3CH), 7.34 and 8.01 (two m, 9 and 1, C-2, -3, -5–8, -10–13); nmr [$(CD_3)_2NCDO$, 140°] δ 1.29 (broad s, 3, CH_3CH), and 4.10 (broad s, 1, CH_3CH).

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 82.97; H, 5.81; N, 11.68.

Registry No.—**1**, 22922-47-0; **3**, 22922-48-1; **4**, 22922-49-2.

Acknowledgment.—The author is indebted to Dr. M. Grostic for mass spectra, Mr. F. A. MacKellar for nmr spectra, Mr. P. A. Meulman for ir spectra, Mrs. Betty F. Zimmer for uv spectra, Mr. N. H. Knight and his associates for analytical data, and Mr. J. Robert Greene for laboratory assistance.

(2) O. Meth-Cohn and H. Suschitzky, *J. Chem. Soc.*, 2309 (1964).

(3) For example, see J. A. Elvidge in "Nuclear Magnetic Resonance for Organic Chemists," D. W. Mathieson, Ed., Academic Press Inc., New York, N. Y., 1967, pp 36–38.

(4) Melting points were taken in capillary tubes and are corrected. The ir spectra were recorded on a Perkin-Elmer Model 421 recording spectrophotometer, the uv spectra on a Cary Model 14 spectrophotometer, and the mass spectra at 70 eV on an Atlas CH-4 spectrometer. The nmr spectra were recorded on a Varian A-60A spectrometer; chemical shifts were measured in parts per million downfield from tetramethylsilane. Skellysolve B is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. The silica gel used for chromatography was obtained from E. Merck AG, Darmstadt, Germany.

(5) R. P. Mull, U. S. Patent 3,093,632 (1963).

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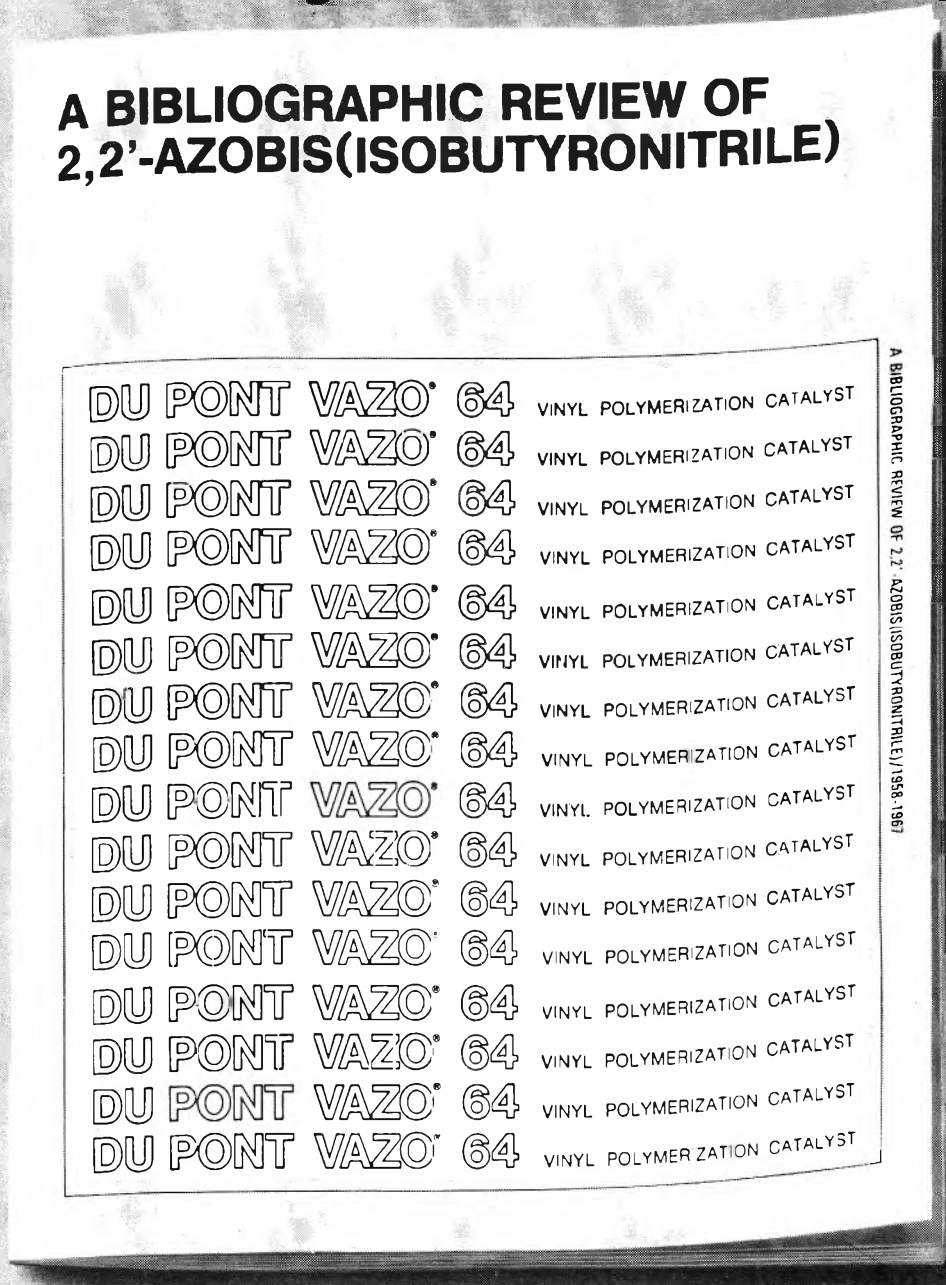

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[1] J. A. Dale, D. L. Dull and H. S. Mosher, J. Org. Chem. **34**, 2543 (1969).

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[1] L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," (New York, 1967), p. 967.

[2] D. V. C. Awang and S. Wolfe, Can. J. Chem. **47**, 706 (1969).

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