VOLUME 37 OCTOBER 20, 1972 NUMBER 21 JOCEAH

THE JOURNAL OF Organic Chemistry

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OCTOBER 20, 1972

Quinazolines and 1,4-Benzodiazepines. LIV.[1] The Base-Catalyzed Rearrangement of 2-Dimethylamino-5-phenyl-7-chloro-3*H*-1,4-benzodiazepine 4-Oxide

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Received March 8, 1972

The reaction of 2-dimethylamino-5-phenyl-7-chloro-3*H*-1,4-benzodiazepine 4-oxide (**2**) with the lithium anion of dimethyl sulfoxide followed by quenching with water has been shown to lead to the indoles **3** and **4** and the quinoline **5**. If the reaction mixture is treated with dimethyl sulfate prior to quenching with water, five products are formed. These are the indoles **6**–**9** and the quinoline **5**. The structures of the products were established by spectral data (**3**, **4**, **8**), single-crystal X-ray analysis (**6**, **7**), and by an independent synthesis (**5**, **9**). A reasonable mechanism is proposed which leads to a common intermediate C from which all of the various products can be derived.

The synthesis of 2-methylamino-5-phenyl-7-chloro-3*H*-1,4-benzodiazepine 4-oxide (**1**) has been described by Sternbach and Reeder.[2,3] Subsequently, the treatment of **1** with sodium hydride and methyl iodide was shown to lead to the dimethylamino analog **2**.[4] As was reported, we have found that the methylation reaction proceeds smoothly and in high yield. However, no results have appeared on the further methylation of **2**.

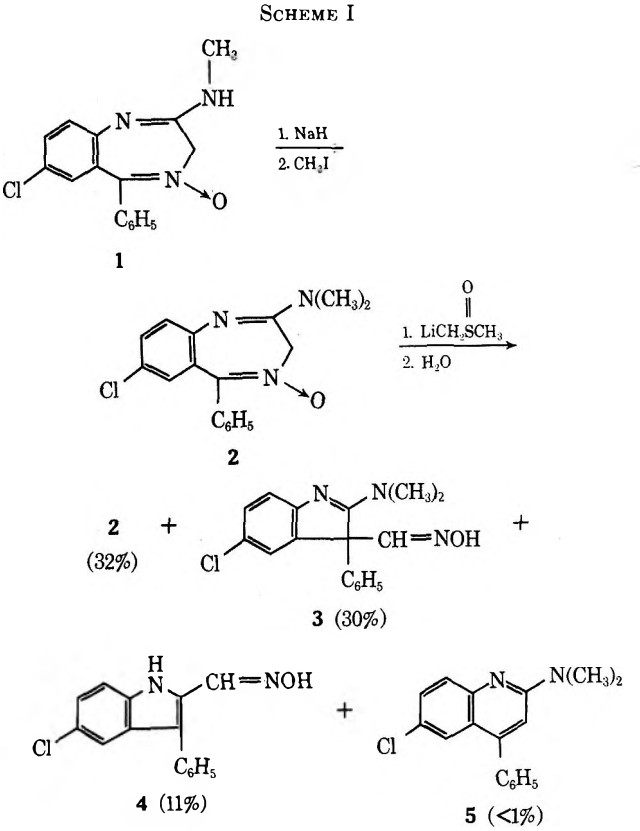
We now wish to report that the reaction of **2** with a strong base followed by a methylating agent does not lead to a simple methylated derivative of **2**, but instead gives only products resulting from a rearrangement.

In order to establish whether this rearrangement was due solely to the base or to a combination of base and methylating agent, we first treated **2** with base only. After treating **2** with the lithium anion of dimethyl sulfoxide (prepared by reaction of dimethyl sulfoxide with *n*-butyllithium) and quenching with water, we found that profound changes had occurred. The isolated reaction products were the indoles **3** and **4** and the quinoline **5**, as outlined in Scheme I. The yields shown are for isolated recrystallized products.

The indole **3** was isolated by trituration of the crude reaction mixture (after work-up) with methylene chloride, and then the products **4** and **5** were separated by preparative thick layer chromatography.

In a reaction, concerned with the methylation, compound **2** was treated with the lithium anion of dimethyl sulfoxide followed by the addition of dimethyl sulfate. The reaction with base yields a deep purple-black solution which turns pale yellow upon addition of dimethyl sulfate in an exothermic reaction. In contrast to the reaction which was quenched with water, the use of dimethyl sulfate as a methylating (and quenching) agent leads to the five rearranged products **5**–**9**. The yields for isolated, purified compounds, which were

SCHEME I



(1) Part LIII: G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Org. Chem.*, **36**, 2968 (1971).

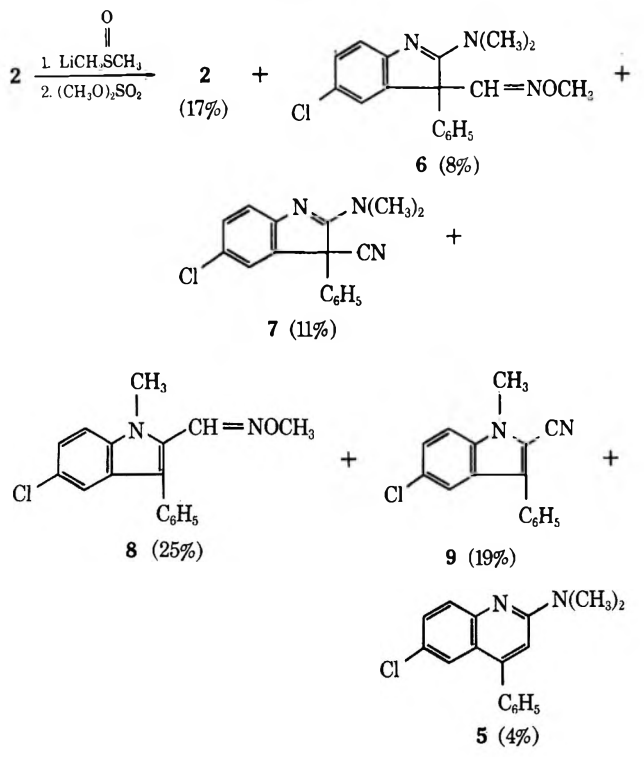
(2) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(3) The generic name is chlordiazepoxide. This compound, as the hydrochloride, is the active component of Librium.

(4) S. Farber, H. M. Wuest, and R. I. Meltzer, *J. Med. Chem.*, **7**, 235 (1964).

determined from one experiment, are given in Scheme II. In repetitive runs, it was sometimes possible to

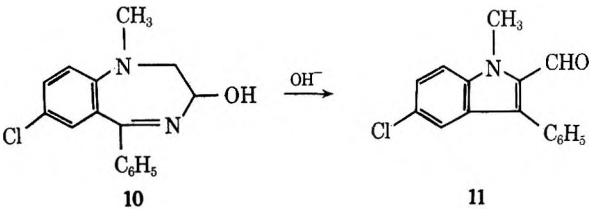
SCHEME II



crystallize the crude reaction mixture directly from methanol to yield either **6** or **8**. In most cases, **6** was obtained preferentially but, in all experiments, thin layer chromatography showed the presence of all five products. The relative yields of the products were not determined in every experiment.

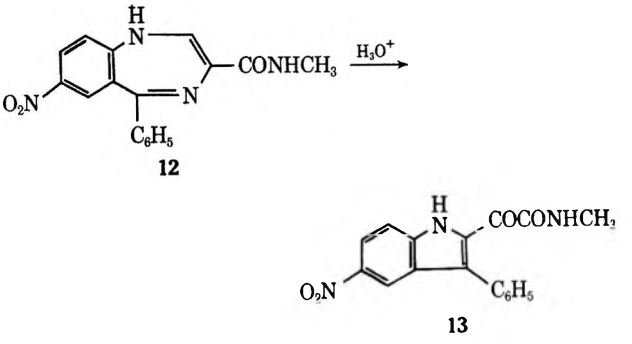
As is shown in Schemes I and II, the quinoline **5** is formed in very low yield in both cases. The product **3**, which was obtained by quenching the reaction with water, appears to be related to the indoles **6** and **7**. The methylation of the oxime anion of **3** (before quenching with water) with dimethyl sulfate would yield the indole **6**, which could lose methanol to give **7**. In a similar manner, the oxime anion of **4** upon methylation and loss of methanol would give the indoles **8** and **9**.[5,7]

Mechanisms.—Although numerous rearrangements of 1,4-benzodiazepines to other heterocyclic systems have been reported,[8] none of these exactly parallels the complex rearrangement reported for **2**. The formation of indoles was observed in two cases. 5-Chloro-1-methyl-3-phenylindole-2-carboxaldehyde (**11**) was formed from the base treatment of **10**.[9] In an acid-

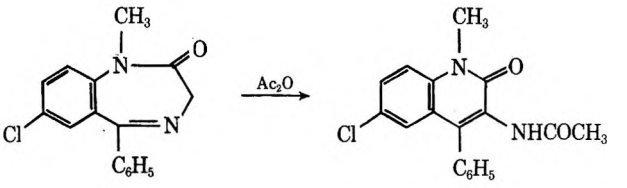


10 **11**

catalyzed rearrangement, the benzodiazepine **12** has been shown[10] to lead to the indole **13**.



The formation of the quinoline **15** from the benzodiazepine **14** has been reported but with the retention of

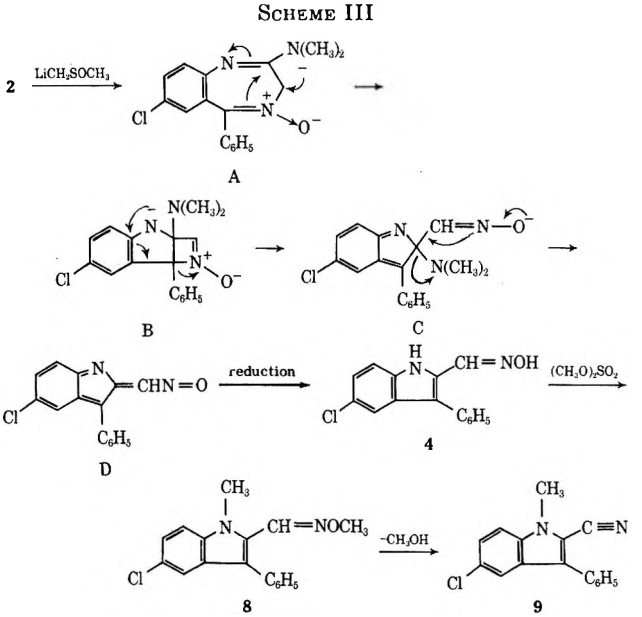


14 **15**

the 4-nitrogen.[11] No reports have appeared on the formation of a quinoline from a benzodiazepine in which the 4-nitrogen has been lost, as is the case in the rearrangement of **2** to give **5**.

A plausible mechanism for the base-catalyzed rearrangement of **2** into the indoles **4**, **8**, and **9** is shown in Scheme III.

SCHEME III



(5) The conversion of either **6** to **7** or **8** to **9** was not verified experimentally, although, on the basis of similar reactions, the loss of methanol from either **6** or **8** does have precedence.[6]

(6) For example, the treatment of oximes with mesyl chloride followed by base treatment has been reported to lead to nitriles: T. J. Bentley, J. F. McGhie, and D. H. R. Barton, *Tetrahedron Lett.*, 2497 (1965).

(7) The ratios of the reaction products **3** to **4** and **6** + **7** to **8** + **9** differ in Schemes I and II. This was not further explored, since the data in each case are based on a single experiment. Slight variations in the reaction conditions and in the work-up could well account for these differences.

(8) For a review see R. Ian Fryer, *J. Heterocycl. Chem.*, **9**, 747 (1972).

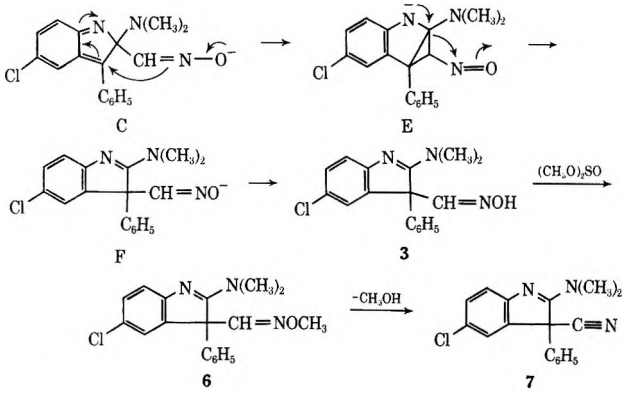
(9) W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, **29**, 1621 (1964).

(10) R. Ian Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **32**, 3798 (1967).

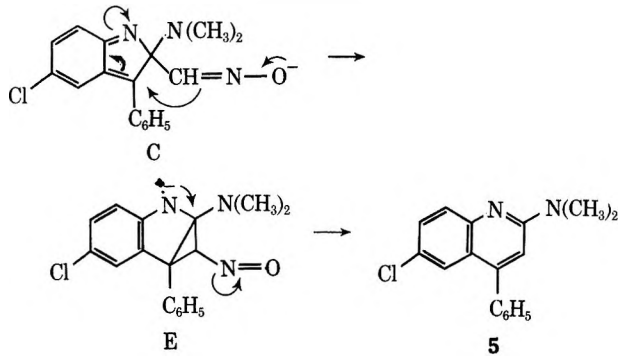
(11) R. Ian Fryer and L. H. Sternbach, *ibid.*, **30**, 524 (1965).

Removal of the proton at the 3 position would give the anion A. Ring closure to B occurs by nucleophilic attack on the amidine rather than the imine–oxide double bond. This might be expected to occur, since the amidine double bond should be more electrophilic. Ring opening of B gives an intermediate C, from which all of the various products can be derived (see also Schemes IV and V). The loss of the dimethyl-

SCHEME IV



SCHEME V



amino group from C would give D which has the gross structure of the products **4**, **8**, and **9**. The exact nature of the reducing agent responsible for the conversion of D into **4** is not known. In the presence of dimethyl sulfate, **4** is methylated to yield **8**, which *via* loss of methanol yields the nitrile **9**.

The formation of **3**, **6**, and **7** also proceeds through the intermediate C, as shown in Scheme IV.

The formation of the cyclopropane intermediate E results from the cyclization of the azomethine bond in C to the 3 position of the indole. Ring opening of E would then give F, which upon protonation yields **3**. The methylation of **3** with dimethyl sulfate gives **6**, which can lose methanol to give **7**.

The formation of the quinoline **5** can also arise from intermediate C, as shown in Scheme V.

The cyclization of C to E proceeds as shown and the quinoline **5** would result from cleavage of the bond bridging the six-membered ring in E with simultaneous loss of nitrous oxide.

Although other possible mechanisms can be envisioned for the rearrangement of **2**, the transformations shown in the preceding schemes are attractive because all of the observed products can be derived from a common intermediate, namely C.

Structure Proof of the Products.—The structures of **6** and **7** were indicated by microanalyses and spectral data, and were confirmed by single-crystal X-ray crystallographic analyses (see crystallography section).

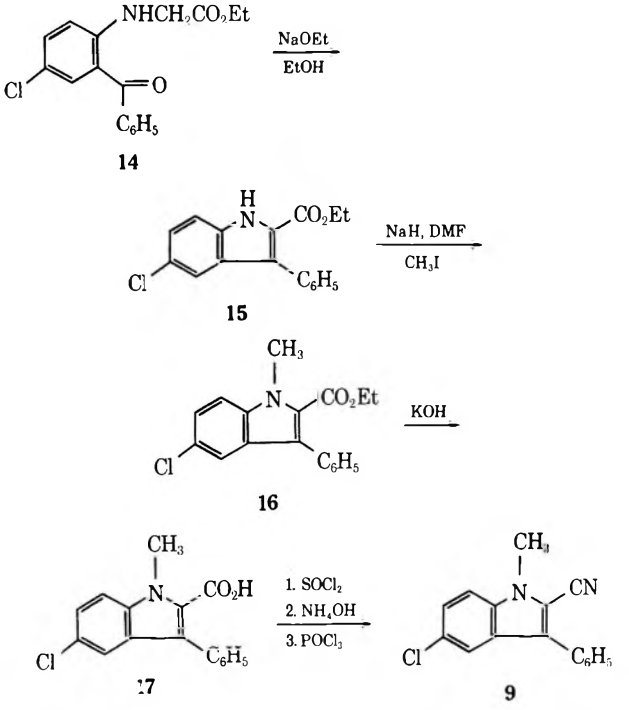
The structures of **5** and **9** were suggested by spectral data and verified by independent synthesis.

Compounds **3**, **4**, and **8** were assigned the structures shown on the basis of microanalyses and spectral data in analogy with the previously determined structures of compounds **6** and **9**. All of the appropriate data for these compounds appear in the Experimental Section.

Synthesis of 5.—The known 2,6-dichloro-4-phenylquinoline[12] was treated with dimethylamine to give 6-chloro-4-phenyl-2-dimethylaminoquinoline (**5**), whose physical properties and spectra were identical with those of the compound which was isolated from the rearrangement of **2**.

Synthesis of 9.—Compound **14** was transformed into **9** as outlined in Scheme VI.

SCHEME VI



The ring closure of **14**[13] to the known indole **15** proceeded smoothly in ethanol with sodium ethoxide as the condensing agent.[14]

The indole **15** was methylated in DMF by treatment with sodium hydride followed by the addition of methyl iodide.[15]

The resulting ester **16** was then converted to the nitrile **9** as described in the literature.[15] All physical properties of this compound were identical with those of the nitrile isolated from the rearrangement of **2**.

Crystallography.—Crystals of **6** are orthorhombic, space group $P2_12_12_1$, with $a = 10.698\ (2)$, $b = 10.252\ (2)$, $c = 15.259\ (3)$ Å, $Z = 4$, $d_{obsd} = 1.30$, $d_{calcd} = 1.299$ g cm^{-3}, $\mu = 20.8$ cm^{-1}. Crystals of **7** are triclinic, space

(12) A. E. Drukker and C. I. Judd, *J. Heterocycl. Chem.*, **3**, 359 (1966).

(13) G. A. Archer and L. H. Sternbach, U. S. Patent 3,317,518 (1966); *Chem. Abstr.*, **65**, 16,988 (1966).

(14) For two different synthesis of **15**, see (a) H. Yamamoto, S. Inaba, T. Hirohashi, and K. Ishizumi, *Chem. Ber.*, **101**, 4245 (1968); (b) S. Inaba, K. Ishizumi, and H. Yamamoto, *Chem. Pharm. Bull.*, **19**, 263 (1971).

(15) Compound **16** has also been prepared directly by a Fischer indole synthesis: H. Yamamoto, *et al.*, South African Patent 68,003,041 (1969); *Chem. Abstr.*, **71**, 124519m (1969).

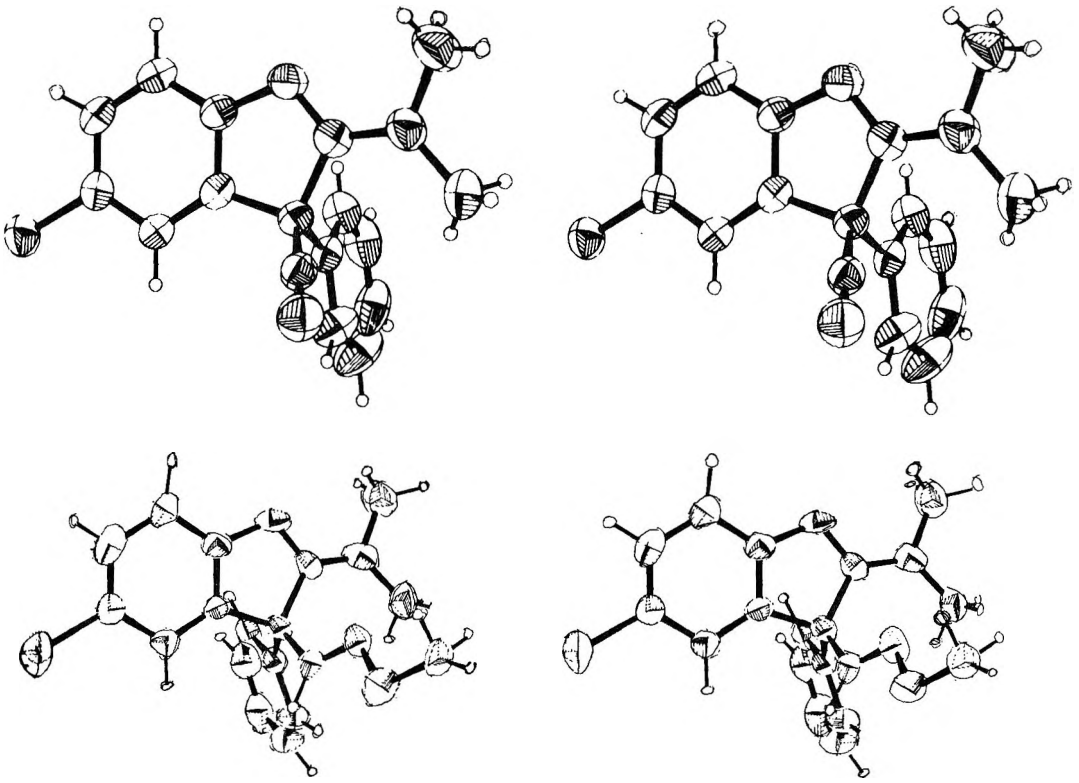


Figure 1.—Stereodrawings of **7** (upper) and **6** (lower). The ellipsoids represent the thermal motions of each atom at the 50% probability level. The two molecules are shown in slightly different orientations in order to reduce overlap of the atoms.

group $P\bar{1}$, with a = 10.758 (3), b = 11.899 (6), c = 12.423 (3) Å, α = 88.91 (3), β = 72.41 (3), γ = 83.08 (3)°, Z = 4, d_{obsd} = 1.30, d_{calcd} = 1.305 g cm^{-3}, μ = 22.0 cm^{-1}. Intensity data for both compounds were collected on a Hilger-Watts Model Y290 four-circle diffractometer by a moving crystal–moving detector method. Nickel filtered Cu K$_\alpha$ radiation and pulse height discrimination were used. The approximate dimensions of the crystals used for data collection were 0.05 × 0.05 × 0.35 mm (**6**) and 0.25 × 0.25 × 0.20 mm (**7**); no absorption corrections were made. Of the 1801 accessible independent reflections of $\theta > 70°$, only 724 had intensities significantly greater than background and these data were used for the structure analysis of **6** (there were 3920 observed data out of a total of 5040 reflections with $\theta < 70°$ for **7**).

Both structures were solved by the heavy atom method starting with Cl coordinates determined from sharpened Patterson functions. The hydrogen atoms were located from difference Fouriers calculated after partial refinement of the structures. The structure of **6** was refined by full-matrix least squares and the structure of **7** was refined by clock-diagonal least squares with the matrix partitioned into nine blocks. In both cases all atoms except hydrogen were assigned anisotropic thermal parameters. The hydrogen parameters were held fixed for **6** but were refined for **7**.

The quantity minimized was

$$\Sigma w \, ||F_o| - |F_c||^2$$

where $w = 1/(a + |F_o| + c|F_o|^2)$, a = 13.3, c = 0.016 Å for **6**, a = 4.5, c = 0.012 Å for **7**.

Standard scattering curves were used for Cl, O, N, C,[16] and H.[17] The Cl curve was corrected for the real and imaginary parts of the anomalous scattering.[18] The refinement was stopped when the shifts of all parameters except those of the hydrogens were less than one-third of the corresponding standard deviations. The difference Fouriers based on the final parameters have no features greater than 0.3 e Å^{-3} in magnitude. The final $R = \Sigma||F_o| - |F_c||/|\Sigma|F_o|$ is 0.048 for **6** and 0.041 for **7**.[19]

The bond lengths and angles in the two structures are in agreement with the expected values. In the $-C_\beta-C_\alpha=NOCH_3$ moiety of **6** the distances and angles are $C_\beta-C_\alpha$, 1.547 (13); $C_\alpha=N$, 1.254 (12); N–O, 1.410 (10); O–CH_3, 1.409 (13) Å; $C_\beta-C_\alpha-N$, 120.5 (9); $C_\alpha-N-O$, 108.7 (8); N–O–CH_3, 108.0 (8)°. Average values for the bond angle and lengths in the $C_\alpha-C\equiv N$ moiety of **7** are $C_\alpha-C$, 1.473 (3); $C\equiv N$, 1.140 (3) Å; $C_\alpha-C-N$, 178.4 (3)°. The conformations of the two crystallographically independent molecules in crystalline **7** are nearly identical and thus a stereoview of only one is shown in Figure 1, together with a stereoview of **6**.

Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. The ir spectra were determined on a Beckman IR-9 spectrometer in chloroform (3% solutions) unless stated otherwise. The nmr spectra were recorded with a Varian A-60 instrument in deuteriochloroform. Absorption values are given in parts per million downfield from tetramethylsilane added as an internal standard. The mass spectra were determined with a CEC 21-110B instrument.

(16) D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18**, 104 (1965).

(17) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

(18) D. T. Cromer, *Acta Crystallogr.*, **18**, 17 (1965).

(19) Listings of structure factors, coordinates, and thermal parameters for **6** and **7** will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-37-3201. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Separation of 3, 4, and 5 from the Reaction of 2 with $LiCH_2SOCH_3$ Followed by Water Treatment.—To 150 ml of dry dimethyl sulfoxide, under argon, was added 46.5 ml of 1.6 *M* *n*-butyllithium in hexane. After the evolution of H_2 had ceased, 18.8 g (60 mmol) of 2 was added in one portion. The resulting deep purple-black solution was stirred for 35 min and quenched with 500 ml of water. The color immediately reverted to pale yellow. After extraction with three 400-ml portions of CH_2Cl_2, the organic solutions were combined, washed with 15% NaCl, dried ($MgSO_4$), and concentrated to yield 17.5 g of sticky yellow solid. This residue was triturated with 250 ml of hot CH_2Cl_2, cooled, and filtered to give 5.6 g (30%) of **3**. The filtrate was concentrated and the residue was separated by preparative thick layer chromatography [benzene–ethyl acetate (5:1) as eluent] to give 800 mg (0.5%) of **5** as a high R_f band and 3 g (11%) of **4** as a low R_f band. From the origin, 6 g (32%) of starting material was recovered.

5-Chloro-2-dimethylamino-3-phenyl-3*H*-indole-3-carboxaldehyde Oxime (3).—This oxime was obtained as colorless prisms by recrystallization from benzene: mp 222–223.5°; ir ($CHCl_3$) 3500–2000, 1610, 1560, 1462, 1404, 1310 cm^{-1}; nmr δ 2.93 [s, 6 H, $N(CH_3)_2$], 7.01 (m, 3 H, aromatic), 7.30 (s, 5 H, aromatic), 8.25 (s, 1 H, CH=N), 11.22 (s, 1 H, OH); mass spectrum *m/e* 313 (M^+), 296 ($M^+ - OH$).

Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39. Found: C, 65.05, 64.94; H, 5.23, 5.21; N, 13.29, 13.32.

5-Chloro-3-phenyl-2-indolecarboxaldehyde Oxime (4).—The indole was recrystallized from methanol–water to give colorless prisms: mp 204–206°; ir ($CHCl_3$) 3400, 3350–2250 cm^{-1}; nmr δ 7.24–7.73 (m, 9 H, aromatic and CH=N), 11.75 and 12.15 (br s, 2 H, NH and OH); mass spectrum *m/e* 270 (M^+), 253 ($M^+ - OH$).

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.72, 66.75; H, 4.13, 4.16; N, 10.41, 10.43.

6-Chloro-2-dimethylamino-4-phenylquinoline (5).—This compound was recrystallized from methanol to give pale yellow needles: mp 93–95°; ir (KBr) 1610, 1600 cm^{-1}; nmr δ 3.06 [s, 6 H, $N(CH_3)_2$], 6.69 (s, 1 H, aromatic), 7.31–7.80 (m, 8 H, aromatic); mass spectrum *m/e* 282 (M^+), 267, 253, 239.

Anal. Calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.16; H, 5.42, 5.50; N, 9.97, 9.90.

Preparation and Separation of Compounds 5–9 (General Procedure).—To 150 ml of dry dimethyl sulfoxide, under argon, was added 46.5 ml of 1.6 *M* *n*-butyllithium in hexane. The resulting solution was stirred at room temperature for approximately 15 min until the evolution of hydrogen had ceased. Compound **2** (18.8 g, 60 mmol) was then added in one portion and, after 15 min, 6.3 ml (66 mmol) of dimethyl sulfate was added. The solution was stirred for 18 hr at room temperature, then poured into ice water; the mixture was extracted with CH_2Cl_2. The organic phase was washed with saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo*. The residue, which was a mixture of solid and gummy material, was dissolved in CH_2Cl_2 and chromatographed on 200 g of aluminum oxide (Woelm, activity I) to give 14.1 g of crude products (benzene as eluent) and 3.2 g of starting material (17% recovered **2**) as a final fraction. The first fraction was separated into three fractions on 20 × 20 cm silica gel thick layer plates (approximately 500 mg per plate) in chloroform–heptane (1:1).

The high R_f (0.48)[20] fraction yielded, after recrystallization from methanol, 4.5 g (25%) of **8**.

The medium R_f (0.25) fraction gave, after recrystallization from methanol, 3.0 g (19%) of **9**.

The material remaining at the origin was recovered and rechromatographed on thick layer plates, using benzene–ethyl acetate (3:1) as eluent, to give the other three products.

The high R_f material (0.52) gave 1.5 g (8%) of **6** after recrystallization from methanol. The medium R_f (0.26) spot yielded 2.0 g (11%) of **7** after recrystallization from 2-propanol. The low R_f (0.18) band gave 0.7 g (4%) of **5** after recrystallization from methanol.

The total yield of recovered products, including starting material, was 84%.

5-Chloro-2-dimethylamino-3-methoxyiminomethyl-3-phenyl-3*H*-indole (6).—This compound was obtained as colorless prisms from methanol or from benzene–hexane: mp 173–175°; ir ($CHCl_3$) 1610, 1580 cm^{-1}; uv max (EtOH) 220 mμ (ϵ 26,800), 287 (17,450), 295 (16,800), 320 (sh, 4,200); nmr δ 3.00 [s, 6 H, $N(CH_3)_2$], 3.85 (s, 3 H, OCH_3), 6.81 (t, J = 1 cps, 1 H, aromatic), 7.12 (d, J = 2 cps, 2 H, aromatic), 7.30 (m, 5 H, aromatic), 7.95 (s, 1 H, CH=N); mass spectrum *m/e* 327.1184 (M^+), 296.0978 ($M^+ - OCH_3$, theory 296.0955).

Anal. Calcd for $C_{18}H_{18}ClN_3O$: C, 65.95; H, 5.53; N, 12.82. Found: C, 66.23; H, 5.62; N, 12.93.

6 HBr.—The hydrobromide was prepared in the usual fashion and recrystallized from ethanol–ether to give colorless prisms, mp 237–239°.

Anal. Calcd for $C_{18}H_{18}ClN_3O \cdot HBr$: C, 52.89; H, 4.68; N, 10.28. Found: C, 52.90; H, 4.52; N, 10.51.

The free base could be recovered by treatment of the salt with $NaHCO_3$.

5-Chloro-3-cyano-2-dimethylamino-3-phenyl-3*H*-indole (7).—The pure nitrile was obtained as colorless prisms by recrystallization from methanol: mp 166–168°; ir ($CHCl_3$) 2240, 1620 cm^{-1}; Raman (solid) 2240 cm^{-1}; nmr δ 3.08 [s, 6 H, $N(CH_3)_2$], 7.01 (m, 1 H, aromatic), 7.17 (br s, 2 H, aromatic), 7.36 (s, 5 H, aromatic); mass spectrum *m/e* 295 (M^+).

Anal. Calcd for $C_{17}H_{14}ClN_3$: C, 69.04; H, 4.77; N, 14.21. Found: C, 68.89; H, 4.75; N, 14.06.

5-Chloro-1-methyl-2-methoxyiminomethyl-3-phenylindole (8).—The product was obtained as colorless needles by recrystallization from methanol: mp 145–147°; ir ($CHCl_3$) 1610 cm^{-1}; nmr δ 3.97 (s, 3 H, NCH_3 or OCH_3), 4.01 (s, 3 H, NCH_3 or OCH_3), 7.24 (d, J = 1 cps, 2 H, aromatic), 7.38 (s, 5 H, aromatic), 7.59 (t, J = 1 cps, 1 H, aromatic), 8.16 (s, 1 H, N=CH); mass spectrum *m/e* 298.0897 (M^+, theory 298.0873), 267.0695 ($M^+ - OCH_3$, theory 267.0689).

Anal. Calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.10, 68.22; H, 5.07, 5.04; N, 9.31, 9.31.

5-Chloro-2-cyano-1-methyl-3-phenylindole (9).—The indole was recrystallized from methanol to give colorless needles: mp 125–127°; ir ($CHCl_3$) 2220 cm^{-1}; nmr δ 3.80 (s, 3 H, NCH_3), 7.04–7.77 (m, 8 H, aromatic); mass spectrum *m/e* 266 (M^+).

Anal. Calcd for $C_{16}H_{11}ClN_2$: C, 72.05; H, 4.16; N, 10.50. Found: C, 71.59, 71.46; H, 4.17, 4.15; N, 10.44, 10.30.

Ethyl 5-Chloro-3-phenylindole-2-carboxylate (15).—To a solution of sodium ethoxide [from 2.53 g (0.11 mol) of sodium] in 400 ml of ethanol was added 32 g (0.1 mol) of **14**. After refluxing for 2 hr (a large amount of precipitate forms) the mixture was poured into a large volume of water and filtered. The solid was recrystallized from methanol to yield 11.3 g (38%) of **15**, mp 173–174° (lit.[14] mp 172–172.5°).

Ethyl 5-Chloro-1-methyl-3-phenylindole-2-carboxylate (16).—To a suspension of 1.47 g of 57% sodium hydride in mineral oil (35 mmol of sodium hydride) in 100 ml of DMF, under argon at room temperature, was added 10 g (33.4 mmol) of **15**. After approximately 20 min, hydrogen evolution had ceased and 6.2 ml (100 mmol) of methyl iodide was added. After stirring for 4 hr at room temperature, the solution was diluted with water and extracted thoroughly with ether. The ether extracts were combined, washed with water, dried ($MgSO_4$), and concentrated to give 10 g (95%) of **16** as a pale yellow solid, mp 82–84° (lit.[15] mp 88–89°). The product was used without further purification.

5-Chloro-1-methyl-3-phenylindole-2-carboxylic Acid (17).—To a solution of 1.85 g (33 mmol) of potassium hydroxide in 100 ml of warm ethanol was added 10 g (32 mmol) of **16** and the solution was refluxed for 45 min. After concentrating *in vacuo*, the residue was dissolved in water, acidified with 3 *N* HCl, and filtered to give 8.7 g (95%) of the acid as an off-white solid, mp 215–218° (lit.[15] mp 211–213°).

5-Chloro-2-cyano-1-methyl-3-phenylindole (9) from 17.—A solution of 1.0 g (3.5 mmol) of **17** in 5 ml of thionyl chloride was refluxed on the steam bath for 15 min and concentrated *in vacuo*. Ammonium hydroxide (10 ml) was added, and the mixture was heated on the steam bath for 20 min, cooled, and filtered to give 800 mg (80%) of the corresponding amide.

The amide was refluxed with 5 ml of phosphorus oxychloride for 10 min. After cooling, the solution was poured over ice, allowed to warm to room temperature, basified with concentrated ammonium hydroxide, cooled, and filtered. The solid so obtained was recrystallized from methanol–water to give 450 mg (60%) of **9**, mp 128–129° (lit.[14] mp 128.5–130.5°). The spectra (ir, nmr, mass spectrum) were identical with those of the product isolated from the rearrangement of **2**.

(20) The R_f values refer to Merck plates. The thick layer separations were done on laboratory-prepared plates on which the products had slightly higher R_f values.

6-Chloro-2-dimethylamino-4-phenylquinoline (5), Prepared from 2,6-Dichloro-4-phenylquinoline.—The dichloroquinoline was prepared according to the procedure of Drukker and Judd.[12] A mixture of 13 g (47.5 mmol) of 2,6-dichloro-4-phenylquinoline, 100 ml of 25% dimethylamine in water, and 50 ml of ethanol was heated in a Parr bomb at 100–110° for 18 hr. After the solution was concentrated to a small volume, the residue was recrystallized from methanol to yield 12.1 g (90%) of 5 as pale yellow needles, mp 98–100°. The spectral data were identical with those for the compound obtained from the rearrangement of 2.

Anal. Calcd for $C_{17}H_{15}ClN_2$: C, 72.21; H, 5.35; N, 9.91. Found: C, 72.24; H, 5.50; N, 9.55.

Registry No.—**2**, 3693-14-9; **3**, 35337-03-2; **4**, 35337-04-3; **5**, 31576-98-4; **6**, 35337-06-5; **6** HBr, 35337-07-6; **7**, 35337-08-7; **8**, 35337-09-8; **9**, 24139-18-2.

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Reactions of Epimeric 2,2′-Diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines

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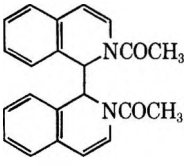
The title compounds are brominated by NBS to yield epimeric 2,2′-diacetyl-4,4′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines rather than 1,1′-dibromo derivatives as reported previously. Cleavage of the 1,1′ bond characterizes attempts to aromatize these compounds by oxidative methods; *e.g.*, the dibromo derivatives are converted to 4-bromoisoquinoline in 90% yield by 5.3 *N* nitric acid at 30°. *dl*- and *meso*-4,4′-dibenzal-1,1′,4,4′-tetrahydro-1,1′-biisoquinolines are recovered in low yields when the title compounds are heated in ethanol with benzaldehyde and concentrated hydrochloric acid; extensive cleavage of the 1,1′ bond again occurs with the formation of 4-benzal-1,4- (and 3,4-) dihydroisoquinoline. 5,5′-Dinitro- and 5-nitro-1,1′-biisoquinoline are described.

Previously it was reported[1] that both epimers of 2,2′-diacetyl-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline (**1a,b**)

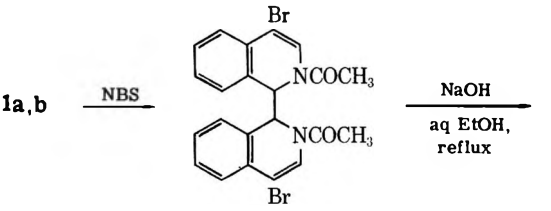


1a, *dl*
b, meso

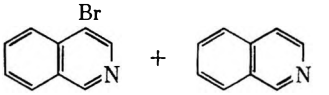
(prepared by the Dimroth reaction from isoquinoline, zinc, and acetic anhydride) and *N*-bromosuccinimide reacted in acetic acid to give epimeric dibromo compounds, $C_{22}H_{18}Br_2N_2O_2$. Alkaline hydrolysis of the latter gave mixtures of isoquinoline and a bromoisoquinoline (approximately equimolar). Based in part on the melting point of the bromoisoquinoline recovered by preparative glc, this compound was considered to be the 1-bromo isomer; the dibromo compounds were then considered to be epimeric 2,2′-diacetyl-1,1′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines.

Subsequent work (mixture melting points, comparison of ir spectra, ^{1}H nmr) has shown that this bromoisoquinoline is actually the 4 isomer. Consequently, the dibromo compounds are reformulated as 2,2′-diacetyl-4,4′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinolines (**2a,b**). This assignment is confirmed by the proton nmr spectrum[2] on the lower melting, more-soluble, *dl* isomer, **2a**.

Cleavage of the 1,1′ bond with formation of a mixture of isoquinoline and 4-bromoisoquinoline is also observed



2a, *dl*
b, meso



when **2a** and **2b** are oxidized by refluxing nitrobenzene. On the other hand, oxidation of **2a** with 5.3 *N* nitric acid at 30° gives 4-bromoisoquinoline in 90% yield.

Aromatization of **2a** without cleavage of the 1,1′ bond so as to recover 4,4′-dibromo-1,1′-biisoquinoline was attempted by the procedure of Knabe.[3] The latter had demonstrated that laudanosine could be oxidized to *N*-methylpapaverinium and *N*-methyl-3,4-dihydropapaverinium salts by mercuric acetate and disodium ethylenediaminetetracetate in aqueous acetic acid; other oxidation conditions had caused cleavage at the 1-methylene bond. However, even after prolonged heating at 80–85° only partial oxidation of **2a** had occurred; small amounts (<15%) of impure 4-bromoisoquinoline were isolated, suggesting that cleavage was still the preferred route.

The conversion of **1a,b** directly to 1,1′-biisoquinoline or derivatives has been further investigated beyond the results reported previously.[1] Extensive cleavage of the 1,1′ bond again characterizes most of the reactions.

(1) A. T. Nielsen, *J. Org. Chem.*, **35**, 2498 (1970).

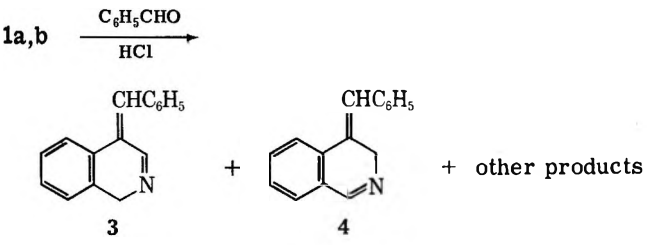
(2) ^{1}H nmr for *dl*-2,2′-diacetyl-4,4′-dibromo-1,1′,2,2′-tetrahydro-1,1′-biisoquinoline: τ (CDCl$_3$) 2.42 (dd, 1, *J* = 7.5, 1.5 Hz, H$_8$), 2.69 (td, 1, *J* = 7.5, 1.5 Hz, H$_6$), 2.94 (s, 1, H$_3$), 3.15 (td, 1, *J* = 7.5, 1.5 Hz, H$_7$), 4.02 (dd, 1, *J* = 7.5, 1.5 Hz, H$_5$), 4.15 (s, 1, H$_1$), 7.83 (s, 3, COCH$_3$).

(3) J. Knabe, *Arch. Pharm. (Weinheim)*, **292**, 416 (1959).

For example, isoquinoline (IQ) is formed from **1a** at room temperature with chloranil in aqueous acetic acid, with activated manganese dioxide in acetonitrile, and with cupric chloride in acetonitrile (the 1:1 complex, $CuCl_2$–IQ, precipitates). Oxidation of **1b** with either 5.3 *N* or 8 *N* nitric acid proceeds rapidly and exothermically at room temperature; isoquinoline is recovered in 90–95% yield. Nitration of **1a** in concentrated sulfuric acid at 3–7° furnishes 5-nitro- and 4,6-dinitroisoquinoline. Under the same conditions of nitration, 1,1′-biisoquinoline was converted to 5,5′-dinitro- and 5′-nitro-1,1′-biisoquinoline (73 and 21%, respectively).

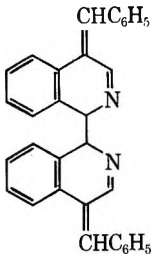
3,3′-Biisoquinoline was isolated in low yield from **1b** by refluxing in nitrobenzene with 10% palladium/charcoal catalyst; the principal product was isoquinoline. In the absence of Pd/C, no biisoquinoline was formed. It has been suggested by Carey and Sasse[4] that 3,3′-biisoquinoline is formed with 1,1′- and 1,3′-biisoquinolines when isoquinoline is heated with rhodium/carbon catalyst.

Since there is substantial evidence[5,6] that 1,2-dihydroisoquinolines are intermediates in the synthesis of 4-benzylisoquinolines from benzylaminoacetaldehyde dialkyl acetals, aromatic aldehyde and acid, the reaction of the 1,2-dihydroisoquinoline derivatives, **1a,b**, with benzaldehyde and hydrochloric acid was examined. A variety of products were formed; the principal one, which again arose from a cleavage of the 1,1′ bond, was a mixture (based on the nmr spectrum) of **3** and **4**.



3 4

Similar isomers have been found previously in this type of reaction.[6] More importantly, two other high-melting isomers were recovered in low yield; their molecular weights and mass spectral behavior indicated that they were derivatives of 1,1′-biisoquinoline. Because the ^1H nmr spectra showed methine but no benzyl methylene protons, the compounds are considered to be epimers **5a,b**. Other compounds, including some isoquinoline,



5a,b

were also isolated in low yield as their picrates, but were not characterized by nmr.

Experimental Section

Oxidation of 2a,b with Nitrobenzene. A.—The meso isomer (**2b**)[1] (4.0 g) was refluxed for 3 hr with 40 ml of nitrobenzene; the poorly soluble amide gradually dissolved to give a yellow solution which turned red, then dark brown. The cooled solution after dilution with 50 ml of 95% ethanol and 200 ml of diethyl ether was extracted with one 80 ml and one 25 ml portion of 3 *N* hydrochloric acid. The combined acid solutions were reextracted with 100 ml of fresh ether (discarded), made basic, and extracted with three 70-ml portions of ether. After drying over anhydrous potassium carbonate, the ether solution was evaporated to leave 2.5 g of red liquid. An analytical glc showed 12.0, 41.6, and 42.7 mol %, respectively, of nitrobenzene, isoquinoline, and 4-bromoisoquinoline (samples of the last two compounds, isolated by preparative glc, had ir spectra identical with those of authentic specimens): ^1H nmr for 4-bromoisoquinoline τ ($CDCl_3$) 0.85 (s, 1, H_1), 1.28 (s, 1, H_3), 1.7–2.5 (m, 4, H_5, H_6, H_7, H_8).

B.—A similar experiment with the *dl* isomer (**2a**) gave 2.66 g of product which contained 27.5 and 66.2 mol %, respectively, of isoquinoline and 4-bromoisoquinoline.

Oxidation of 2a with Nitric Acid.—**2a**[1] (1.5 g) was added with stirring to 30 ml of 5.3 *N* nitric acid at 29°. The temperature rose during 5 min to 31° and held for about 15 min; some oxides of nitrogen were evolved. Stirring was continued at 29° for 3.5 hr. Although the solid never dissolved completely, its character changed. After diluting with 10 ml of water and cooling to −15°, the solid was filtered, washed twice with 2–3 ml of cold water and dried, 1.36 g (84%). [From the mother liquors and washings after basification there was recovered 0.07 g (5.6%) of solid, mp 40–41°, whose ir spectrum was identical with that of 4-bromoisoquinoline.] Recrystallization of a small portion from dilute nitric acid gave felted, flat needles of 4-bromoisoquinolinium nitrate, mp 172–173° dec.

Anal. Calcd for $C_9H_7BrN_2O_3$: Br, 29.48; N, 10.34. Found: Br, 29.44; N, 10.28.

The balance of the salt in a minimum of cold water was made basic; white plates, mp 42–43°, separated upon cooling. Again the ir spectrum was identical with that for 4-bromoisoquinoline; mixture melting point was undepressed.

Oxidation of 1b with Nitrobenzene. A. Without Catalyst.—Refluxing 1.6 g of **1b**[1] with 15 ml of nitrobenzene under nitrogen for 3 hr followed by isolation of basic material in a conventional manner gave 1.13 g (95%) of isoquinoline (ir spectrum same as that of an authentic sample).

When the above reaction was attempted at 120–125° for 8 hr, under nitrogen and with stirring, the starting amide was recovered quantitatively.

B. With Catalyst.—A slurry of 2.0 g of **1b**, 1.0 g of 10% Pd/C, and 20 ml of nitrobenzene was flushed well with dry nitrogen, then stirred and heated at 120–130° for 3.5 hr. The cooled solution was diluted with 50 ml of benzene, filtered, and extracted with 50 ml of 2.4 *N* hydrochloric acid, followed by 25 ml of water. The combined aqueous extracts were reextracted once with benzene, made basic with concentrated ammonium hydroxide, and chilled overnight at 5°. The solid which separated was filtered, washed with water and dried, 0.4 g (27%). After two recrystallizations from cyclohexane–benzene (6:4) the melting point was 198–199°; the ir spectrum was the same as that for authentic 3,3′-biisoquinoline,[7] mp 197–198°.

Anal. Calcd for $C_{18}H_{12}N_2$: C, 84.35; H, 4.72; N, 10.93; mol wt, 256. Found: C, 84.51; H, 4.71; N, 10.87; mol wt (vpo), 250.

From the basic aqueous mother liquors remaining after removal of the above solid product, there was isolated through ether extraction 0.91 g (61%) of isoquinoline (ir spectrum) and a few crystals of acetanilide, mp 113–116° (ir spectrum).

Formation of the 3,3′-biisoquinoline in this catalyzed oxidation was not reproducible; in many experiments only a trace or none of this compound was found. Cleavage to isoquinoline was consistently 65–70% under these same conditions; at 100–102° the yield of isoquinoline was only 9% after 6 hr; at 130–140° after 4 hr, it was 85%.

(4) J. C. Carey and W. H. F. Sasse, *Aust. J. Chem.*, **21**, 207 (1968). Compare, however, H. Rapoport, R. Iwamoto, and J. R. Tretter, *J. Org. Chem.*, **25**, 372 (1960), who reported that no biaryl was formed by catalytic dehydrogenation when isoquinoline was refluxed for 24 hr with 5% Pd/C.

(5) J. M. Bobbitt, D. P. Winter, and J. M. Kiely, *ibid.*, **30**, 2459 (1965), and references therein.

(6) D. W. Brown, S. F. Dyke, and M. Sainbury, *Tetrahedron*, **25**, 101 (1969); S. F. Dyke, M. Sainbury, D. W. Brown, M. N. Palfreyman, and D. W. Wiggins, *ibid.*, **27**, 281 (1971).

(7) F. H. Case, *J. Org. Chem.*, **17**, 471 (1952).

Oxidation of 1b with Nitric Acid.—The meso epimer **1b** (1.2 g) was slurried with 30 ml of 5.3 *N* nitric acid at 24°. Within 5 min the temperature had increased to 27° and oxides of nitrogen were being evolved. After 10 more min all of the solid had dissolved (temperature 26°). After standing overnight at 25°, the solution was cooled and made basic with concentrated ammonium hydroxide. Isoquinoline (0.85 g, 93%) separated as a pale yellow oil; the ir spectrum was identical with that for authentic isoquinoline.

With 8 *N* nitric the reaction was more rapid and exothermic; the yield of isoquinoline was 95%.

Nitration of 1a.—Compound **1a**[1] (3.44 g; 0.01 mol) was added during 5 min to 30 ml of 96% sulfuric acid at 10–15°. To the resulting slurry was added with stirring 4.5 g (0.044 mol) of powdered potassium nitrate over 1.75 hr while maintaining a temperature of 3–7°. The acetyl compound gradually dissolved, and the color changed from pale orange to dark amber; some frothing occurred. After 1 hr at 5°, the solution was poured over 100 g of ice and made basic with cold, concentrated ammonium hydroxide. The yellow solid was filtered, washed well with cold water and dried, 3.55 g, mp 100–130° (dec).

The crude product was separated into a poorly soluble fraction (1.5 g; mp 165–175°) and a soluble fraction by boiling with 100 ml of 95% ethanol and cooling to 5°. Recrystallization of the former from ethanol gave rosettes melting at 182–183°. The analyses and molecular weight indicate a dinitroisoquinoline.[8] The ^{1}H nmr spectrum is consistent with that required for **4,6-dinitroisoquinoline**. This structure was established unequivocally through use of the Eu(fod)$_3$ shift reagent[9] in $CDCl_3$. As expected, the singlet signals assigned to H_1 and H_3 showed the greatest downfield shift and were broadened. The protons on the benzo ring became well resolved: the signals assigned to H_8 shifted the most, since this proton is closest to the heteroatom, and showed only the splitting expected for ortho coupling (9 Hz); H_5 showed splitting due to meta coupling (2 Hz), whereas H_7, which was shifted the least, appeared as a doublet of doublets (both ortho and meta splitting). If this compound had been the 4,7 isomer, the H_8 signal would have again been shifted further downfield than those for the two other benzo protons but would have shown only meta splitting. Signals appeared at τ (Polysol-d^{10}) 1.32 (6-line multiplet, 2, J_{78} = 9 Hz, J_{57} = 2 Hz, H_7 and H_8), 0.73 (m, 1, J_{57} = 2 Hz plus another 1 Hz splitting, H_5), 0.63 (s, 1, H_1 or H_3), 0.23 (s, 1, H_3 or H_1).

Anal. Calcd for $C_9H_5N_3O_4$: C, 49.32; H, 2.30; N, 19.17; mol wt, 219.15. Found: C, 49.32; H, 2.44; N, 18.93; mol wt (mass spectrum), 219.

From the alcohol soluble fraction, by incremental precipitation with water, there was ultimately recovered 0.9 g of off-white needles melting about 90°. Recrystallization from water gave long felted white needles, obviously hydrated, since they crumbled to a powder when vacuum dried, mp 107–108°. The ir spectrum was identical with that of authentic 5-nitroisoquinoline, whose melting point is reported[11] to be 110°; the ^{1}H nmr spectrum agrees with that expected for the 5-nitro isomer—τ ($CDCl_3$) 2.12 (t, 1, J = 8 Hz, H_7), 1.52 (d, 1, J_{67} = 8.5 Hz, J_{68} = 1 Hz, H_6), 1.38 (d, 1, J = 6.5 Hz, H_4), 1.27 (d, 1, J_{78} = 8.5 Hz, J_{68} = 1 Hz, H_8), 1.08 (d, 1, J = 6.5 Hz, H_3), 0.43 (s, 1, H_1).

Anal. Calcd for $C_9H_6N_2O_2$: C, 62.06; H, 3.47; N, 16.09; mol wt, 174.16. Found: C, 61.82; H, 3.18; N, 16.12; mol wt (mass spectrum), 174.

Reaction of Benzaldehyde and 1a.—A crude sample (mp 195–200°) of 1a (3.5 g, 0.01 mol) was refluxed for 6 hr with 4.4 g (0.04 mol) of benzaldehyde, 50 ml of concentrated hydrochloric acid and 50 ml of 95% ethanol. After cooling and diluting with 100 ml of water, the solution was stored overnight at 5°; a small amount of yellow brown gum separated. The supernatant was decanted and saved (see below); the gum was heated with a few ml of ethanol and cooled. The white solid (0.04 g, mp >300°) was filtered and recrystallized from 90% ethanol containing several drops of hydrochloric acid: colorless, coarse prisms melting at 338–341°. This compound is the dihydrochloride of one of the epimers of 4,4′-dibenzal-1,1′,4,4′-tetrahydro-1,1′-biisoquinoline (see below).

Anal. Calcd for $C_{32}H_{26}Cl_2N_2 \cdot 2H_2O$: C, 70.45; H, 5.54; Cl, 13.00; N, 5.14. Found: C, 70.63; H, 5.27; Cl, 13.36, 13.07; N, 5.07, 5.17.

The picrate derived from this salt decomposed at 315–318° after recrystallization from ethanol as yellow felted needles.

Anal. Calcd for $C_{44}H_{30}N_8O_{14} \cdot H_2O$: C, 57.89; H, 3.53; N, 12.28. Found: C, 58.25; H, 3.52; N, 12.29.

The aqueous supernatant was extracted twice with 100-ml portions of diethyl ether to remove excess benzaldehyde, made basic with 25% aqueous sodium hydroxide, and extracted with three 50 ml portions of benzene. The combined benzene extracts were dried and evaporated to leave 4 g of gummy residue. The latter was triturated with 40 ml of ether–benzene (3:1); the white solid was then filtered, washed with more solvent and dried, 0.24 g (5.5%), mp 270–300°. The extracts were saved (C). This solid was next extracted with 15 ml of boiling benzene to separate the two isomers present.

A. Benzene-Soluble Isomer.—Evaporation of the benzene left a solid, mp 280–283°, which melted at 285–286° after recrystallization from 95% ethanol. The analyses, ^{1}H nmr spectrum, solubility behavior, and melting point suggest that this is the *dl* epimer of **4,4′-dibenzal-1,1′ 4,4′-tetrahydro-1,1′-biisoquinoline, 5a**: τ ($CDCl_3$) 4.39 (s, 1, H_1), 2.93 (s, 5, $H_{aromatic}$ in phenyl ring), 2.62–1.72 (m, 4, $H_{aromatic}$), 1.52 (s, 1, benzal methine), 1.06 (s, 1, H_3).

Anal. Calcd for $C_{32}H_{24}N_2$: C, 88.04; H, 5.54; N, 6.42. Found: C, 88.08; H, 5.52; N, 6.26; mol wt (mass spectrum), 436.

The picrate was obtained as plates after recrystallization from ethanol, mp 268–269° dec.

Anal. Calcd for $C_{44}H_{30}N_8O_{14}$: C, 59.06; H, 3.38; N, 12.52. Found: C, 58.97; H, 3.45; N, 12.66.

B. Benzene-Insoluble Isomer.—This compound was purified by dissolving in 20 ml of dimethylformamide, filtering, and adding 100 ml of diethyl ether. The white, microcrystalline powder was filtered, washed three times with ether, three times with water, and vacuum dried for several days at 68° (25 mm): mp 328–329° dec; absorptions due to NH and carbonyl stretching frequencies were absent in the ir spectrum; mass spectrum *m/e*, 436 (parent), 218 (M/2, base peak), the peak at *m/e* = 91 which would correspond to the loss of a benzyl fragment was very weak; τ (CF_3COOH) 3.72 (s, 1, H_1), 2.70 (s, 5, $H_{aromatic}$ phenyl ring), 1.15–2.05 (m, 4, $H_{aromatic}$), 1.01 (s, 1, benzal methine), 0.45 (s, 1, H_3).

The evidence is consistent with those expected for the meso epimer of **4,4′-dibenzal-1,1′,4,4′-tetrahydro-1,1′-biisoquinoline, 5b.**

Anal. Calcd for $C_{32}H_{24}N_2$: C, 88.04; H, 5.54; N, 6.42. Found: C, 87.84; H, 5.66; N, 6.46, 6.36.

Solutions of this compound have a blue-purple fluorescence. Its picrate, obtained from alcohol as long thin needles, decomposed at 317–320°.

C. 4-Benzal-1,4- (and 3,4-) dihydroisoquinoline.—The ether–benzene extract (see above) was diluted with 100 ml of *n*-hexane and chilled; a pale yellow solid (0.9 g, 20%, mp 90–110°) separated. Additional material was isolated as follows. The mother liquors were evaporated and the very gummy residue boiled with 25 ml of cyclohexane; the chilled solution was decanted from about 1 g of tar (discarded) and evaporated. Trituration of this residue with two small volumes of cold *n*-hexane to remove oily material left more crystalline solid. (The material in these hexane extracts gave a picrate melting at 223–225° after recrystallization from ethanol; a mixture melting point with isoquinoline picrate was not depressed; the ir spectra were identical.) Recrystallization of this solid from *n*-hexane gave a product melting at 99.5–100.5° (by way of comparison the melting point of 4-benzylisoquinoline is 119–120°[12]). The parent peak in the mass spectrum was 219; fragments of mass 128 (M − 91) and mass 91 (benzyl) were present but only had a very low intensity. The ^{1}H nmr spectrum confirmed the absence of a benzyl group (no benzyl methylene signal), but also suggested that the product was roughly a 2:1 mixture of isomers: τ ($CDCl_3$) 5.90, 5.62 (2 s, 2 total, protons of methylene group in the nitrogen bearing ring), 2.78 (s, 5, $H_{aromatic}$ in phenyl ring), 2.67–1.85 (m, 4, $H_{aromatic}$), 1.60 (s, 1, benzal methine), 0.84,

(8) A. Claus and K. Hoffmann, *J. Prakt. Chem.*, **47** (2), 252 (1893), prepared a dinitroisoquinoline, mp 283.5°, by the action of fuming nitric acid on isoquinoline in fuming sulfuric acid, but did not establish the position of the substituents.

(9) R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971).

(10) A proprietary, deuterated solvent made by Stohler Isotope Chemicals, Azusa, Calif.

(11) F. Fortner, *Monatsh. Chem.*, **14**, 146 (1893).

(12) M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **78**, 4090 (1956).

0.76 (2 s, 1 total, H_1 or H_3 in nitrogen ring, depending on isomeric form).

Anal. Calcd for $C_{16}H_{13}N$: C, 87.64; H, 5.97; N, 6.39. Found: C, 87.76; H, 5.98; N, 6.30.

The picrate after two recrystallizations from 95% ethanol melted at 190–192° (reported[12] for 4-benzylisoquinolinium picrate, 195–196°).

Anal. Calcd for $C_{22}H_{16}N_4O_7$: C, 58.93; H, 3.60; N, 12.50. Found: C, 58.62; H, 3.47; N, 12.17.

Small quantities of two other picrates were also isolated when the crude benzal dihydroisoquinoline was treated with picric acid and the salts were fractionally crystallized. One melted at 229–230° (dec) after recrystallization from ethanol; on admixture with isoquinoline picrate, the melting point was 200–210°.

Anal. Calcd for $C_{22}H_{14}N_4O_7$: C, 59.19; H, 3.16; N, 12.55. Found: C, 59.44; H, 3.22; N, 12.49, 12.47.

A hydrobromide prepared from this picrate decomposed at 308–312° after recrystallization from absolute ethanol; its elemental analyses, like that of the picrate, also suggested a lower hydrogen content than that demanded by a salt of **3** or **4**.

Anal. Calcd for $C_{16}H_{12}BrN$: C, 64.45; H, 4.06; Br, 26.80; N, 4.70. Found: C, 64.57; H, 4.04; Br, 26.63; N, 4.59.

The free base from the bromide partially melted, then resolidified at 157–159°, and finally remelted at 225–230°. The base peak (*m/e*) in the mass spectrum was 217; a small peak at 218 (M + 1) was present but there were no peaks at *m/e* 434–436 (coupled products). Fragments of mass 91 (benzyl) and M − 91 were not present.

The other picrate after recrystallization from acetonitrile decomposed at 266–267°; admixture with the picrate of dibenzal tetrahydrobiisoquinoline, mp 268–269° (see above), depressed the melting point to 245–250°. The ir spectra of these two compounds also differed. Perhaps this compound is the picrate of 4,4′-dibenzyl-1,1′-biisoquinoline, but it was not investigated further.

Anal. Calcd for $C_{44}H_{30}N_8O_{14}$: C, 59.06; H, 3.38; N, 12.52. Found: C, 58.95; H, 3.28; N, 12.49.

5,5′-Dinitro-1,1′-biisoquinolin eand 5-Nitro-1,1′-biisoquinoline.—1,1′-Biisoquinoline (8.7 g; 0.039 mol) was nitrated by the procedure of Le Fèvre and Le Fèvre[13] for making 5-nitroisoquinoline. The dried crude product (12.2 g) was dissolved in 2 l. of boiling xylene, filtered from 1.49 of inorganic salts, and chilled to 0°; 8.6 g (72.9%) of dinitro compound was recovered, decomposing at 265–270° after turning black at 250°. A portion was recrystallized from dimethylformamide as pinkish white, feathery needles, melting at 293–294° dec if plunged into a bath preheated to 290°. If heated from room temperature, the compound turned black at 265°, then decomposed at 270–280°: τ ($CF_3COCF_3 \cdot 1.6D_2O$) 2.37 (d, 2, H_7, H_8), 1.25 (m, 1, H_6), 1.05 (s, 2, H_3, H_4).

Anal. Calcd for $C_{18}H_{10}N_4O_4$: C, 62.43; H, 2.94; N, 16.18. Found: C, 62.76; H, 2.82; N, 15.78, 15.87.

Evaporation of the xylene left 2.2 g (20.6%) of solid which was recrystallized from 95% ethanol, mp 186–187° dec. The analyses and nmr are consistent with those required for **5-nitro-1,1′-biisoquinoline**: τ ($CF_3COCF_3 \cdot 1.6D_2O$) 2.65–1.79 (m, 6, H_7, $H_{7'}$, H_8, $H_{8'}$, $H_{5'}$, $H_{6'}$), 1.68–1.44 (m, 3, H_6, $H_{3'}$, $H_{4'}$), 1.28 (s, 2, H_3, H_4).

Anal. Calcd for $C_{18}H_{11}N_3O_2$: N, 13.95. Found: N, 14.04.

Registry No.—**1a**, 25080-52-8; **1b**, 25055-08-7; **2a**, 35202-34-7; **2b**, 35202-35-8; **3**, 35202-36-9; **3** picrate, 35249-61-7; **4**, 35202-37-0; **4** picrate, 35202-38-1; **5a**, 35202-39-2; **5a** picrate, 35202-40-5; **5b**, 35202-41-6; **5b** dihydrochloride, 35202-42-7; **5b** picrate, 35202-43-8; 4-bromoisoquinoline, 1532-97-4; 4-bromiisoquinolinum nitrate, 35202-45-0; 3,3′-biisoquinoline, 35202-46-1; 4,6-dinitroisoquinoline, 35202-47-2; 5-nitroisoquinoline, 607-32-9; 4,4′-dibenzyl-1,1′-biisoquinoline picrate, 35202-49-4.

Acknowledgment.—The assistance of Dr. R. L. Atkins in elucidating the structure of 4,6-dinitroisoquinoline is appreciated.

(13) C. G. La Fèvre and R. J. W. Le Fèvre, *J. Chem. Soc.*, 1470 (1935).

Synthesis and Reactions of 2-Alkylthio-s-triazolo[1,5-*b*]isoquinolin-5(10*H*)-ones

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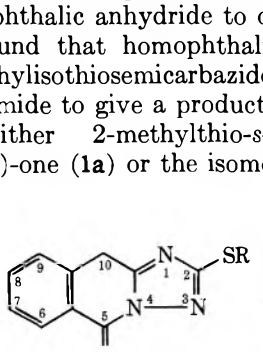
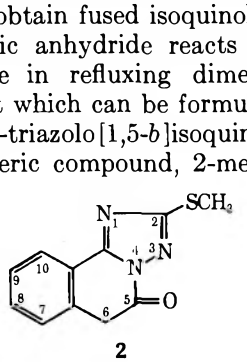
Homophthalic anhydride reacted with *S*-alkylisothiosemicarbazides to give 2-alkylthio-*s*-triazolo[1,5-*b*]isoquinolin-5(10*H*)-ones (**1**). Compounds **1** coupled with diazonium salts to give the 10-arylhydrazones of 5,10-dihydro-2-alkylthio-*s*-thiazolo[1,5-*b*]isoquinoline-5,10-diones (**6**) and condensed with aromatic aldehydes to form the 10-arylmethylene derivatives **11**. Compounds **1** also condensed with nitroso compounds to yield the 10-arylimino derivatives **17**, which on hydrolysis afforded 5,10-dihydro-2-alkylthio-*s*-triazolo[1,5-*b*]isoquinoline-5,10-diones (**18**). Formylation of **1a** gave 5,10-dihydro-2-methylthio-5-oxo-*s*-triazolo[1,5-*b*]isoquinoline-10-carboxaldehyde (**19**).

During investigation of the condensation reactions of homophthalic anhydride to obtain fused isoquinolines, we found that homophthalic anhydride reacts with *S*-methylisothiosemicarbazide in refluxing dimethylformamide to give a product which can be formulated as either 2-methylthio-*s*-triazolo[1,5-*b*]isoquinolin-5(10H)-one (**1a**) or the isomeric compound, 2-methylthio-*s*-triazolo[5,1-*a*]isoquinolin-5(6*H*)-one (**2**). The 2-ethylthio (**1b**) and 2-benzylthio (**1c**) analogs were similarly prepared.



1a, R = CH_3
b, R = C_2H_5
c, R = $CH_2C_6H_5$

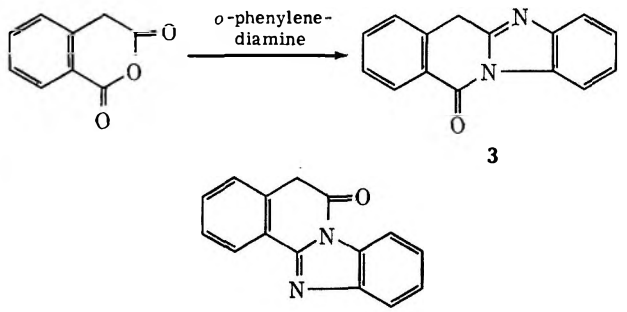


2

The available data are compatible with the linear structure **1**, rather than the angular structure **2**. Homophthalic anhydride has been reported to react with hydrazine to yield *N*-aminohomophthalimide,[1] and to condense with *o*-phenylenediamine to give mainly the linear product **3** and not **4**.[2-5]

The ir spectrum of **1a** shows carbonyl absorption at 1720 cm^{-1}. For a comparison between the ir spectra

(1) G. Rosen and F. D. Popp, *J. Heterocycl. Chem.*, **6**, 9 (1969).
(2) A. Bistrzycki and K. Fassler, *Helv. Chim. Acta*, **6**, 519 (1923).
(3) M. F. Sartori, A. Oken, and H. E. Schroeder, *J. Org. Chem.*, **31**, 1498 (1966).
(4) E. Schefczik, *Justus Liebigs Ann. Chem.*, **729**, 83 (1969).
(5) A. Mustafa, M. I. Ali, and A. A. El-Sayed, *ibid.*, **739**, 68 (1970).



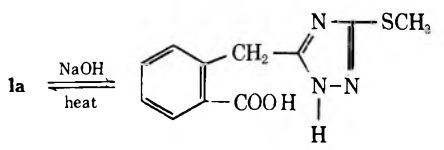
3

4

of **1a** and those of its coupling product **6a** and its benzylidene derivative **11a**; see below.

The nmr spectrum (TFA) of **1a** shows a methyl group (s) at δ 2.90 ppm and a methylene group (s) at 5.10. Three of the aromatic protons appear as a multiplet centered at δ 7.25 and the fourth appears as a multiplet centered at 8.0. The methylene signal disappeared when the spectrum was taken in DMSO-d_6 plus D_2O.

Compound **1a** undergoes ring opening in aqueous sodium hydroxide to give 3-*o*-carboxybenzyl-5-methylthio-1,2,4-triazole (**5**), which can be isolated on acidification. When **5** is heated above its melting point or in boiling dimethylformamide, it reverts to the original compound **1a**.



5

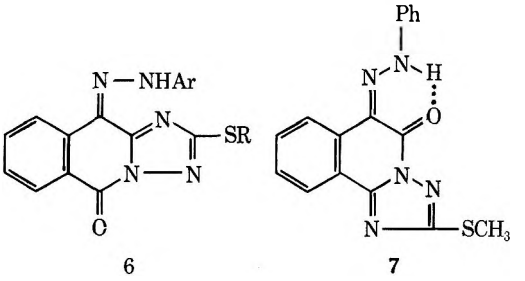
Compound **5** also has been obtained when the reaction between homophthalic anhydride and *S*-methylisothiosemicarbazide was carried out in dimethylformamide at room temperature for several days.

The pyridone ring in **1a** also was opened by the action of phenylhydrazine to give the phenylhydrazide of **5**.

Compounds **1** coupled with aryldiazonium salts in pyridine to yield the corresponding 10-arylazo derivatives, more properly represented as 5,10-dihydro-2-alkylthio-*s*-triazolo[1,5-*b*]isoquinoline-5,10-dione 10-arylhydrazones (**6a–l**) (see Table I, Experimental Section). Unlike azo compounds obtained from diazonium salts coupled with aliphatic carbon atoms, which absorb strongly at ~280 nm, the uv spectrum of **6a** shows an absorption maximum at 446 nm; similar hydrazones are known to exhibit strong absorption at wavelengths higher than 320 nm.[6]

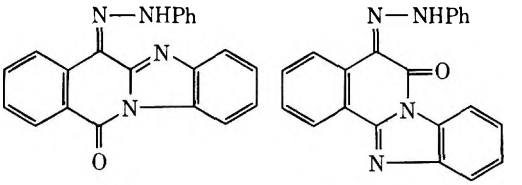
The ir spectral data provide further evidence that the starting compound has the linear structure **1a**. Thus the phenylhydrazone **6a** shows carbonyl absorption at 1720 cm^{-1}, almost with no shift from that of the starting compound **1a**. If this phenylhydrazone derivative has formula **7** (derived from the angular structure **2**), it would reveal a large downward shift in the frequency of the CO group, due to the conjugation of the C=O with C=N and the strong chelation that would be expected to occur between the hydrazone H and the CO group.[6] On the other hand, the linear formula

(6) H. C. Yao and P. Resnick, *J. Amer. Chem. Soc.*, **84**, 3514 (1962).



6 7

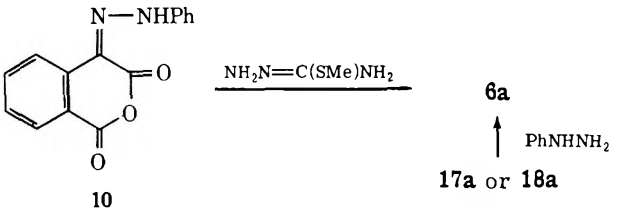
6a affords structural environment for the CO group which is similar to that of the starting material **1a**. The relation between CO absorption in **1a** and **6a** is substantiated by the absence of any significant shift in the CO absorption in **3** and its phenylhydrazone derivative **8**.[5] On the other hand, the ir spectra of the angular compound **4** and its phenylhydrazone derivative **9**[5] reveal a considerable downward shift in the CO absorption.



8 9

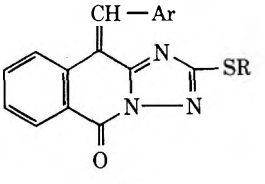
ν_{CO} of **8**, 1693 cm^{-1} ν_{CO} of **9**, 1642 cm^{-1}
ν_{CO} of **3**, 1684 cm^{-1} ν_{CO} of **4**, 1705 cm^{-1}

The phenylhydrazone **6a** also has been prepared by heating the phenylazo derivative, **10**,[7] of homophthalic anhydride with *S*-methylisothiosemicarbazide.



10

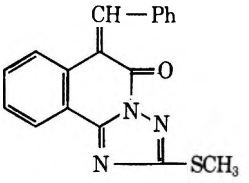
Compounds **1** condensed with aromatic aldehydes, in refluxing acetic acid in the presence of anhydrous sodium acetate, to give 10-arylmethylene-2-alkylthio-*s*-triazolo[1,5-*b*]isoquinolin-5(10*H*)-ones (**11a–j**) (see



11

Table II, Experimental Section). The ir spectrum of the benzylidene derivative **11a** shows carbonyl absorption near 1717 cm^{-1}, similar to that of the starting compound **1a**. Again, if the starting material has the angular structure **2**, the CO group of its benzylidene derivatives **12** will be conjugated with C=C double bond, a combination which is known to lower the stretching frequency of the CO group.[8] The absence

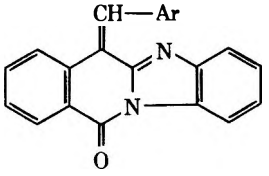
(7) W. Dieckmann and W. Meiser, *Chem. Ber.*, **41**, 3253 (1908).
(8) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen Ltd., London, 1957, p 136.



12

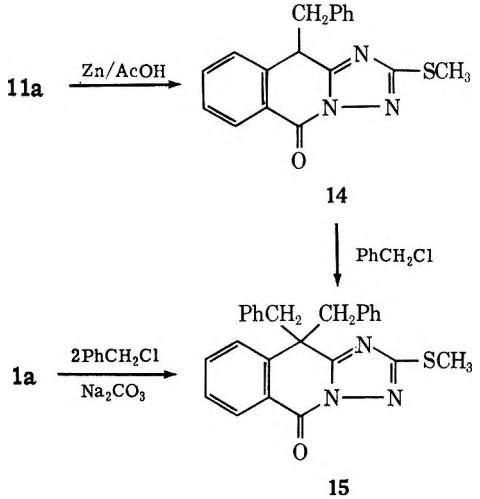
of such a shift in the ir spectrum of **11a** is in favor of the linear structure **1a**.

In a similar manner, we have prepared the arylmethylene derivatives **13a** and **13b**, from **3** and *p*-chloro- and *p*-nitrobenzaldehyde, respectively.

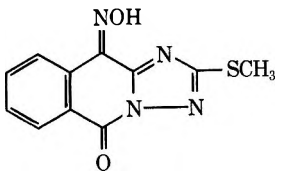


13a, Ar = C_6H_4Cl-*p*
b, Ar = $C_6H_4NO_2$-*p*

The benzylidene derivative **11a** is reduced by zinc dust and acetic acid (or by thiophenol at 140°) to form 10-benzyl-2-methylthio-*s*-triazolo[1,5-*b*]-isoquinolin-5(10*H*)-one (**14**). Reaction of the latter with benzyl chloride in presence of sodium carbonate yielded the 10,10-dibenzyl derivative **15**. The latter compound

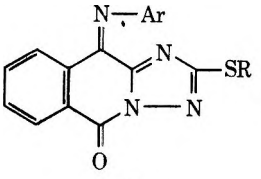


was also obtained from the reaction of **1a** with an excess of benzyl chloride. Compound **1a** underwent nitrosation at the methylene group on treatment with nitrous acid to give the oximino derivative **16**.

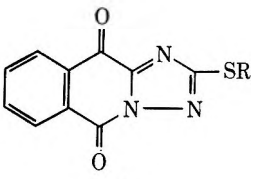


16

Compounds **1** reacted with nitroso compounds to yield 10-arylimino-2-alkylthio-*s*-triazolo[1,5-*b*]isoquinolin-5-(10*H*)-ones (**17a–d**) (see Table III, Experimental Section), which were hydrolyzed by a hydrochloric–acetic mixture to give the diketo compounds 5,10-dihydro-2-alkylthio-*s*-triazolo[1,5-*b*]isoquinoline-5,10-diones (**18**).



17

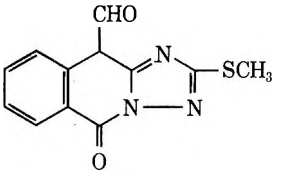


18

Compounds **17a** and **18a** reacted with phenylhydrazine to form the phenylhydrazone derivative **6a**.

The diketo compound **18a** condensed with *o*-phenylenediamine in refluxing acetic acid to give a product formulated as **17e**.

Formylation of **1a** with dimethylformamide and phosphorus oxychloride gave 5,10-dihydro-2-methylthio-5-oxo-*s*-triazolo[1,5-*b*]isoquinoline-10-carboxaldehyde (**19**), which was characterized as its phenylhydrazone and semicarbazone.



19

Experimental Section

Ir spectra (KBr disks, unless otherwise stated) were recorded on a Perkin-Elmer 457 grating ir spectrophotometer. Nmr spectra were recorded on a Varian A-60A spectrophotometer, with TMS as internal reference. The uv spectrum was recorded on a Beckman DK spectrophotometer.

2-Methylthio-*s*-triazolo[1,5-*b*]isoquinolin-5(10*H*)-one (1a).—A mixture of 16.3 g (0.1 mol) of homophthalic anhydride, 27.7 g (0.12 mol) of *S*-methylisothiosemicarbazide hydriodide, and 16.4 g (0.2 mol) of anhydrous fused sodium acetate in 50 ml of dry dimethylformamide was gently heated, with shaking, to boiling. The source of heat was removed, and the reaction mixture, which continued to boil on its own accord, was shaken for 10 min, left to cool somewhat, and then poured into ~200 ml of cold water. The greenish white precipitate that separated was filtered off, washed with little ethanol, and finally crystallized from dimethylformamide to give 17 g (73.5%) of **1a**, mp 255°.

Anal. Calcd for $C_{11}H_9N_3OS$: C, 57.11; H, 3.92; N, 18.18; S, 13.86; mol wt, 231.3. Found: C, 57.40; H, 4.00; N, 17.90; S, 13.80; *m/e* 231.

The 2-ethylthio analog **1b** was similarly prepared using *S*-ethylisothiosemicarbazide hydriodide. A 70% yield of **1b** was obtained, recrystallized from dimethylformamide, mp 224°.

Anal. Calcd for $C_{12}H_{11}N_3OS$: C, 58.75; H, 4.52; S, 13.07. Found: C, 58.87; H, 4.72; S, 12.93.

The 2-benzylthio analog **1c** was similarly obtained using *S*-benzylisothiosemicarbazide hydrochloride, in ~40% yield. It was crystallized from ethanol, mp 195°.

Anal. Calcd for $C_{17}H_{13}N_3OS$: C, 66.41; H, 4.26; S, 10.43. Found: C, 66.14; H, 4.50; S, 10.62.

3-(*o*-Carboxybenzyl)-5-methylthio-*s*-triazole (**5**). A.—A mixture of 8.1 g (0.05 mol) of homophthalic anhydride, 13.9 g (0.06 mol) of *S*-methylisothiosemicarbazide hydriodide and 8.2 g (0.1 mol) of anhydrous fused sodium acetate in 50 ml of dry dimethylformamide was left at room temperature for several days with occasional shaking (little methanethiol evolved). The reaction mixture was poured into 200 ml of cold water and left for some time. The crystalline white precipitate that separated was filtered off and recrystallized from ethanol to give 4 g (33%) of **5**, mp 195° dec (solidified and then melted again at ~250°), not depressed on admixture with the product prepared as described in B below.

Anal. Calcd for $C_{11}H_{11}N_3O_2S$: C, 52.99; H, 4.45; S, 12.86. Found: C, 52.85; H, 4.45; S, 13.01.

B.—A solution of 4.6 g of **1a** in 50 ml of 5% NaOH was refluxed until it lost its fluorescence (~3 hr), and the solution was left to cool and was acidified with dilute acetic acid. The white precipitate formed was collected, washed with water, and crystallized from ethanol to give 3 g (61%) of **5**, mp 195°, not depressed on admixture with the previous compound.

Cyclization of 5 to 1a. A.—Two grams of **5** was refluxed in 10 ml of dimethylformamide for 15 min and then poured into 50 ml of cold water. The greenish precipitate formed was filtered off, triturated with a solution of sodium carbonate, and washed with water. It was crystallized from dimethylformamide to give 1 g (53%) of **1a**, mp and mmp 255°.

B.—Two grams of **5** was heated in an oil bath at 200° (bath temperature) for 15 min. The reaction mixture was worked up as above to yield 1.2 g (64%) of **1a**.

Phenylhydrazide of 5.—A suspension of 2 g of **1a** and 1.1 g of phenylhydrazine in 30 ml of ethanol was refluxed for 3 hr and left overnight. The orange crystals that separated were filtered off, washed with a small amount of ethanol, and recrystallized from dilute dioxane to give 1.8 g (60%) of the phenylhydrazide of **5**, mp 240°.

Anal. Calcd for $C_{17}H_{17}N_5OS$: C, 60.15; H, 5.05. Found: C, 60.44; H, 4.91.

5,10-Dihydro-2-alkylthio-*s*-triazolo[1,5-*b*]isoquinoline-5,10-dione 10-Arylhydrazones (6a–l). General Procedure.—About 2 g of **1** was dissolved in 40 ml of pyridine, cooled in an ice bath, and treated with an equimolecular amount of the appropriate diazotized aniline. The mixture was left for 1 hr and then poured into cold water. The precipitate was collected, dried, and crystallized from the proper solvent. See Table I.

TABLE I

5,10-DIHYDRO-2-ALKYLTHIO-*s*-TRIAZOLO[1,5-*b*]ISOQUINOLINE-5,10-DIONE 10-ARYLHYDRAZONES (6)

Compd	R	Ar	Solvent of crystn[a]	Mp, °C	Yield, %[b]
6a	CH_3	C_6H_5	A	238	90
6b	CH_3	$C_6H_4CH_3$-*p*	A	258	92
6c	CH_3	$C_6H_4OCH_3$-*p*	B	233	82
6d	CH_3	$C_6H_4OC_2H_5$-*p*	B	205	82
6e	CH_3	C_6H_4Br-*p*	A	245	87
6f	CH_3	$C_6H_4NO_2$-*p*	A	280	79
6g	C_2H_5	C_6H_5	B	205	90
6h	C_2H_5	$C_6H_4OCH_3$-*p*	B	165	84
6i	C_2H_5	C_6H_4Br-*p*	B	197	87
6j	C_2H_5	$C_6H_4NO_2$-*p*	A	258	76
6k	$C_6H_5CH_2$	C_6H_5	A	230	75
6l	$C_6H_5CH_2$	C_6H_4Br-*p*	B	203	75

[a] A, nitrobenzene; B, acetic acid. [b] Satisfactory analytical data (±0.4%) were reported for all compounds: **6a** (C, H, N, S); **6b**, **6g**, **6h** (C, H, S); **6c** (S, Br); all others, S only.

Reaction of Phenylazohomophthalic Anhydride (10) with *S*-Methylisothiosemicarbazide Hydriodide.—A mixture of 2.6 g of **10**, 2.8 g of *S*-methylisothiosemicarbazide hydriodide, 2 g of fused anhydrous sodium acetate, and 10 ml of dry dimethylformamide was heated gently, with shaking, to boiling. The reaction mixture (heating discontinued) was then shaken occasionally for 10 min and poured into cold water. The precipitate formed was collected, washed with ethanol, and crystallized from nitrobenzene to give 2.8 g (85%) of **6a**, mp and mmp 238°.

10-Arylmethylene-2-alkylthio-*s*-triazolo[1,5-*b*]isoquinolin-5(10*H*)-ones (11). General Procedure.—A mixture of 2 g of **1**, 3 g of anhydrous fused sodium acetate, 20 ml of acetic acid, and an equimolecular amount of the appropriate aldehyde was refluxed for 3 hr. The reaction mixture was cooled and poured into cold water. The precipitate formed was collected, washed with water, and finally crystallized from the proper solvent. See Table II.

12-*p*-Chloro- (13a) and 12-*p*-Nitrobenzylidenebenzimidazo[1,2-*b*]isoquinolin-5(12*H*)-one (13b).—A mixture of 2 g of **4**, 3 g of fused anhydrous sodium acetate, 20 ml of acetic acid, and 0.9 g of *p*-chlorobenzaldehyde was refluxed for 20 min. The reaction mixture was left to cool and the solid **13a** that separated was filtered off, washed with water, and finally crystallized from dioxane, mp 245°, yield 82%.

TABLE II

10-ARYLMETHYLENE-2-ALKYLTHIO-*s*-TRIAZOLO[1,5-*b*]-ISOQUINOLIN-5(10*H*)-ONES (11)

Compd	R	Ar	Solvent of crystn[a]	Mp, °C	Yield, %[b]
11a	CH_3	C_6H_5	A	165	87
11b	CH_3	$C_6H_5OCH_3$-*p*	A	145	85
11c	CH_3	C_6H_4Cl-*o*	A	201	85
11d	CH_3	$C_6H_4NO_2$-*p*	B	260	89
11e	C_2H_5	C_6H_5	C	149	84
11f	C_2H_5	$C_6H_5CH{=}CH$	A	177	79
11g	C_2H_5	$C_6H_4NO_2$-*p*	A	211	89
11h	$CH_2C_6H_5$	C_6H_5	A	155	77
11i	$CH_2C_6H_5$	C_6H_4Cl-*p*	A	175–176	90

[a] A, acetic acid; B, dimethylformamide; C, dilute dioxane. [b] Satisfactory analytical data (±0.4%) were reported for all compounds: **11a** (C, H, N, S); **11e**, **11g**, **11h** (C, H, S); **11i** (S, Cl); all others, S only.

Anal. Calcd for $C_{22}H_{13}ClN_2O$: C, 74.05; H, 3.67. Found: C, 74.40; H, 3.84.

The *p*-nitrobenzylidene derivative **13b** was similarly prepared in 85% yield. It was crystallized from dimethylformamide, mp 280°.

Anal. Calcd for $C_{22}H_{13}N_3O_3$: C, 71.93; H, 3.57. Found: C, 72.26; H, 3.78.

10-Benzyl-2-methylthio-*s*-triazolo[1,5-*b*]isoquinolin-5(10*H*)-one (14). A.—A solution of 1 g of **11a** in 20 ml of acetic acid was gradually treated with 1 g of zinc dust. The mixture was then refluxed till the yellow color of the solution disappeared. The solution was filtered and the filtrate was diluted with water. The product **14** was collected and crystallized from acetic acid as pale yellow crystals, mp 225°, yield 62%. **14** was readily soluble in 5% aqueous sodium hydroxide and gave a green fluorescent solution.

Anal. Calcd for $C_{18}H_{15}N_3OS$: C, 67.26; H, 4.70; *S*, 9.98. Found: C, 67.43; H, 4.77; S, 9.94.

B.—A mixture of 1 g of **11a**, 0.5 g of thiophenol, and 1 drop of piperidine was heated at 140° for 2 hr. The mass was triturated with little ethanol and then crystallized from acetic acid to give pale yellow crystals of **14**, mp 225°, not depressed on admixture with the above product.

10,10-Dibenzyl-2-methylthio-*s*-triazolo[1,5-*b*]isoquinolin-5-(10*H*)-one (15). A.—A suspension of 0.5 g of **14** in 20 ml of 10% sodium carbonate solution and 10 ml of ethanol was treated with 0.3 g of freshly distilled benzyl chloride. The whole was refluxed for 3 hr, diluted with water, and cooled. The solid that separated was filtered off and crystallized from ethanol to give colorless crystals of **15**, mp 160°, not depressed on admixture with a sample prepared as described in B below.

Anal. Calcd for $C_{25}H_{21}N_3OS$: C, 72.96; H, 5.14; S, 7.79. Found: C, 73.01; H, 5.22; S, 7.78.

B.—A mixture of 2.3 g (1 mol) of **1a**, 50 ml of 10% sodium carbonate solution, 20 ml of ethanol, and 2.6 g (2 mol) of benzyl chloride was refluxed for 3 hr. The reaction mixture was cooled and poured into cold water. The precipitate formed **15**, which was collected, washed with water, and finally crystallized from ethanol, mp 160°.

5,10-Dihydro-2-methylthio-*s*-triazolo[1,5-*b*]isoquinoline-5,10-dione 10-Oxime (16).—A suspension of 1 g of **1a** in 5 ml of concentrated hydrochloric acid and 20 ml of water was cooled to 0° and treated with 0.3 g of sodium nitrite in 10 ml of water with stirring. The solid that separated was collected, washed with water, and finally crystallized from acetic acid to give 0.85 g (75%) of **16**, mp 235–236°.

Anal. Calcd for $C_{11}H_8N_4O_2S$: C, 50.75; H, 3.09; S, 12.31. Found: C, 51.10; H, 2.90; S, 12.21.

10-Arylimino-2-alkylthio-*s*-triazolo[1,5-*b*]isoquinolin-5(10*H*)-ones (17).—A cold solution of 3.14 g of *p*-nitrosodimethylaniline hydrochloride in 100 ml of methanol was treated with a cold solution of 0.8 g of sodium hydroxide in 50 ml of methanol. This mixture was added to an equimolecular amount of **1** in 50 ml of dimethylformamide. The reaction mixture was left overnight and then poured into cold water. The blue precipitate formed was collected, washed with water and then with ethanol, and finally crystallized from benzene. See Table III.

TABLE III

10-ARYLIMINO-2-ALKYLTHIO-s-TRIAZOLO[1,5-b]ISOQUINOLIN-5(10H)-ONES (17) AND 5,10-DIHYDRO-2-ALKYLTHIO-s-TRIAZOLO-[1,5-b]ISOQUINOLINE-5,10-DIONES (18)

Compd	R	Ar	Solvent of crystn[a]	Mp, °C	Yield, %[b]
17a	CH_3	$C_6H_4N(CH_3)_2$-p	A	218	62
17b	C_2H_5	C_6H_5	A	175	67
17c	C_2H_5	$C_6H_4N(CH_3)_2$-p	A	205	64
17d	$CH_2C_6H_5$	$C_6H_4N(CH_3)_2$-p	A	162	59
18a	CH_3		B	255	72
18b	C_2H_5		B	188	68
18c	$CH_2C_6H_5$		B	194	61

[a] A, benzene; B, acetic acid. [b] Satisfactory analytical data (±0.4%) were reported for all compounds: **17a, 17c, 18a** (C, H, S); all others, S only.

Reaction of 1b with Nitrosobenzene.—A mixture of 1 g of **1b**, 0.5 g of nitrosobenzene, and 20 ml of ethanol was refluxed for 1 hr. The reaction mixture was left to cool whereas a bluish white precipitate was formed. The precipitate was collected and crystallized from benzene to give 1 g of **17b**, mp 175°.

Reaction of 17a with Phenylhydrazine.—A suspension of 1.2 g of **17a** and 0.4 g of phenylhydrazine was refluxed in 30 ml of ethanol for 3 hr. The orange crystals formed were collected, washed with little ethanol, and recrystallized from nitrobenzene to give 0.7 g (63%) of **6a**, mp and mmp 238°.

5,10-Dihydro-2-alkylthio-s-triazolo[1,5-b]isoquinoline-5,10-diones (18).—A solution of 2 g of **17** in 20 ml of acetic acid was treated with 5 ml of concentrated hydrochloric acid (the blue color of the solution turned brown). The solution was poured into cold water and the precipitate formed was collected, washed with water, and crystallized from the proper solvent to give **18** (see Table III): ir of **18a**, 1735 (CO), 1720 cm^{-1} (CO amide).

Reaction of 18a with Phenylhydrazine.—A suspension of 1.2 g of **18a** and 0.6 g of phenylhydrazine was refluxed in 30 ml of ethanol for 3 hr. The product obtained was collected, washed with little ethanol, and crystallized from nitrobenzene to give 1.2 g (72%) of **6a**, mp and mmp 238°.

10-o-Aminophenylimino-2-methylthio-s-triazolo[1,5-b]isoquinolin-5(10H)-one (17e).—A mixture of 0.6 g of **18a** and 0.3 g of o-phenylenediamine was refluxed in 20 ml of acetic acid for 15 min. The product was collected and crystallized from dimethylformamide to give 0.7 g (85%) of **17e**, mp 275°.

Anal. Calcd for $C_{17}H_{13}N_5OS$: C, 60.87; H, 3.91; S, 9.56. Found: C, 60.90; H, 4.20; S, 9.45.

5,10-Dihydro-2-methylthio-5-oxo-s-triazolo[1,5-b]isoquinoline-10-carboxaldehyde (19).—To a solution of 3 ml of phosphorus oxychloride in 10 ml of dimethylformamide was added 4 g of finely powdered **1a**. The reaction mixture was heated on a water bath for 6 hr, left to cool, and treated with ~50 ml of cold 10% NaOH solution. The solid that separated was filtered off, washed with water, and crystallized from ethanol to give 3.1 g (70%) of yellow crystals of **19**, mp 280°. When this compound was left for some time, its yellow color turned to green; thus it was identified as its derivatives.

The phenylhydrazone of **19** was prepared by heating **19** with phenylhydrazine in boiling ethanol for 10 min. The yellow solid that separated was filtered off and crystallized from acetic acid, mp 245°.

Anal. Calcd for $C_{18}H_{15}N_5OS$: C, 61.87; H, 4.32; N, 20.05. Found: C, 61.59; H, 4.48; N, 20.37.

The semicarbazone was similarly prepared. It was crystallized from dimethylformamide, mp 260°.

Anal. Calcd for $C_{13}H_{12}N_6O_2S$; C, 49.36; H, 3.83; S, 10.14. Found: C, 49.60; H, 4.10; S, 10.20.

Registry No.—**1a**, 35146-79-3; **1b**, 35146-80-6; **1c**, 35146-81-7; **5**, 35146-82-8; **5** phenylhydrazide, 35146-83-9; **6a**, 35146-84-0; **6b**, 35146-85-1; **6c**, 35146-86-2; **6d**, 35146-87-3; **6e**, 35146-88-4; **6f**, 35146-89-5; **6g**, 35146-90-8; **6h**, 35146-91-9; **6i**, 35146-92-0; **6j**, 35146-93-1; **6k**, 35146-94-2; **6l**, 35146-95-3; **11a**, 35191-68-5; **11b**, 35191-69-6; **11c**, 35191-70-9; **11d**, 35191-71-0; **11e**, 35211-91-7; **11f**, 35191-72-1; **11g**, 35191-73-2; **11h**, 35191-74-3; **11i**, 35191-75-4; **13a**, 35146-96-4; **13b**, 35146-97-5; **14**, 35146-98-6; **15**, 35146-99-7; **16**, 35147-00-3; **17a**, 35147-01-4; **17b**, 35147-02-5; **17c**, 35147-03-6; **17d**, 35147-04-7; **17e**, 35147-05-8; **18a**, 35147-06-9; **18b**, 35147-07-0; **18c**, 35147-08-1; **19**, 35147-09-2; **19** phenylhydrazone, 35147-10-5; **19** semicarbazone, 35147-11-6.

Acknowledgment.—The authors wish to thank Dr. A. S. Shawali of the same department for his help with the spectral data.

Reactions of Vinyl Azides with α-Keto Phosphorus Ylides. Synthesis of N^1-Vinyltriazoles

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The reaction of vinyl azides (**1**) with α-ketophosphoranes (**2**) provides a convenient synthesis of 1-vinyl-1,2,3-triazoles (**3**). No reaction of the ylide with the C=C and/or C=O function occurred at room temperature, as was inferred by nmr analysis of the crude reaction products. An nmr criterion is described to eluciate the stereochemistry of the trisubstituted olefinic N-1 substituents of the adducts. This criterion is further used to determine unambiguously the stereochemistry of the first bis(vinyl azide), **6**, prepared from dibenzalacetone (**4**).

Recently, two methods have been developed for the synthesis of N^1-vinyltriazoles. The first method involves the condensation of active methylene compounds with vinyl azides under basic conditions.[1] This method is applicable to simple vinyl azides,[2] but fails when α-azidovinyl ketones are used as substrates. Only tarry materials are then produced. The second method consists of reacting vinyl azides with acetylenic compounds[3] by the well-known 1,3-dipolar cycloaddition process.[4] In most cases, however, the method suffers from the disadvantage of producing the two possible regioisomeric[5] triazoles. In the present paper,

(1) G. L'abbé and A. Hassner, *J. Heterocycl. Chem.*, **7**, 361 (1970); G. L'abbé, *Ind. Chim. Belge*, **36**, 3 (1971).

(2) G. L'abbé and A. Hassner, *Angew. Chem.*, **83**, 103 (1971); *Angew. Chem., Int. Ed. Engl.*, **10**, 98 (1971).

(3) G. L'abbé, J. E. Galle, and A. Hassner, *Tetrahedron Lett.*, 303 (1970); G. L'abbé and A. Hassner, *Bull. Soc. Chim. Belg.*, **80**, 209 (1971).

(4) R. Huisgen, *Angew. Chem.*, **75**, 741 (1963); *Angew. Chem. Int. Ed. Engl.*, **2**, 633 (1963); *J. Org. Chem.*, **33**, 2291 (1968); G. L'abbé, *Chem. Rev.*, **69**, 345 (1969).

(5) A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

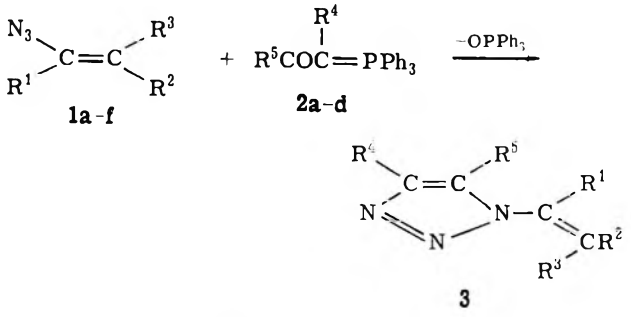
TABLE I

SYNTHESIS OF N^1-VINYLTRIAZOLES

Ylide 2	Vinyl azide 1	Reaction time at room temperature	Vinyltriazole 3 R¹	R²	R³	R⁴	R⁵	No.	Isolated yield, %	Mp, °C
2a	1a	1 month	Ph	H	H	Me	Me	3a	54	76–77
2b	1a	3 weeks	Ph	H	H	H	Me	3b	*a*	Orange liquid
2b	1b	0.5 hr	H	PhCO	H	H	Me	3c	98	142–142.5
2b	1c	4.5 months	PhCO	H	Me	H	Me	3d	20	109–110
2b	1d	1 month	PhCO	H	Ph	H	Me	3e	*a*	Red oil
2b	1e	30 days	PhCO	H	*m*-$NO_2C_6H_4$	H	Me	3f	75	162–163
2c	1a	3.5 months	Ph	H	H	H	Ph	3g	*a*	Orange oil
2c	1b	1.5 hr	H	PhCO	H	H	Ph	3h	95	132–133
2c	1c	4.5 months	PhCO	H	Me	H	Ph	3i	15	103.5–104.5
2c	1d	2 months	PhCO	H	Ph	H	Ph	3j	44	109–111
2c	1f	8 days	PhCO	H	*p*-$NO_2C_6H_4$	H	Ph	3k	63	161–162
2d	1b	1 day	H	PhCO	H	H	*p*-$NO_2C_6H_4$	3l	96	174.5–175.5
2d	1d	7.5 months	PhCO	H	Ph	H	*p*-$NO_2C_6H_4$	3m	60	78–79
2d	1f	8 days	PhCO	H	*p*-$NO_2C_6H_4$	H	*p*-$NO_2C_6H_4$	3n	64	89–90
2d	1e	47 days	PhCO	H	*m*-$NO_2C_6H_4$	H	*m*-$NO_2C_6H_4$	3o	64	62–65, 158–160[b]

[a] A sample of the pure triazole has been isolated by column chromatography on silica gel (EtOAc). [b] This triazole seems to exist in two different crystalline forms with different melting points and different ir (KBr) spectra. The ir spectra in DMSO solution, as well as the nmr spectra, are the same.

a third and regiospecific method is described for the synthesis of N^1-vinyltriazoles (**3**), based on the reactions of vinyl azides (**1**) with α-ketophosphoranes (**2**).



1a–f **2a–d** **3**

1a, R^1 = Ph; $R^2 = R^3$ = H
b, $R^1 = R^3$ = H; R^2 = PhCO
c, R^1 = PhCO; R^2 = H; R^3 = Me
d, R^1 = PhCO; R^2 = H; R^3 = Ph
e, R^1 = PhCO; R^2 = H; R^3 = *m*-$NO_2C_6H_4$
f, R^1 = PhCO; R^2 = H; R^3 = *p*-$NO_2C_6H_4$

2a, $R^4 = R^5$ = Me
b, R^4 = H; R^5 = Me
c, R^4 = H; R^5 = Ph
d, R^4 = H; R^5 = *p*-$NO_2C_6H_4$

In the formal sense, four different pathways can be envisaged for the reactions of α-ketophosphoranes with the vinyl azides studied in this work: *i.e.*, reaction of the ylide with (1) the azide function,[6] (2) the C=C bond,[7] (3) the β-carbon atom of β-azidovinyl ketones (β-ketovinylation[8] followed by transylidation[7]), and (4) the C=O bond of azidovinyl ketones (Wittig reaction[9]).

To determine the reaction course, equimolar amounts of the two reagents were allowed to react in dichloromethane at room temperature to completion. The mixtures were then analyzed by nmr. In all but two cases (namely with vinyl azide **1c**) the nmr spectra indicated the formation of vinyltriazoles (**3**) exclusively. With α-azidoethylideneacetophenone (**1c**), decomposition of the azide to untractable tars (*ca.* 15%) under the basic conditions competed with triazole formation. The results are summarized in Table I (optimalization of the yields was not attempted).

All isolated products exhibited analytical and spectral data in accordance with the assigned structures. The regiochemistry of this reaction has been well established[6] and is further substantiated in this work by the isolation of the known triazoles **3b** and **3g**.

The stereochemistry about the olefinic C=C bond, however, was considered in more detail, since cis–trans isomerization might have occurred under the basic reaction conditions.[10] That this is not the case was evident from the nmr spectra. The 100-MHz spectra of compounds **3c** (C_6D_6) and **3l** ($CDCl_3$) showed two doublets in the aromatic region ($\tau \sim 2$), characteristic of an AB system with a coupling constant of 14 Hz (*trans*-vinyl hydrogens, ir 950 cm^{-1}). We were also able to elucidate by nmr ($CDCl_3$) the configuration of the other disubstituted vinyltriazoles (trisubstituted olefins). Indeed, the methyl protons of the R^3 substituent in compounds **3d** (τ 8.18) and **3i** (τ 8.12) were shielded by ~0.15 ppm relative to the parent olefin (τ 8.00). This effect is attributed to the ring current of the triazole group in cis position to the methyl substituent. An even more pronounced effect was observed for the *o*-phenyl protons of R^3 in compounds **3e**, **3j**, and **3m**, which absorbed in the region τ 3.0–3.4 (multiplet). The corresponding ortho protons in *trans*-chalcone resonated at τ 2.4–2.8. The absorption patterns of the other examples in Table I were much more complex, but detailed analysis with a 100-MHz instrument pointed to the same conclusion.

The absence of isomerization was also indicated by the reaction of β-azidoacrylonitrile (**1g**) with *p*-nitrobenzoylmethylenetriphenylphosphorane (**2d**). The synthetic method used to prepare **1g** furnished a cis-

(6) G. R. Harvey, *J. Org. Chem.*, **31**, 1587 (1966); P. Ykman, G. L'abbé, and G. Smets, *Tetrahedron*, **27**, 845, 5623 (1971).

(7) H. J. Bestmann and R. Zimmerman, *Fortschr. Chem. Forsch.*, **20**, 1 (1971).

(8) M. I. Rybinskaya, A. N. Nesmeyanov, and N. K. Kochetkov, *Usp. Khim.*, **38**, 961 (1969); *Russ. Chem. Rev.*, **38**, 433 (1969).

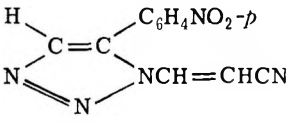
(9) A. W. Johnson, "Ylid Chemistry," A. T. Blomquist, Ed., Academic Press, New York, N. Y., 1966, p 132.

(10) A. Hassner, G. L'abbé, and M. J. Miller, *J. Amer. Chem. Soc.*, **93**, 981 (1971).

trans mixture in a ratio of 37:63 (see Experimental Section). When this mixture was allowed to react to completion with the ylide, the two geometrical vinyltriazoles (**3p**) were obtained in the same cis–trans ratio (quantitative yield). Structure assignment of the isomeric vinyltriazoles **3p** was based on the coupling constants of the olefinic protons, being 9.5 (cis) and 14 Hz (trans).

$N_3CH{=}CHCN + p\text{-}NO_2C_6H_4COCH{=}PPh_3 \xrightarrow[-OPPh_3]{2\ days}$

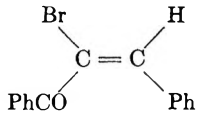
cis–trans-**1g** **2d**



cis–trans-**3p**

The nmr criterion described above can now be used to determine the stereochemistry of the first bis(vinyl azide), **6**, prepared in this laboratory. The synthetic method consists of treating **5** (the bromine adduct of **4**) with 4 equiv of sodium azide in dimethylformamide at room temperature (Scheme I). The mechanism of step **5** → **6** is described elsewhere for mono-α-azidovinyl ketones,[10] and the stereochemistry of **6** is deduced from the nmr spectra ($CDCl_3$) of the triazole adducts **7** and **8**. The latter were obtained by reaction of **6** with 1 equiv of benzoylmethylenetriphenylphosphorane (**2c**) at room temperature. Compounds **7** and **8** exhibited an upfield shift for the *o*-phenyl protons in β position with respect to the triazole group, thus indicating their stereochemistry. Similarly, when **6** was treated with 2 equiv of *p*-nitrobenzoylmethylenetriphenylphosphorane (**2d**) to completion (2 months at room temperature), the corresponding yellow bistriazole (70%, mp 265–267°) showed an upfield multiplet absorption at τ 2.85–3.00 (DMSO-d_6 at 80°) for the ortho hydrogen atoms under discussion.

A comparison of the phenyl absorption patterns of compounds **4** and **6** showed a downfield shift of the ortho hydrogen atoms in the case of **6**. This has been attributed by Hemetsberger, Knittel, and Weidmann[11] to the anisotropic effect of the vinylic azide function in the cis position. As noticed elsewhere,[10] this criterion should be used with caution since the same effect has been found for olefin **9** which has the phenyl group in cis position to the C=O function. However, it is worthwhile to note here that the deshielding effect

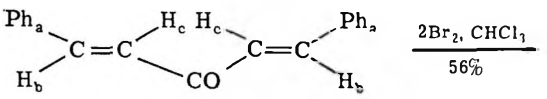


9

seems to be a general phenomenon of cis-β-arylvinyl azides, whereas it only occurs in exceptional cases with *cis*-β-arylvinyl ketones, depending on the spacial position of the C=O group.

(11) H. Hemetsberger, D. Knittel, and H. Weidmann, *Monatsh. Chem.*, **100**, 1599 (1969).

SCHEME I

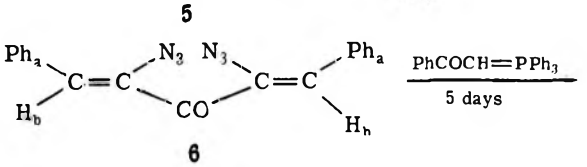


4

τ_a = 2.3–2.8 (m, 10 H)
τ_b = 2.25 (br d, 2 H, J = 16 Hz)
τ_c = 2.9 (d, 2 H, J = 16 Hz)

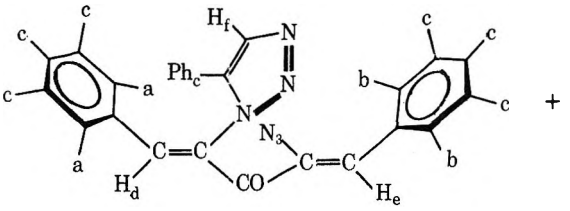
$(PhCHBrCHBr)_2C{=}O \xrightarrow[80\%]{4\ NaN_3,\ DMF}$

5



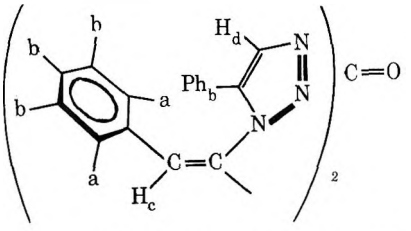
6

τ_a = 2.05–2.35 (m, 4 ortho H), 2.5–2.75 (m, 6 meta and para H)
τ_b = 3.38 (s, 2 H)



7 (49%, yellow, mp 138° dec)

τ_a = 2.9–3.1 (m, 2 H)
τ_b = 2.1–2.4 (m, 2 H)
τ_c = 2.5–2.9 (m, 11 H)
τ_d = 2.20 (br s, 1 H)
τ_e = 3.63 (s, 1 H)
τ_f = 2.10 (s, 1 H)



8 (10%, white, mp 103–105°)

τ_a = 3.15–3.45 (m, 4 H)
τ_b = 2.6–3.0 (m, 16 H)
τ_c = 2.32 (br s, 2 H)
τ_d = 2.15 (s, 2 H)

Experimental Section

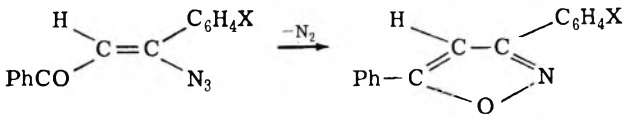
α-Styryl azide (**1a**),[12] *trans*-phenyl β-azidovinyl ketone (**1b**),[13] α-azidoethylideneacetophenone (**1c**),[10] and α-azidochalcone (**1d**),[10] were prepared as reported.

α-Azido-(*m*-nitrobenzylidene)acetophenone (**1e**) was prepared by reaction of the dibromide of *m*-nitrobenzylideneacetophenone (0.1 mol) with 2 equiv of sodium azide in dry DMF (200 ml) at room temperature for 5 hr. The solution was then poured into a mixture of water–chloroform, and the chloroform layer washed several times with water and dried ($MgSO_4$). After the solvent was removed *in vacuo*, a yellow residue was obtained, composed of **1e** and **11** (25% by nmr). Fractional crystalliza-

(12) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967); A. Hassner and F. W. Fowler, *J. Org. Chem.*, **33**, 2686 (1968).

(13) A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR*, **170**, 600 (1966); *Proc. Acad Sci. USSR*, **170**, 916 (1966).

tion from ethyl acetate yielded the isoxazole **11** (mp 169–170°) and the pure azide **1e** (48%, mp 82–84°). The origin of the isoxazole **11** is supposed to be the vinyl azide **10**, which can be deduced from the complex mechanistic scheme of the reaction.[10]



10, X = *m*-NO_2 **11**, X = *m*-NO_2
12, X = *p*-NO_2 **13**, X = *p*-NO_2

α-Azido(p-nitrobenzylidene)acetophenone (**1f**) was similarly prepared from the dibromide of *p*-nitrobenzylideneacetophenone and 2 equiv of sodium azide in DMF at room temperature for 2 hr. After work-up, the azide residue was contaminated with the isoxazole **13** (20% by nmr). The mixture was treated with $CHCl_3$ and cooled to yield **13** (mp 225°). The residual orange oil was finally crystallized from methanol and furnished the pure azide **1f** in 43–55% yield (mp 108°, lit.[11] 112.5°).

β-Azidoacrylonitrile (**1g**).—Acrylonitrile was treated with IN_3 by the method of Hassner, *et al.*,[12] to yield the IN_3 adduct in 68% yield. The product was purified by column chromatography on silica gel ($CHCl_3$) and treated with 2 equiv of sodium azide in DMF at room temperature for 3 days. After work-up in the usual manner, a brown liquid was obtained, composed of *cis*-**1g** (37%, doublets at τ 2.95 and 5.25, J = 7.5 Hz) and *trans*-**1g** (63%, doublets at τ 2.90 and 4.90, J = 14 Hz).

α,α-Bis(azidodibenzal)acetone (**6**).—Compound **5**, prepared from dibenzalacetone (**4**) and bromine in 56% yield, was treated with 4 equiv of sodium azide in dry DMF at 10° for 6 hr. The reaction mixture was worked up in the usual manner and yielded a yellow-brown residue. Recrystallization from MeOH–$CHCl_3$ furnished a yellow, crystalline product (**6**) in 70–80% yield (dec pt 93°), ir (KBr) 2120 and 1625 cm^{-1}. *Anal.* Calcd for $C_{17}H_{12}N_6O$ (316): C, 64.55; H, 3.79; N, 26.58. Found: C, 64.65; H, 3.75; N, 26.40.

General Procedure for the Synthesis of 1-Vinyl-1,2,3-triazoles (**3, 7, and 8**).—Equimolar amounts (0.01 mol) of ylide **2** and azide **1** were treated in 50 ml of CH_2Cl_2 at room temperature to completion (checked by ir). Triazole **3p** precipitated completely and triazole **3o** partially from the solution. To isolate the other triazoles, the solvent was removed and the residue crystallized from methanol (**3c, 3f, 3h, 3k, 3l, 3m, 3n, 3o**) or fractionally crystallized from ether (**3a, 3d, 3i, 3j**) and/or $CHCl_3$–pentane (**7** and **8**). Triazoles **3b, 3e,** and **3g** together with triphenylphosphine oxide were isolated in nearly quantitative yield and a sample of each was purified by column chromatography on silica gel (EtOAc as the eluent). The solid triazoles were recrystallized from the appropriate solvents and analyzed. Their C, H, and N analyses were within 0.3%.

Registry No.—**1e**, 35213-03-7; **1f**, 26087-02-5; *cis*-**1g**, 35213-05-9; *trans*-**1g**, 35213-06-0; **3a**, 35213-07-1; **3b**, 27643-29-4; **3c**, 35225-67-3; **3d**, 35225-68-4; **3e**, 35261-89-3; **3f**, 35225-69-5; **3g**, 27643-30-7; **3h**, 35225-71-9; **3i**, 35261-90-6; **3j**, 35225-72-0; **3k**, 35225-73-1; **3l**, 35225-74-2; **3m**, 35225-75-3; **3n**, 35225-76-4; **3o**, 35225-77-5; **4**, 35225-79-7; **6**, 35225-80-0; **7**, 35225-81-1; **8**, 35261-91-7; **11**, 31609-82-2; **13**, 31108-56-2.

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Photochemistry in the Tetrazole–Azidoazomethine System. A Facile Synthesis of 9*H*-Pyrimido[4,5-*b*]indoles

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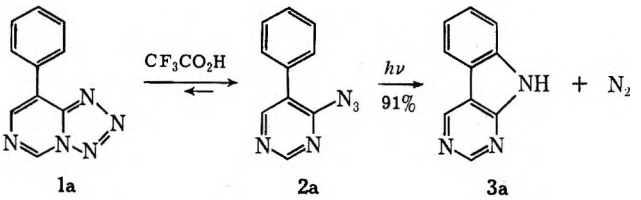
The photolysis of 8-(phenyl)-, 8-(*p*-toluyl)-, 8-(*p*-methoxyphenyl)-, and 8-(*p*-chlorophenyl)tetrazolo[1,5-*c*]-pyrimidines in trifluoroacetic acid produces in high yield the corresponding 7-substituted 9*H*-pyrimido[4,5-*b*]-indoles. Evidence suggests that the reaction arises from acid-catalyzed conversion of the tetrazole to the isomeric azide which subsequently photolyzes to produce the indole derivative. In contrast to the high yield photolyses of the 8-phenyl derivatives in trifluoroacetic acid, photolysis or thermolysis in nonpolar media proceeded slowly and in poorer yield. The quantum yield for photolysis of the 8-phenyl derivative at 300 nm is 0.45, indicative of a reaction of high efficiency.

For several years we have been interested in both the photophysical and photochemical properties associated with 2-substituted biaryl derivatives.[2] The high yield cyclizations of 2-substituted groups to the adjacent aryl ring in biphenyls suggested such processes might be of synthetic utility in heterocyclic biaryl systems. Recently, we noted in a preliminary report that photolysis of 8-phenyltetrazolo[1,5-*c*]pyrimidine, **1a**, in trifluoroacetic acid produced the 9*H*-pyrimido-[4,5-*b*]indole, **3a**, in high yield.[3] In view of the synthetic potential of this method in yielding this here-



1a **2a** **3a**

tofore neglected ring system[4] in high yield, we have explored the generality of this method by studying several substituted derivatives. We wish to report here the synthetic expedient of the acid-catalyzed control of the tetrazole–azidoazomethine equilibrium and a general high yield synthesis of 9*H*-pyrimido-[4,5-*b*]indoles.

Synthesis.—Limitations in preparative photochemi-

(1) (a) Ohio State University Fellow, 1970–1971; (b) Alfred P. Sloan Foundation Fellow (1970–1972), Camille and Henry Dreyfus Teacher-Scholar Awardee, 1971.

(2) (a) J. S. Swenton, *Tetrahedron Lett.*, 2855 (1967); (b) *ibid.*, 3421 (1968); (c) J. S. Swenton, T. J. Ikeler, and B. H. Williams, *J. Amer. Chem. Soc.*, **92**, 3103 (1970); (d) J. S. Swenton, T. J. Ikeler, and B. H. Williams, "Excited State Chemistry," J. N. Pitts, Ed., Gordon and Breach, New York, N. Y., 1970, pp 93–106; (e) G. Smyser, M. S. Thesis, The Ohio State University, 1971.

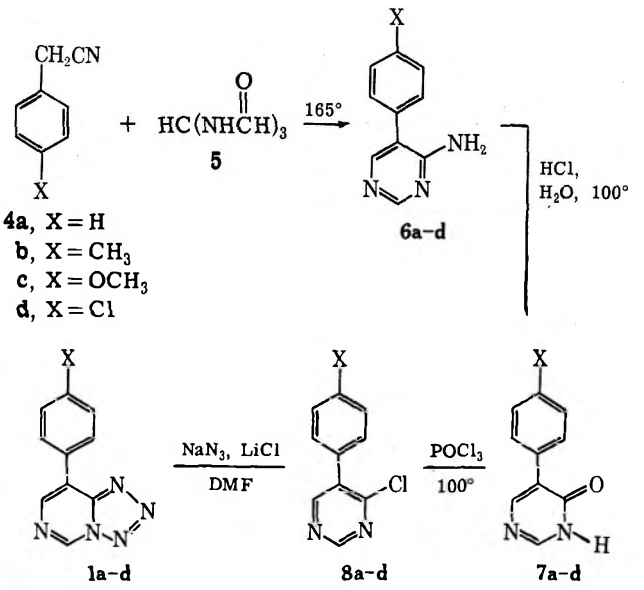
(3) J. A. Hyatt and J. S. Swenton, *J. Heterocycl. Chem.*, **9**, 409 (1972).

(4) Two examples of this ring system have been reported: (a) K. E. Schulte, J. Reisch, and U. Stoess, *Angew. Chem., Int. Ed. Engl.*, **4**, 1081 (1965); (b) R. Gluchkov, V. Volokova, and O. Y. Magidson, *Khim. Farm. Zh.*, **1**, 25 (1967).

cal methods for substituted derivatives of a parent system often arise from two sources. First, the electronic nature of the group can effect the excited state electron distribution and thus markedly alter the reactive properties of the excited state.[2d] Second, the substituent itself may be photochemically labile under the reaction conditions. Thus, a possibility limiting the usefulness of this photolytic method was that, in the highly acidic trifluoroacetic acid, aromatic rings bearing electron-donating groups would be subject to photochemical change.[5] A particular instance is that of a halogen substituent which, while a useful handle for further synthetic manipulation, is often cleaved under photochemical conditions.[6] With these considerations and those of preparative convenience in mind, we selected the *p*-toluyl, *p*-methoxyphenyl, and *p*-chlorophenyl derivatives as models to test the generality of the preparative process.

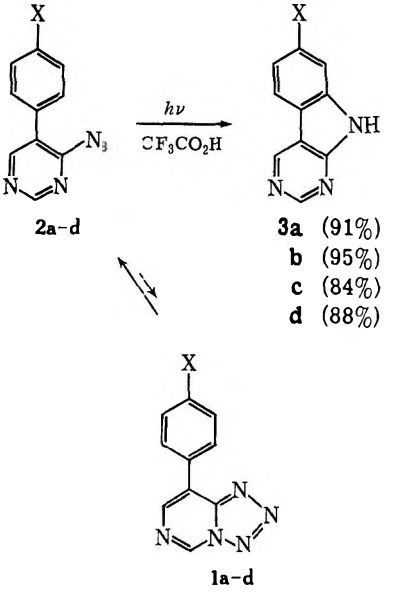
The synthesis of these compounds is outlined in Scheme I. The reaction of tris(formylamino)methane[7] with the substituted phenylacetonitriles according to the procedure of Tsatsaronis and coworkers[8] readily afforded the 4-amino-5-(para-substituted phenyl)-pyrimidines (**6a–d**). Hydrolysis of the aminopyrimidines in concentrated hydrochloric acid[9] gave the 4-pyrimidones (**7a–d**) which were treated with phosphorus oxychloride[9] to yield the 4-chloro derivatives **8a–d**. The reaction of these 4-chloropyrimidines with sodium azide–lithium chloride in *N*,*N*-dimethylformamide gave high yields of products exhibiting the characteristic tetrazole absorption in the ir at *ca.* 9.4 μ.[10] None of the products (**1a–d**) exhibited the characteristic azide absorption at *ca.* 4.7 μ in KBr or neutral solution phase spectra. Thus, spectroscopic data established that compounds **1a–d** exist nearly exclusively in neutral media as the tetrazole tautomer.

SCHEME I



Preparative Photolyses.—While photolyses of the tetrazole **1a** in benzene proceeded slowly to produce the indole **3a** in low yield, photolysis of **1a** in trifluoroacetic acid produced the indole in 91% yield. Likewise, photolyses of **1b–d** in trifluoroacetic acid afforded one product in high yield and purity. The structures of the photoproducts **3a–d** were assigned as the respective 7-substituted 9*H*-pyrimido[4,5-*b*]indoles **10a–d** on the basis of their elemental analyses, ir, nmr, uv, and mass spectral properties. Under our photolysis conditions, products derived from modification of either the methoxy or halogen linkage of **3c** or **3d** were not detected.

To compare the efficiency of the tetrazole photolysis in trifluoroacetic acid with that of the 2-azidobiphenyls, the quantum yield for the parent system was measured at 300 nm. The observed quantum yields for disappearance of **2a** and appearance of **3a** were measured as 0.42 and 0.49, being quite analogous to those recorded for 2-azidobiphenyl itself (Φ = 0.42).[2c] In contrast to the 2-azidobiphenyls which produce from 3 to 16% yields of azo compounds upon direct irradiation, no analogous products were detected in the photolysis of azides **2a–d**.



Thermolyses.—The thermolysis of 2-azidobiaryls is also known to produce carbazoles in high yield from the classic studies of Smith and coworkers.[11] Furthermore, Wentrup and Crow[12] have described the facile formation of 1-cyanoimidazoles **11** upon pyrolysis of certain tetrazolo[1,5-*c*]pyrimidines **9**. To check if the thermal route possessed synthetic advantage over the photochemical process, the thermolysis of **1a** was briefly explored. While **1a** did decompose in refluxing *o*-dichlorobenzene, the indole, **3a** was produced in only

(5) Aromatic photosubstitution is quite facile in numerous systems. For leading references see (a) E. Havinga and M. Kronenberg, *Pure Appl. Chem.*, **16**, 137 (1968); (b) R. L. Letsinger and J. H. McCain, *J. Amer. Chem. Soc.*, **91**, 6425 (1969).

(6) (a) J. P. Pinhey and R. D. G. Rigby, *Tetrahedron Lett.*, 1267 (1969); (b) L. R. Hamilton and P. J. Kropp, *ibid.*, 1625 (1971); (c) R. A. F. Deeleman, H. C. van der Plas, A. Koudijs, and P. S. Darwinkel-Resseeuw, *ibid.*, 4159 (1971).

(7) H. Bredereck, R. Gompper, H. Rempfer, K. Klemm, and H. Keck, *Chem. Ber.*, **92**, 329 (1959).

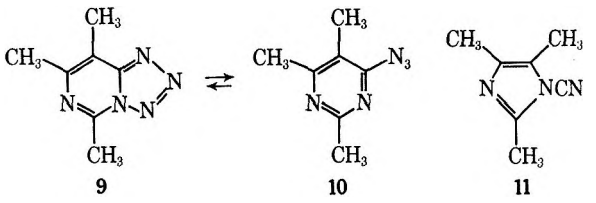
(8) (a) G. Tsatsaronis and F. E. Effenberger, *ibid.*, **94**, 2876 (1961); (b) G. Tsatsaronis and A. Kehayoglow, *J. Org. Chem.*, **35**, 438 (1970).

(9) W. Davies and H. Piggot, *J. Chem. Soc.*, 347 (1945).

(10) E. Lieber, D. Levering, and C. Patterson, *Anal. Chem.*, **23**, 1594 (1951).

(11) (a) P. Smith and J. Boyer, *J. Amer. Chem. Soc.*, **73**, 2626 (1951); (b) P. Smith, B. Brown, R. Putney, and P. Reinick, *ibid.*, **75**, 6335 (1953); (c) P. Smith and B. Brown, *ibid.*, **73**, 2438 (1951); (d) P. Smith, J. Clegg, and J. Hall, *J. Org. Chem.*, **23**, 524 (1958).

(12) C. Wentrup and W. Crow, *Tetrahedron*, **26**, 4915 (1970).



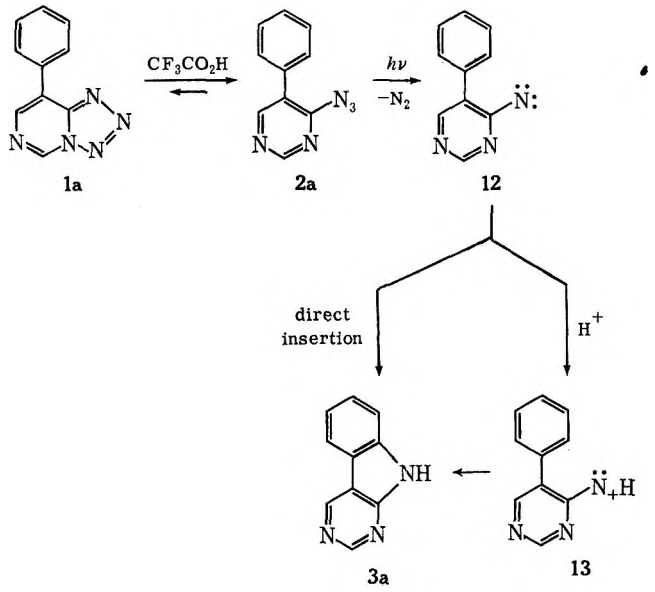
9 10 11

50% yield in addition to an equal quantity of uncharacterized tarry residue. When the tetrazole **1a** was refluxed in trifluoroacetic acid (bp 72°) for 3 hr in the dark only a trace of **11a** was noted by tlc in addition to unreacted starting material. Since thermolysis did not appear synthetically more advantageous than the photochemical route, our studies were terminated at this point.

Discussion

The present study has demonstrated the photolysis of biaryltetrazoles in acid media is a high yield route to the 9*H*-pyrimido[4,5-*b*]indole ring system. The reaction is conveniently viewed as involving a shift of the tetrazole–azidoazomethine equilibrium in the acid media to the azide tautomer and its subsequent photolysis (Scheme II). Such an effect of acid on the

SCHEME II



1a **2a** **12** **3a** **13**

position of the tetrazole–azidoazomethine equilibrium has been noted previously in several systems.[13] This point was confirmed in our work by noting that the ir spectra of tetrazoles **1a–d** in trifluoroacetic acid showed strong azide absorption at *ca.* 4.5 μ and nearly complete absence of the characteristic tetrazole absorption at 9.4 μ. The identity within experimental error of the quantum yield of **1a** photolysis and that of 2-azidobiphenyl itself (0.48 *vs.* 0.42) strongly suggests that the initial photochemical reaction is loss of nitrogen to produce the corresponding nitrene **12**. This step can be followed by nitrene insertion to produce **3a**. However, in the high acidic trifluoroacetic acid, protonation would result in formation of the nitrenium ion[14] **13**, which would be most reasonably followed by cyclization and proton loss to yield **3a**.[15] While evidence is not available to distinguish between these two possibilities, the total absence of azo compounds from direct photolysis of these pyrimidine systems contrasts with the 3 to 16% yield of azo compounds produced by 2-azidobiphenyls. The latter bimolecular products, which were attributed to the reactions of a triplet nitrene in the biphenyl system, are either not characteristic processes in the heterocyclic series or else not produced due to the highly acidic media. In view of the high yield results obtained in our model systems, the photolysis of related tetrazoles in trifluoroacetic acid promises to be not only of synthetic utility but also a convenient method of studying the reactions of heteroaromatic nitrenes and/or nitrenium ions.

Experimental Section

Melting points were determined in a Thomas-Hoover apparatus and are corrected. Infrared spectra were taken as Nujol mulls on a Perkin-Elmer Model 137 spectrophotometer; only prominent bands are reported. Nmr spectra were obtained on a Varian A-60A instrument in the specified solvent with tetramethylsilane as internal standard. Mass spectra were determined with an AEI MS-9 instrument at an ionizing potential of 70 eV. Ultraviolet spectra were determined in 95% ethanol solution with a Cary Model 14 recording spectrophotometer. All elemental analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark, on sublimed samples. All photolyses were performed with a bank of 16 RPR-3000-Å lamps.

8-Phenyltetrazolo[1,5-*c*]pyrimidine, 1a, and 9*H*-pyrimido[4,5-*b*]indole, 3a, have been previously reported.[3]

4-Amino-5-(*p*-toluyl)pyrimidine (6b).—A mixture of 25.0 g (0.18 mol) of *p*-methylbenzyl cyanide, 53.0 g (0.36 mol) of tris(formamino)methane, 3.0 g of *p*-toluenesulfonic acid, and 35 ml of formamide was heated at 170–180° for 10 hr. The cooled reaction mixture was acidified with 10% hydrochloric acid, diluted with 50 ml of water, and treated with decolorizing charcoal. The clarified solution was basified with 10% sodium hydroxide solution and the precipitated product chromatographed on 300 g of Florisil (5% methanol in chloroform as eluent). Recrystallization of this material from benzene yielded 13.0 g (39%) of white crystalline product: mp 166.5–167.0°; ir 2.97, 3.12, and 6.12 μ; nmr ($CDCl_3$) δ 8.50 (s, 1 H), 8.10 (s, 1 H), 7.25 (s, 4 H), 5.42 (br s, 2 H), and 2.38 (s, 3 H).

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.18; H, 5.92; N, 22.82.

5-(*p*-Toluyl)pyrimidone-4 (7b).—A solution of 10.0 g (0.054 m) of 4-amino-5-(*p*-toluyl)pyrimidine, **6b**, in 35 ml of concentrated hydrochloric acid was heated at 70–90° for 10 hr in a rapid stream of hydrogen chloride. The precipitated hydrochloride salt of product was filtered off, the filtrate yielding 3.0 g of unreacted starting amine. The crude hydrochloride was slurried in 35 ml of water, 30% aqueous sodium hydroxide added until solution was effected, and the solution diluted with 50 ml of water. Saturation of this solution with carbon dioxide yielded the crude product which was recrystallized from methanol to yield 6.0 g (86%) of **7b**: mp 191.5–192.5°; ir 6.05 μ; nmr ($CDCl_3$) δ 11.1 (br s, 1 H), 8.16 (s, 1 H), 8.09 (s, 1 H), 7.4 (center of AB quartet, J = 8.5 Hz, 4 H), and 2.42 (s, 3 H).

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.02; H, 5.53; N, 15.06.

4-Chloro-5-(*p*-toluyl)pyrimidine (8b).—A mixture of 5.0 g (0.026 mol) of **7b** and 15 ml of freshly distilled phosphorus oxychloride was refluxed for 0.75 hr. After removal of excess phosphorus oxychloride *in vacuo*, the resulting oily residue was treated with 200 ml of ice water. The precipitated solid was collected and recrystallized from *n*-hexane to yield 3.75 g (71%) of white crystalline material: mp 78.5–79.5°; ir 6.55, 12.32, 13.03, 13.18,

(13) (a) C. Temple, R. McKee, and J. Montgomery, *J. Org. Chem.*, **30**, 829 (1965); (b) N. Smirnova, I. Postovskii, N. Vereshchagina, and I. Ludina, *Chem. Heterocycl. Compounds (USSR)*, **4**, 130 (1971) (English translation); (c) C. Wentrup, *Tetrahedron*, **26**, 4969 (1970).

(14) For a review see P. G. Gassman, *Accounts Chem. Res.*, **3**, 26 (1970).

(15) A similar proposal has been advanced to account for the products involving nucleophilic aromatic substitution from deoxygenation of nitrosobenzene in triethyl phosphite containing acetic acid: R. J. Sundberg, R. H. Smith, and J. E. Bloor, *J. Amer. Chem. Soc.*, **91**, 3392 (1969).

14.00, and 14.60 μ; nmr ($CDCl_3$) δ 8.94 (s, 1 H), 8.64 (s, 1 H), 7.32 (s, 4 H), and 2.42 (s, 3 H).

Anal. Calcd for $C_{11}H_9N_2Cl$: C, 64.56; H, 4.48; N, 13.60; Cl, 17.32. Found: C, 64.85; H, 4.85; N, 13.20; Cl, 17.38.

8-(*p*-Toluyl)tetrazolo[1,5-*c*]pyrimidine (1b).—A solution of 3.50 g (0.017 mol) of **8b**, 1.10 g (0.017 mol) of sodium azide, and 0.71 g (0.017 mol) of lithium chloride in 25 ml of *N*,*N*-dimethylformamide was stirred for 8 hr at RT. The reaction mixture was then poured into 300 ml of ice water and the resulting light yellow solid recrystallized from ethanol to afford 3.53 g (98%) of pure product: mp 125–126.5°; ir 6.24 and 9.35 μ; nmr ($CDCl_3$) δ 9.59 (s, 1 H), 8.50 (s, 1 H), 7.76 (center of AB quartet, J = 7.5 Hz, 4 H), and 2.43, (s, 3 H).

Anal. Calcd for $C_{11}H_9N_5$: C, 62.53 H, 4.30; N, 33.18. Found: C, 62.47; H, 4.26; N, 33.37.

7-Methyl-9*H*-pyrimido[4,5-*b*]indole (3b).—A solution of 0.50 g (0.024 mol) of **1b** in 50 ml of trifluoroacetic acid was irradiated through Pyrex for 2 hr and the trifluoroacetic acid removed *in vacuo*. The residue was diluted with 50 ml of water and made basic with 10% sodium hydroxide, and the aqueous layer extracted with ether (6 × 30 ml). Removal of the ether from the sodium sulfate dried organic phase yielded a solid product which was recrystallized from benzene–ethanol to yield 0.42 g (95%) of white solid: mp 228.5–230.5°; ir 6.18, 6.24, 10.12, 12.41, and 13.35 μ; nmr (DMSO-d_6) δ 12.1 (br s, 1 H), 9.36 (s, 1 H), 8.90 (s, 1 H), 8.11 (d, J = 8 Hz, 1 H), 7.23 (m, 2 H), and 2.47 (s, 3 H).

Anal. Calcd for $C_{11}H_9N_3$: C, 72.10; H, 4.95; N, 22.95. Found: 72.02; H, 4.97; N, 22.72.

4-Amino-5-(*p*-methoxyphenyl)pyrimidine (6c).—A mixture of 30 g (0.20 mol) of *p*-methoxyphenylacetonitrile, 58 g (0.40 mol) of tris(formamino)methane, 3 g of *p*-toluenesulfonic acid, and 35 ml of formamide was reacted in a manner analogous to that of **6b**. Recrystallization of the crude material from benzene yielded 20.2 g (51%) of **6c**: mp 165.5–167.5°; ir 2.98, 3.10, and 6.12 μ; nmr ($CDCl_3$) δ 8.46 (s, 1 H), 8.07 (s, 1 H), 7.12 (center of AB quartet, J = 9 Hz, 4 H), 5.39 (br s, 2 H), and 3.78 (s, 3 H).

Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.74; H, 5.27; N, 20.71.

5-(*p*-Methoxyphenyl)pyrimidone-4 (7c). In a manner analogous to that of **7b** a solution of 9.0 g (0.045 mol) of **6c** in 35 ml of concentrated hydrochloric acid was treated with dry hydrogen chloride at 80–90° for 12 hr. Work-up of the reaction yielded 2.1 g of recovered starting material in addition to the pyrimidone. Recrystallization of the product from methanol yielded 5.82 g (83%) of **7c**: mp 205.5–206.5°; ir 6.02, 8.05, and 9.75 μ; nmr (DMSO d_6) δ 12.5 (br s, 1 H), 8.11 (br s, 2 H), 7.43 (center of AB quartet, J = 8.5 Hz, 4 H), and 3.79 (s, 3 H).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34 H, 4.98; N, 13.85. Found: C, 65.21; H, 4.96; N, 13.83.

4-Chloro-5-(*p*-methoxyphenyl)pyrimidine (8c).—A mixture of 9.0 g (0.045 mol) of **7c** and 20 ml of phosphorus oxychloride was refluxed for 1 hr and the excess phosphorus oxychloride removed *in vacuo*. Treatment of the residual oil with ice water yielded a crude yellow solid which was recrystallized from *n*-hexane to give 5.62 g (57%) of product: mp 95.5–96.5°; ir 6.21, 8.05, and 13.10 μ; nmr ($CDCl_3$) δ 8.86 (s, 1 H), 8.56 (s, 1 H), 7.16 (center of AB quartet, J = 8.5 Hz, 4 H), and 3.78 (s, 3 H).

Anal. Calcd for $C_{11}H_9N_2OCl$: C, 59.88; H, 4.11; N, 12.69; Cl, 16.07. Found: C, 60.03; H, 4.22; N, 12.68; Cl, 16.25.

8-*p*-(Methoxyphenyl)tetrazolo[1,5-*c*]pyrimidine (1c).—A solution of 4.50 g (0.020 mol) of **8c**, 1.70 g (0.025 mol) of sodium azide, and 1.10 g (0.025 mol) of lithium chloride in 35 ml of *N*,*N*-dimethylformamide was stirred for 8.5 hr at room temperature. Work-up as previously described followed by recrystallization of the crude product from ethanol yielded 4.35 g (95%) of **1c**: mp 146.5–147.5°; ir 6.23, 8.05, and 9.31 μ; nmr ($CDCl_3$) δ 9.56 (s, 1 H), 8.48 (s, 1 H), 7.60 (center of AB quartet, J = 8.5 Hz, 4 H), and 3.85 (s, 3 H).

Anal. Calcd for $C_{11}H_9N_5O$: C, 58.14; H, 3.99; N, 30.82. Found: C, 57.84; H, 4.02; N, 30.48.

7-Methoxy-9*H*-pyrimido[4,5-*b*]indole (3c).—Photolysis of 0.50 g (0.0023 mol) of **1c** in 50 ml of trifluoroacetic acid for 1.75 hr followed by work-up as usual yielded **3c** as a yellow crystalline product. Sublimation of this material *in vacuo* followed by recrystallization from benzene yielded 0.36 g (84%) of white crystalline **3c**: mp 238.5–239.5°; ir 6.16 and 7.92 μ; nmr (DMSO-d_6) δ 12.15 (br s, 1 H), 9.32 (s, 1 H), 8.90 (s, 1 H), 8.12 (d, J = 8.0 Hz, 1 H), 7.04 (m, 2 H), and 3.88 (s, 3 H).

Anal. Calcd for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.14; H, 4.68; N, 20.91.

4-Amino-5-(*p*-chlorophenyl)pyrimidine (6d).—A mixture of 30.4 g (0.20 mol) of *p*-chlorophenylacetonitrile, 57.0 g (0.40 mol) of tris(formamino)methane, 3.5 g of *p*-toluenesulfonic acid, and 35 ml of formamide was stirred at 155–160° for 11 hr. Work-up of the reaction as for **6b**, followed by recrystallization of the crude material from ethanol, yielded 28.2 g (68%) of the pyrimidine as light tan product, mp 205.5–206.5°. Sublimation followed by recrystallization from ethanol yielded the analytical sample: mp 207.5–208.5°; ir 2.95, 3.10, and 6.04 μ; nmr (DMSO-d_6) δ 8.31 (s, 1 H), 7.96 (s, 1 H), 7.43 (s, 4 H), and 6.67 (br s, 2 H).

Anal. Calcd for $C_{10}H_8N_3Cl$: C, 58.41; H, 3.92; N, 20.43; Cl, 17.24. Found: C, 58.39; H, 3.88; N, 20.80; Cl, 17.58.

5-(*p*-Chlorophenyl)pyrimidone-4 (7d).—A solution of 15.0 g of **6d** in 50 ml of concentrated hydrochloric acid was heated at 80–90° for 12 hr in a stream of hydrogen chloride gas. After work-up in the usual manner there was obtained 4.2 g of unreacted amine in addition to product. Recrystallization of the crude product from methanol yielded 10.2 g (94%) of white crystalline material: mp 254.5–256.5°; ir 6.03, 7.30, and 8.02 μ; nmr (DMSO-d_6) δ 8.61 (br s, 1 H), 8.20 (d, J = 2 Hz, 2 H), 7.63 (center of AB quartet, and J = 9 Hz, 4 H).

Anal. Calcd for $C_{10}H_7N_2OCl$: C, 58.13; H, 3.42; N, 13.55. Found: C, 57.73; H, 3.73; N, 13.46.

4-Chloro-5-(*p*-chlorophenyl)pyrimidine (8d).—A mixture of 5.0 g (0.024 mol) of **7d** and 20 ml of phosphorus oxychloride was refluxed for 0.75 hr. Work-up as for **8b** gave after recrystallization from hexane 5.10 g (94%) of faintly yellow crystalline product: mp 111.5–113.5°; ir 6.57, 9.20, 10.08, and 13.92 μ; nmr ($CDCl_3$) δ 9.0 (s, 1 H), 8.67 (s, 1 H), 7.45 (s, 4 H).

While colorless material could be obtained by sublimation which was homogeneous by tlc under several sets of conditions, acceptable combustion analytical data (±0.3%) could not be obtained. Even column chromatographed material did not yield acceptable analyses. The data given below comprise the average of three determinations.

Anal. Calcd for $C_{10}H_6N_2Cl_2$: C, 53.37; H, 2.69; N, 12.45; exact mass, 223.9908. Found: C, 53.95; H, 2.86; N, 12.12; exact mass, 223.9905.

8-(*p*-Chlorophenyl)tetrazolo[1,5-*c*]pyrimidine (1d).—A solution of 4.50 g (0.020 mol) of **8d**, 1.60 g (0.025 mol) of sodium azide, and 1.05 g (0.025 mol) of lithium chloride in 75 ml of *N*,*N*-dimethylformamide was stirred at room temperature for 14 hr. The usual work-up followed by recrystallization of the crude product from ethanol gave 4.12 g (89%) of yellow crystalline material: mp 149.5–151.5°; ir 6.22, 9.32, 11.31, and 12.03 μ; nmr ($CDCl_3$) δ 9.64 (s, 1 H), 8.56 (s, 1 H), and 7.83 (center of AB quartet, J = 9 Hz, 4 H).

Anal. Calcd for $C_{10}H_6N_5Cl$: C, 51.85; H, 2.61; N, 30.23; Cl, 15.30. Found: C, 51.87; H, 2.80; N, 30.44; Cl, 15.60.

7-Chloro-9*H*-pyrimido[4,5-*b*]indole (3d).—Photolysis of 0.50 g (0.002 mol) of **1d** in 50 ml of trifluoroacetic acid for 3.0 hr followed by the usual work-up, continuous ether extraction of the basic aqueous suspension, and recrystallization of the crude product from methanol gave 0.39 g (88%) of white crystalline product: mp 287.5–289.5°; ir 8.02, 8.25, 10.09, 11.00, 11.51, and 12.42 μ; nmr (DMSO-d_6) δ 9.39 (s, 1 H), 8.90 (s, 1 H), 8.20 (d, J = 8.0 Hz, 1 H), and 7.33 (m, 2 H).

Anal. Calcd for $C_{10}H_6N_3Cl$: C, 58.98; H, 2.97; N, 20.64; Cl, 17.41. Found: C, 58.80; H, 3.02; N, 20.76; Cl, 17.43.

Thermolysis of 8-Phenyltetrazolo[1,5-*c*]pyrimidine (1a).—A solution of 0.5 g of **1a** in 50 ml of *o*-dichlorobenzene was refluxed until all the tetrazole had disappeared (8.0 hr). Removal of the solvent from the orange colored reaction mixture followed by recrystallization of the residue from benzene yielded 0.22 g (50%) of 9*H*-pyrimido[4,5-*b*]indole as identified by mp and ir comparison with known material. Thermolysis of the tetrazole in refluxing trifluoroacetic acid for 3 hr in the dark yielded recovered starting material.

Quantum Yield Determination for the Photolysis of 8-Phenyltetrazolo[1,5-*c*]pyrimidine (1a).—The quantum yield determinations for the photolysis of **1a** were measured using a cylindrical photolysis cell containing two compartments, each 2 cm in diameter and having a 5-cm optical path. The cell was constructed from 2-cm Pyrex tubing and had quartz faces and a quartz divider separating the two compartments. The light source was a Bausch and Lomb high intensity grating monochromator set at 3000 Å. Quantum yield measurements were performed as pre-

viously described on 5×10^{-3} *M* solutions of 1a in trifluoroacetic acid. Typical light intensities were on the order of 2.4×10^{-6} einsteins/15 ml min.[16] The product analysis was by uv at 261.5 nm while that for loss of starting material was measured at 295.0 nm; an isosbestic point was observed at 280.0 nm. The quantum yield measurements were independent of conversion between 0.25 and 7.0% giving average quantum yields of $\Phi_{2a} = 0.42 \pm 0.10$ and $\Phi_{3a} = 0.49 \pm 0.05$.

(16) Potassium ferrioxolate actinometry was employed: C. G. Hatchard and C. A. Parker, *Proc. Roy. Soc., London*, **235**, 518 (1956).

Registry No.—1a, 35202-17-6; 1b, 35202-18-7; 1c, 35202-19-8; 1d, 35202-20-1; 3b, 35202-21-2; 3c, 35340-32-0; 3d, 35202-22-3; 6b, 35202-23-4; 6c, 35202-24-5; 6d, 35202-25-6; 7b, 35202-26-7; 7c, 35202-27-8; 7d, 35202-28-9; 8b, 35202-29-0; 8c, 35202-30-3; 8d, 33258-76-3.

Acknowledgment.—We gratefully acknowledge partial support from the Eli Lilly Co., Indianapolis, Ind.

Alkali-Induced Reactions of *N*-Nitrosooxazolidones and *N*-Nitrosoacetylamino Alcohols Containing Cyclopropyl Groups[1]

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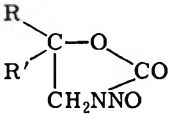
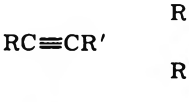
The reactions of 5-cyclopropyl-5-phenyl-3-nitrosooxazolidone (6), 5,5-dicyclopropyl-3-nitrosooxazolidone (7), and 5-cyclopropyl-5-methyl-3-nitrosooxazolidone (8) under alkaline conditions are described. When methanolic solutions of 6 are treated with aqueous hydroxide, about 90% yields of cyclopropylphenylacetylene (9a) are obtained. On similar treatment, 7 yields about 52% dicyclopropylacetylene (9b) together with about 21% 2,2-dicyclopropylvinyl methyl ether (10b), and 8 yields only 16% cyclopropylmethylacetylene (9c) together with about 64% a nearly 1:1 mixture of the *Z* and *E* forms of 2-cyclopropyl-1-propenyl methyl ether (10c). When a cyclohexene solution of 6 is added to a suspension of lithium ethoxide in cyclohexene, an 84% yield of 9a is obtained. On similar treatment, 7 yields 64% 9b and about 13% 7-(dicyclopropylmethylene)bicyclo[4.1.0]-heptane (5b), while 8 yields about 26% 9c and 44% 7-(2-cyclopropylpropylidene)bicyclo[4.1.0]heptane (5c). Mechanisms which involve unsaturated carbonium ions and unsaturated carbenes are advanced to explain the results. Treatment of a cyclohexene–pentane solution (containing a small amount of Aliquat, a long chain quaternary ammonium chloride) of 2-(*N*-nitrosoacetylamino)-1,1-dicyclopropylethanol (17) with 50% sodium hydroxide afforded a 64% yield of 5b. Similar treatments of 1-(*N*-nitrosoacetylamino)-2-cyclopropyl-2-propanol (18) yielded 52% 5c.

The reactions of 5,5-disubstituted-3-nitrosooxazolidones (1) with bases in polar media have been studied.[3a] When one or both R groups are phenyl, acetylenes (2) are formed. When alkyl groups are involved, disubstituted aldehydes (3) and/or rearranged ketones (4) are formed. If the reactions are carried out in cyclohexene with lithium ethoxide, substituted ethylidenecyclopropanes (5) are produced.[3b]



1



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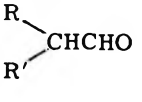

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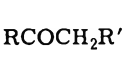

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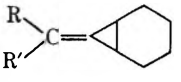
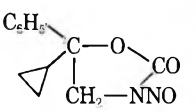


5b, R = R′ = Δ
c, R = Δ; R′ = CH_3

The present work was undertaken to find out how compounds such as 1 with cyclopropyl groups would behave under similar conditions. Cyclopropyl groups were chosen because they are between aryl groups and alkyl groups[4] in their tendency to participate in reactions involving cationic intermediates. Accordingly, 5-cyclopropyl-5-phenyl-3-nitrosooxazolidone (6), 5,5-dicyclopropyl-3-nitrosooxazolidone (7), and 5-cyclopropyl-5-methyl-3-nitrosooxazolidine (8) were prepared by procedures similar to those described,[3] and were treated with bases under the two different sets of reaction conditions discussed below.



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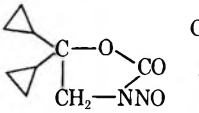

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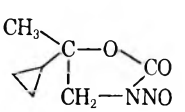
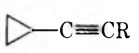
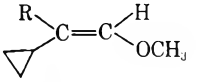


8

I. Treatment with Methanolic Potassium Hydroxide.—When methanolic solutions of the nitrosooxazolidones at room temperature were treated with methanolic potassium hydroxide, vigorous reactions occurred to yield mainly cyclopropylphenylacetylene (9a) from 6, dicyclopropylacetylene (9b), and 2,2-dicyclopropylvinyl methyl ether (10b) from 7, and cyclopropylmethylacetylene (9c) and both isomers of 2-cyclopropyl-1-propenyl methyl ether (10c) from 8. The results are listed in Table I.



9a, R = C_6H_5
b, R = Δ
c, R = CH_3



10b, R = Δ
c, R = CH_3

These results seem best explained by assuming that the intermediate (A), similar to one previously postulated,[3b] undergoes a trans elimination *via* rotamers B and C to yield the isomeric intermediates D and E as shown in Scheme I. Each of these can give rise to

(1) This work was supported largely by Grant G-12445X from the National Science Foundation.

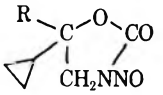
(2) This work was taken from the Ph.D. thesis presented by S. Gromelski to The Ohio State University, 1971.

(3) (a) M. S. Newman and A. Kutner, *J. Amer. Chem. Soc.*, **73**, 4199 (1951); (b) M. S. Newman and A. O. M. Okorodudu, *J. Org. Chem.*, **34**, 1220 (1969).

(4) Y. E. Rhodes and T. Takino, *J. Amer. Chem. Soc.*, **92**, 5270 (1970).

TABLE I

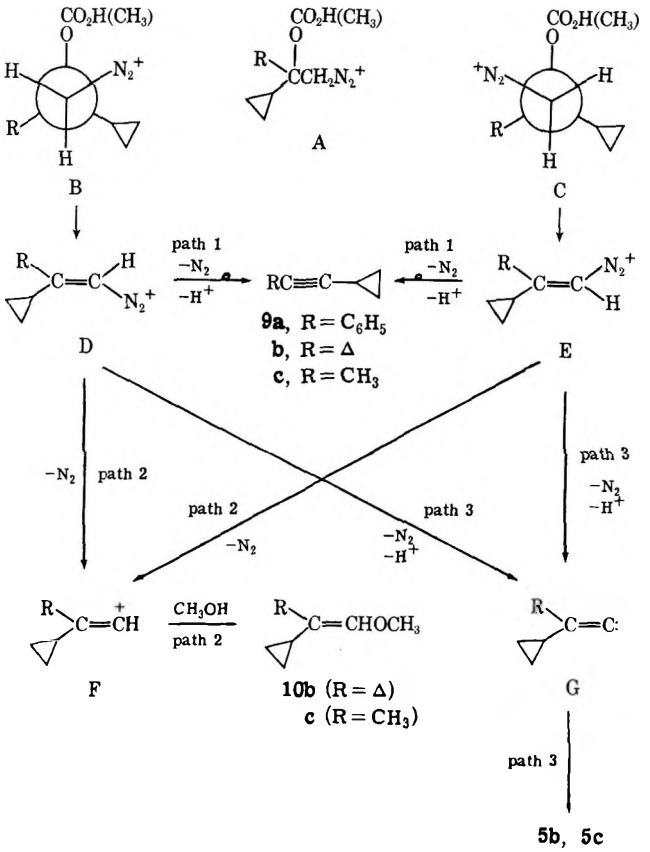
ALKALINE DECOMPOSITION OF NITROSOOXAZOLIDONES CONTAINING CYCLOPROPYL GROUPS



Compd	Method		Product	Yield, %
6 (R = C_6H_5)	*a*		9a	90[c]
	b			84
7 (R = ◁)	*a*		9b	52[d]
			10b[e]	21[d]
	b	9b		64[d]
			5b	13
				64[f]
8 (R = CH_3)	*a*		9c	16
			(*Z*)-10c[g]	33[h]
			(*E*)-10c[g]	31[h]
	b	9c		26
			5c	44
				52[i]

[a] Treatment of methanolic nitrosooxazolidones with aqueous methanolic hydroxide, method I in text. [b] Treatment of nitrosooxazolidones with lithium ethoxide in cyclohexene, method II in text. [c] Isolated yield. [d] Determined by glpc. [e] Isolated by glpc. [f] Obtained by treatment of 17 with base using Stark's procedure.[15] [g] See ref 20 for nomenclature. [h] Relative amounts of *Z* and *E* forms determined by nmr.[19] [i] Obtained from 18.

SCHEME I



an acetylene by migration of the group trans to the diazo group with loss of nitrogen and a proton (path 1). Alternately, D and E may lose nitrogen to yield F (path 2), or nitrogen and a proton to yield G (path 3).[3b,5] Because of other studies,[6] we believe the path involving F is involved in the reactions which take place in methanol. The unsaturated carbonium ions (F) react with methanol to yield **10b** and the isomeric ethers **10c**. Since the steric requirements of methyl and cyclopropyl groups in F are probably nearly the same, the fact that about equal amounts of the isomeric ethers **10c** are obtained (see Table I) is readily understood. When the R groups in **1** are *tert*-butyl and methyl, the isomer in which the methoxy group is trans to the *tert*-butyl group predominates.[7] The acetylenes may be formed directly from D and E or from F.

To rationalize our results pertaining to the relative amounts of acetylene and vinyl ether formed, we assume that a phenyl group has a larger steric effect than a cyclopropyl group and the latter a slightly larger effect than a methyl group. We also assume that rearrangement of a phenyl group in intermediates of type D, E, and F occurs more readily than that of a cyclopropyl group and that methyl has little, if any, tendency to migrate because no 2-butyne is formed on treatment of the dimethyl analog of **8** with base.

Judging from the fact that the amount of vinyl ether formed increases in going from **6** to **7** to **8**, the preference of the intermediates D and E to decompose by path 2 rather than by path 1 is inversely related to the migration tendencies of the groups originally attached at the 5 position in the nitrosooxazolidones **6–8**. Unfortunately, no information can be gained about the relative migration aptitudes of phenyl and cyclopropyl[8] in this reaction because, even if the amount of phenyl migration could be determined by isotopic labeling of **6**, the result would probably hinge on the proportions of D and E formed and not on migration aptitudes. Presumably, D would be present in larger amount than E in the case where R = C_6H_5, since B should be favored over C because of steric reasons. However, there seems to be little chance to prepare the stereoisomeric intermediates D and E by other means as all attempts to nitrosate a pure trans unsaturated urethane $RCH{=}CHNHCO_2H_5$ failed.[9]

Finally, it should be noted that the treatment of 5,5-disubstituted nitrosooxazolidones (**1**) containing one or more cyclopropyl groups constitutes a new and effective synthesis of arylcyclopropylacetylenes[10] and of dicyclopropylacetylene.[11]

II. Treatment with Lithium Ethoxide in Cyclohexene.—When solutions of **6**, **7**, and **8** in cyclohexene were added to a stirred suspension of lithium ethoxide in cyclohexene the products listed in Table I were obtained. These reaction conditions were chosen because they favor the formation of unsaturated car-

(5) J. Hine, "Divalent Carbon," Ronald Press, New York, N. Y., 1964, pp 89–90.

(6) M. S. Newman and C. D. Beard, *J. Amer. Chem. Soc.*, **93**, 7564 (1970).

(7) Unpublished results by W. Liang.

(8) Studies on the products formed by rearrangement of a series of substituted *p*-tosylhydrazones of formula $(R)_2CCH{=}NNHSO_2C_7H_7$ *via* a carbenic intermediate, $(R)_2CCH$: led to the following migratory aptitudes, C_6H_5 (41.0), Δ (12.6), CH_3 (4.5): Unpublished results by H. Shechter and A. Kraska. See the Ph.D. thesis of A. Kraska, The Ohio State University, 1971.

(9) Unpublished experiments by Dr. Zia ud Din.

(10) Compare J. K. Crandall and D. J. Keyton, *Chem. Commun.*, 1069 (1968).

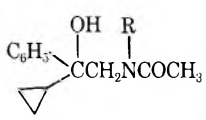
(11) G. Kobrick and D. Merkel, *Angew. Chem., Int. Ed. Engl.*, **9**, 243 (1970).

bene.[3b,12] As can be seen from the results reported in Table I, the amount of acetylene formed in these reactions is roughly the same as that obtained in the methanolic potassium hydroxide experiments. We believe that acetylene formation proceeds essentially by way of B → C and D → E as discussed above in part I, with the difference that the competition in decomposition of D and E is now between paths 1 and 3. The proportions which go through the unsaturated carbenes (G) yield the substituted bicyclo[4.1.0]-heptanes (**5b**, **5c**).

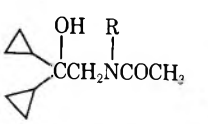
In the case of **6**, only path 1 is followed to afford an 84% yield of **9a**. In the cases of both **7** and **8**, path 3 is followed to a slightly greater extent to yield 7-(dicyclopropylmethylene)bicyclo[4.1.0]heptane (**5b**, R = R′ = △) and 7-(2-cyclopropylpropylidene)bicyclo-[4.1.0]heptane (**5c**, R = △, R′ = CH_3) than is path 2 in the cases in which the vinyl ethers **10b** and **10c** are formed.

Small amounts of dicyclopropyl ketone (**11**) and of cyclopropyl cyclopropylmethyl ketone (**12**) were isolated in studies on **7** under both of the above reaction conditions. Since similar products had been obtained in related work,[13] we studied the alkaline decomposition of **7** in water–glyme with and without added lithium nitrate. When lithium nitrate was absent, the yields of **9b**, **11**, and **12** were 48, 26, and 5.8%, respectively. When the solvent was saturated with lithium nitrate, no **9b** was formed and **11** and **12** were obtained in 31 and 27% yields, respectively. Thus, the yield of rearranged ketone (**12**) is markedly increased by lithium nitrate as in the previous work[13] (see ref 13 for comments).

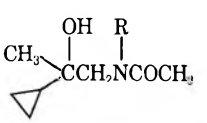
Since an improved method for generating unsaturated carbenes has recently been developed here,[14] the oxazolidones which served as precursors to **6**, **7**, and **8** were hydrolyzed to the corresponding amino alcohols which were acetylated to the acetylamino alcohols **13**–**15**, which were nitrosated to yield **16**–**18**. Treatment of cyclohexene–pentane solutions of **17** and **18** containing a small percent of a quaternary ammonium chloride with sodium hydroxide by the Starks procedure[15] afforded good yields of the corresponding bicycloheptane derivatives **5b** and **5c**. Thus, the formation of bicyclo[4.1.0]heptanes is favored by following the nitrosoacetylamino alcohol route,[14] whereas the formation of acetylenes is best carried out by starting with nitrosooxazolidones (**1**).[3a] However, in the case of **16**, an 89% yield of cyclopropyl-



13, R = H
16, R = NO



14, R = H
17, R = NO



15, R = H
18, R = NO

phenylacetylene (**9a**) was isolated with no trace of a bicycloheptane observed. Hence, when a phenyl group is present, the formation of acetylene is predominant regardless of the method.

(12) M. S. Newman and T. B. Patrick, *J. Amer. Chem. Soc.*, **91**, 6461 (1969).
(13) M. S. Newman and C. D. Beard, *ibid.*, **92**, 4309 (1970).
(14) M. S. Newman and Z. ud Din, *Syn. Commun.*, **1**, 247 (1971).
(15) C. M. Starks, *J. Amer. Chem. Soc.*, **93**, 195 (1971).

Experimental Section[16]

Reformatsky Reactions.—Improved yields of hydroxy esters used in this work were obtained when only one equivalent of activated zinc[17] was used instead of the usual excess and when ether–benzene was the solvent instead of benzene alone. The mixture was held at reflux until the zinc disappeared and no longer. In a typical reaction 30 ml of benzene was distilled from a three-necked flask containing 38 g (0.58 g-atom) of zinc[17] and 200 ml of benzene. A solution of 85 g of cyclopropyl phenyl ketone in 170 ml of dry ether was added and the mixture was heated to reflux. After a small addition of methyl α-bromoacetate and an induction period of 1 hr, 89 g (0.58 mol) of bromo ester was added in portions so that the reaction was not too vigorous. After all the zinc had disappeared (2–3 hr in all), the solution was cooled and treated with 130 ml of 1:1 acetic acid–water. The aqueous layer was reextracted several times with ether–benzene and the combined organic layers were washed with 130 ml of 1:1 ammonium hydroxide–water. The reaction mixture was then worked up as usual to yield 109 g (85%) of methyl 3-cyclopropyl-3-phenyl-3-hydroxypropionate,* bp 102–105° (0.3 mm).

Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.9; H, 7.3. Found: C, 70.7; H, 7.2.

In a similar way, methyl 3,3-dicyclopropyl-3-hydroxypropionate,* bp 57–60° (0.4 mm), and methyl 3-cyclopropyl-3-hydroxybutyrate,* bp 75–77° (8 mm), were obtained in 72 and 76% yields, from dicyclopropyl ketone and cyclopropyl methyl ketone, respectively.

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.8. Found: C, 64.9; H, 8.9.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.8; H, 8.9. Found: C, 60.6 H, 9.0.

Synthesis of Oxazolidones.—In a typical reaction sequence 3-cyclopropyl-3-phenyl-3-hydroxypropionate was converted into 5-cyclopropyl-5-phenyloxazolidone as follows. To a solution of 5.0 g (0.023 mol) of hydroxy ester in 2.5 ml of absolute methanol was added 1.1 g (0.034 mol) of anhydrous hydrazine. The resulting solution (exothermic reaction) was allowed to stand overnight and the solvent was removed on a rotary evaporator. A solution of the oily residue in 88 ml of 0.5 *N* hydrochloric acid was slowly treated at 0–5° with 1.73 g (0.025 mol) of sodium nitrite in 20 ml of water. Benzene–chloroform (1:1) was added together with a little urea. The organic layer was separated and added dropwise to refluxing benzene. After all gas evolution had ceased, the cooled solution yielded a solid which was recrystallized from benzene–pentane to yield 3.5 g (78%) of 5-cyclopropyl-5-phenyl-2-oxazolidone,* mp 119.5–120.5°.

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.4; N, 6.9. Found: C, 70.6; H, 6.7; N, 7.0.

In a similar way, 5,5-dicyclopropyl-2-oxazolidone,* mp 80.5–81.5°, and 5-cyclopropyl-5-methyl-2-oxazolidone,* mp 58.5–59.5°, were obtained in 73 and 75% yields, respectively.

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.6; H, 7.8; N, 8.4. Found: C, 64.6; H, 7.9; N, 8.3.

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.6; H, 7.8; N, 9.9. Found: C, 59.4; H, 7.8; N, 9.8.

Preparation of 6, 7, and 8.—In a typical procedure a solution of 1.05 g (0.016 mol) of nitrosyl chloride[18] in 15 ml of pure acetic anhydride was added slowly to a solution of 3.0 g (0.015 mol) of 5-cyclopropyl-5-phenyl-2-oxazolidone in 30 ml of dry pyridine held at 0–5°. After 1 hr the mixture was poured on ice. A benzene–ether extract was washed with 10% hydrochloric acid and worked up in the usual way. The yellow oily residue was

(16) All melting and boiling points are uncorrected. Microanalyses by M-H-W Laboratories, Garden City, Mich., and Chemalytics, Tempe, Ariz. Ir spectra were recorded on a Perkin-Elmer Infracord. Nmr spectra were taken in CCl_4 and recorded on an A-60 instrument, Varian Associates, Palo Alto, Calif., and are reported as τ relative to tetramethylsilane as 10.0. A Varian Aerograph, Model 1200, flame ionization detector gas chromatograph was used for glpc. The phrase "worked up as usual" means that, after the organic solution was washed with water and saturated salt solution and dried by passage through a cone of anhydrous $MgSO_4$, the solvents were removed on a rotary evaporator. The nmr spectra of all compounds marked with an asterisk are recorded in the Ph.D. thesis of S. Gromelski, OSU, 1971, and are consistent with the structures proposed.
(17) L. F. Fieser and W. S. Johnson, *ibid.*, **62**, 576 (1940).
(18) Obtained in a 12-oz metal cylinder from Matheson Gas Products, Joliet, Ill.

taken up in chloroform and filtered through silica gel. On concentration and recrystallization of the solid from chloroform–pentane there was obtained 3.03 g (89%) of **6**, mp 51–52°.

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.1; H, 5.2. Found: C, 62.4; H, 5.3.

In a similar way, 5,5-dicyclopropyl-2-oxazolidone was converted in 96% yield into **7**, a yellow oil: ir (neat) 6.6 μ, 1515 cm^{-1} (N=O), 5.5 μ, 1818 cm^{-1} (C=O); nmr (in CCl_4) τ 6.30 (s, 2, CH_2N), 8.45–9.00 (m, 2, c-$CHCH_2CH_2$), and 9.25–9.60 (m, 8, c-$CHCH_2CH_2$). Because **7** was unstable and a liquid, no attempt was made to prepare an analytical sample. All yields of products were calculated by assuming the oil was 100% **7**. Similarly, **8** was obtained in 95% yield as a yellow oil: ir (neat) 6.58, 5.48 μ, nmr (CCl_4) τ 6.30 (s, 2, CH_2N), 8.42 (s, 3, CH_3), 8.52–8.95 (m, 1, c-$CHCH_2CH_2$), 9.30–9.65 (m, 4, c-$CHCH_2CH_2$). The oil was stable enough to send for analysis.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.4 H, 5.9; N, 16.4. Found: C, 49.7; H, 5.7; N, 16.4.

2-Acetylamino-1,1-dicyclopropylethanol* (**14**).—To a solution of 2 g of potassium hydroxide in 3 ml of water was added 1.0 g (6 mmol) of 5,5-dicyclopropyl-2-oxazolidone. The mixture was held at reflux for 30 min and was then cooled (N_2 to prevent access of CO_2 from air). A solution of the organic layer in 5 ml of absolute methanol was treated during 10 min with 0.7 g (6.8 mmol) of pure acetic anhydride. The mixture was then refluxed for 30 min and volatile material removed on a rotary evaporator. The residue was recrystallized from benzene–pentane to yield 0.95 g (87%) of **14**, mp 95–96°.

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.6; H, 9.3; N, 7.6. Found: C, 65.5; H, 9.4; N, 7.4.

2-(*N*-Nitrosoacetylamino)-1,1-dicyclopropylethanol* (**17**).—A stirred slurry of 0.44 g (2.4 mmol) of **14**, 0.62 g of freshly fused potassium acetate, 0.06 g of phosphorus pentoxide, and 3 ml of glacial acetic acid was maintained at 15–20° while a solution of 0.48 g (7.3 mmol) of nitrosyl chloride in 3 ml of acetic acid was added dropwise during 10 min. After 2 hr at 15–20° the mixture was poured on ice and a cold methylene chloride extract was washed with cold saturated potassium carbonate solution until the washings were slightly basic. The cold methylene chloride layer was evaporated under a pressure of 0.4 mm to constant weight. There was obtained 0.45 g (89%) of **17** as a yellow oil: ir (neat) 2.75, 5.78, and 6.55 μ; nmr ($CDCl_3$) τ 5.95 (s, 2, CH_2N), 7.18 (s, 3, $COCH_3$), 7.55 (s, 1, OH), 8.90–9.50 (m, 2, c-$CHCH_2CH_2$), 9.50–9.90 (m, 8, c-CCH_2CH_2).

1-Acetylamino-2-cyclopropyl-2-propanol* (**15**).—As in the case of **14**, 5-cyclopropyl-5-methyl-2-oxazolidone was converted into **15**, bp 118–119° (0.3 mm), mp 62–64°, in 83% yield. The sublimed analytical sample of **15** melted at 63.5–65.0°.

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.2; H, 9.5; N, 8.9. Found: C, 61.2; H, 9.6; N, 8.9.

1-(*N*-Nitrosoacetylamino)-2-cyclopropyl-2-propanol* (**18**).—As above for **17**, 1.0 g of **15** was converted into 0.96 g (81%) of **18**, a yellow oil: ir (neat) 2.75, 5.72, and 6.58 μ; nmr ($CDCl_3$) τ 6.05 (s, 2, CH_2N), 7.20 (s, 3, $COCH_3$), 7.35 (s, 1, OH), 8.93 (s, 3, CCH_3), 9.10–9.60 (m, 1, c-$CHCH_2CH_2$), 9.60–9.95 (m, 4, c-$CHCH_2CH_2$). Both **17** and **18** were used shortly after they were made.

2-Acetylamino-1-cyclopropyl-1-phenylethanol (**13**).—As in the case of **14**, 5-cyclopropyl-5-phenyl-2-oxazolidone was converted into **13**, mp 120.5–121.0°, in 75% yield.

Anal. Calcd for $C_{13}H_{17}NO$: C, 71.3; H, 7.8; N, 6.4. Found: C, 71.2; H, 8.0; N, 6.2.

2-(*N*-Nitrosoacetylamino)-1-cyclopropyl-1-phenylethanol (**16**).—As in the case of **17**, a 95% yield of **16** (mp 72–74°; ir bands at 6.62, 5.72, and 2.70 μ) was obtained after crystallization from benzene–pentane.

Decomposition of Nitroso Compounds in Methanolic Potassium Hydroxide.—The apparatus consisted of a one-neck round-bottom flask equipped with a magnetic stirrer and a pressure equalizing dropping funnel connected to a gas collecting device. A strong (about 50%) solution of potassium hydroxide in water was added dropwise to a stirred solution of the nitroso compound (about 0.005 mol) in 20 ml of methanol at room temperature. After about 3 min the evolution of nitrogen was complete (usually quantitative). The mixture was stirred for 15 min and poured into water. The products were isolated by ether extraction and the ether removed by atmospheric distillation through a small packed column. The residue was analyzed by glpc using methyl cyclopropyl ketone as standard. Each of the products was isolated by preparative glpc using an $8^3/_4 \times {}^3/_8$ in. column containing 15% SE-30 (a silicone gum) on 60–80 mesh Chromosorb W (diatomaceous earth) at 125–150° and identified as described below.

Cyclopropylphenylacetylene (**9a**).—In a run involving 0.01 mol of **6**, **9a** was isolated as the only volatile product in 90% yield as a colorless oil: bp 71–72° (1 mm); ir 4.48 μ; nmr (CCl_4) τ 2.45–2.95 (m, 5, ArH), 8.45–8.85 (m, 1, c-$CHCH_2CH_2$), 9.15–9.45 (m, 4, c-$CHCH_2CH_2$).

Anal. Calcd for $C_{11}H_{10}$: C, 92.9; H, 7.1. Found: C, 92.9; H, 7.1.

Cyclopropylmethylacetylene (**9c**).—Obtained from runs with **8** **9c** was a colorless liquid: ir 4.45 μ; nmr (CCl_4) τ 8.28 (d, J = 2 Hz, 3, CH_3), 8.90–9.15 (m, 1, $CHCH_2CH_2$), 9.25–9.55 (m, 4, $CHCH_2CH_2$) on glpc at 125°.

Anal. Calcd for C_6H_8: C, 90.0; H, 10.0. Found: C, 90.0; H, 10.0.

2-Cyclopropyl-1-methoxy-1-propene (**10c**).—The stereoisomers of **10c** were obtained as one fraction by glpc at 125° which had a longer retention time than **9c**. The ir spectrum had a strong band at 8.2 μ and the nmr (CCl_4) showed bands at τ 4.26 (m, 1, =CH), 6.5 (s, 3, OCH_3), 8.52 (s, 3, $=CCH_3$), 8.76 (s, 3, $=CCH_3$) 9.35–9.80 (m, 5, c-$CHCH_2CH_2$). Integration of the methyl resonances showed that the isomer in which the CH_3O group is trans to the methyl group (τ 8.76),[19] the *Z* isomer,[20] was 48% and the *E* isomer (methyl group 8.52) was 52%.

Anal. (of *Z* and *E* forms). Calcd for $C_7H_{12}O$: C, 75.0; H, 10.7. Found: C, 75.2; H, 10.6.

On treatment of this mixture with 2,4-DNPH reagent[21] a 2,4-dinitrophenylhydrazone [mp 132.5–133.5°; nmr (CCl_4) τ 0.85–2.20 (m, 4, NH, ArH), 2.38 (d, J = 5 Hz, 1, CH=N), 8.10–8.40 (m, 1, CHCH=N), 8.72 (d, J = 6 Hz, 3, CH_3CH), 9.10–9.80 (m, 5, c-$CHCH_2CH_2$)] was obtained.

Anal. Calcd for $C_{12}H_{14}N_4O_4$: C, 51.8; H, 5.0; N, 20.1. Found: C, 51.6; H, 5.0; N, 20.3.

Dicyclopropylacetylene (**9b**).—This acetylene was isolated by preparative glpc as the first fraction in runs using **7**. In analytical runs in which methylcyclopropyl ketone was the standard, about 52–53% yields of **9b** [ir (neat) 3.28, 3.38, and 7.0 μ; nmr (CCl_4) τ 8.80–9.20 (m, 1, c-$CHCH_2CH_2$), 9.25–9.60 (m, 4, c-$CHCH_2CH_2$)] were obtained.

Anal. Calcd for C_8H_{10}: C, 90.6; H, 9.4. Found: C, 90.4; H, 9.4.

2,2-Dicyclopropyl-1-methoxyethylene (**10b**).—This vinyl ether was obtained as the fraction with the longest retention time on glpc analysis of the products obtained from **7**. In analytical runs in which methylcyclopropyl ketone was used as internal standard 21–22% yields of **10b** [mol wt 138 (mass spectrum); ir (neat) 8.2 μ (=COC); nmr (CCl_4) τ 4.24 (s, 1, =CH), 6.45 (s, 3, OCH_3), 9.10–9.80 (m, 10, c-$CHCH_2CH_2$)] were obtained.

Anal. Calcd for $C_9H_{14}O$: C, 78.3; H, 10.2. Found: C, 78.4; H, 10.4.

Compound **10b** was further characterized by treatment with 2,4-DNPH[21] to yield a yellow 2,4-dinitrophenylhydrazone: mp 143–144.5°; nmr (CCl_4) 0.74–2.22 (m, 4, NH, ArH), 2.40 (d, J = 6 Hz, 1, CH=N), 8.20–8.50 (m, 1, CHCH=N), 9.10–9.80 (m, 10, c-$CHCH_2CH_2$).

Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.3; H, 5.3; N, 18.4. Found: C, 55.6; H, 5.6; N, 18.4.

Dicyclopropyl ketone was identified by comparison (ir, nmr, glpc retention time) with an authentic sample.

Cyclopropyl cyclopropylmethyl ketone was obtained by glpc (longer retention time than dicyclopropyl ketone) as a colorless oil: mol wt 124 (mass spectrum); ir (neat) 5.9 μ; nmr (CCl_4) τ 7.60 (d, J = 7 Hz, 2, $COCH_2CH$), 7.80–8.25 (m, 1, c-$COCHCH_2CH_2$), 9.00–9.35 (m, 4, c-$COCHCH_2CH_2$), 9.40–9.95 (m, 5, c-$CH_2CHCH_2CH_2$); semicarbazone mp 114–115°, alone and mixed with the semicarbazone of the ketone prepared in 45% yield from the reaction of cyclopropylmagnesium bromide with

(19) This assignment was made by Dr. C. Meyers, Southern Illinois University.

(20) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Reid, *J. Amer. Chem. Soc.*, **90**, 509 (1968), and ref 1b therein.

(21) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley, New York, N. Y., 1964, p 253.

cyclopropylacetonitrile. The mass spectra and ir were identical.[22,23]

Decomposition of Nitrosoacetylamino Alcohols in Cyclohexene.—In a typical experiment a solution at 10–15° of 0.74 (0.004 mol) of **18** in 10 ml each of pentane and cyclohexene containing 0.2 g of Aliquat 336[24] was treated slowly with a solution of 1 g of sodium hydroxide in 1 ml of water.[15] After 15 min the theoretical amount of nitrogen had been collected and the mixture was allowed to come to room temperature. The mixture was washed with water. The organic layer was filtered through a cone of anhydrous magnesium sulfate and concentrated to about 4 ml by fractionation through a small packed column. There was no evidence (glpc) for the presence of **9c** in the distillate or the concentrate. Further fractionation afforded 0.33 g (52%) of **5c**, bp 48° (0.4 mm), identical with the sample prepared from **8**.

In a similar experiment a 64% yield of **5b**, bp 74° (0.4 mm), was obtained from **17**.

Registry No.—**5b**, 35200-94-3; **5c**, 35200-95-4; **6**, 35200-96-5; **7**, 35200-97-6; **8**, 35200-98-7; **9a**, 21777-85-5; **9b**, 27998-49-8; **9c**, 35201-01-5; **10b**, 34189-07-6; **10b** 2,4-DNP, 35200-78-3; (*Z*)-**10c**, 35200-79-4; (*E*)-**10c**, 35200-80-7; **10c** 2,4-DNP, 35200-81-8; **13**, 35200-82-9; **14**, 35200-83-0; **15**, 35200-84-1; **16**, 35249-60-6; **17**, 35200-85-2; **18**, 35200-86-3; methyl 3-cyclopropyl-3-phenyl-3-hydroxypropionate, 35200-87-4; methyl 3,3-dicyclopropyl-3-hydroxypropionate, 35200-88-5; methyl 3-cyclopropyl-3-hydroxybutyrate, 35200-89-6; 5-cyclopropyl-5-phenyl-2-oxazolidinone, 35200-90-9; 5,5-dicyclopropyl-2-oxazolidinone, 35200-91-0; 5-cyclopropyl-5-methyl-2-oxazolidinone, 35200-92-1; cyclopropyl cyclopropylmethyl ketone, 14113-96-3.

(22) L. Michiels, *Bull. Cl. Sci., Acad. Roy. Belg.*, **10**, (1912) [C 1105 (1912)], report mp 82–83° for the semicarbazone of the ketone prepared by reaction of cyclopropyl cyanide with cyclopropylmethylmagnesium bromide. We believe their ketone was not the expected one.

(23) The nmr spectrum for cyclopropylmethyl ketone, reported by M. Hanack and H. M. Ensslin, *Ann.*, **697**, 100 (1966), has a quartet at τ 7.5 which is not present in the pure sample that we obtained.

(24) Methyl tricaprylammonium chloride obtained from General Mills Chemicals, Kankakee, Ill.

A Direct Synthesis of Benzo[*b*]thiophene-2-carboxylate Esters Involving Nitro Displacement

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Received May 11, 1972

Facile, one-step synthesis of methyl benzo[*b*]thiophene-2-carboxylates from *o*-nitrobenzaldehydes and methyl 3-aminobenzo[*b*]thiophene-2-carboxylates from *o*-nitrobenzonitriles are described. Both reactions involve nucleophilic displacement of activated nitro functions followed by base-catalyzed ring closures.

The first synthesis of benzo[*b*]thiophene-2-carboxylic acid was reported by Friedländer and Lenk.[1] The acid was formed by a series of reactions involving alkylation of *o*-mercaptobenzaldehyde with chloroacetic acid followed by ring closure in fused alkali. Modifications of this procedure were used in the preparation of 5-nitrobenzo[*b*]thiophene-2-carboxylic acid[2–4] and 5,6-dimethoxybenzo[*b*]thiophene-2-carboxylic acid.[5,6] A further modification of this general ring-closure principle, but starting with *o*-methylmercaptoacetophenone, has been reported recently by Ruwet and Renson.[7] The disadvantages of these approaches have been the inaccessibility of the starting materials and the low overall yields obtained. A second method, reported by Campaigne and Cline[8] and improved upon by Chakrabarti and coworkers,[9] involved oxidative cyclization of β-aryl-α-mercaptoacrylic acids and gave high yields especially in aryl systems containing methoxyl functions. A related synthesis was reported by Ruwet and Renson.[10]

An even less accessible group of compounds has been the 3-aminobenzo[*b*]thiophene-2-carboxylie acids. Friedländer and Laske[11] reported the synthesis of the parent compound by a sequence involving alkylation of *o*-mercaptoaniline with chloroacetic acid, diazotization, displacement by cyanide ion, and, finally, fusion with alkali. More recently, a synthesis of ethyl 3-aminobenzo[*b*]thiophene-2-carboxylate was reported by Carrington and coworkers.[12] This compound was prepared by a ring-opening rearrangement of 3-chloro-1,2-benzisothiazole.[13] The generality of these methods again suffers from inaccessibility of starting materials.

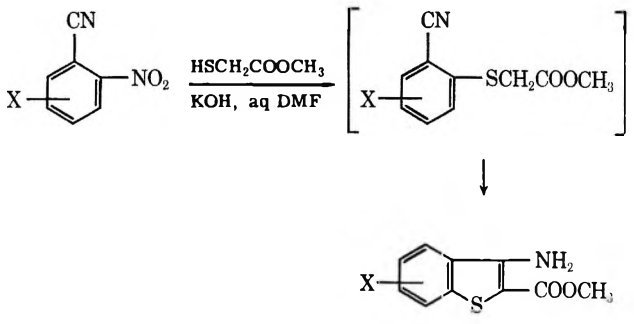
The author wishes to report facile, one-step syntheses of both methyl 3-aminobenzo[*b*]thiophene-2-carboxylates from *o*-nitrobenzonitriles and methyl benzo[*b*]-thiophene-2-carboxylates from *o*-nitrobenzaldehydes. The ease of nucleophilic displacement of activated nitro functions in aromatic systems has been known for some time, and scattered examples of its utility occur throughout the chemical literature. Bunnett and coworkers[14] studied the relative displacement rates by piperidine in substituted 2,4-dinitrobenzenes. They found the rate of nitro displacement was more than 200 times that of chlorine and was nearly equal to fluorine. In similar studies, Bolto and Miller,[15] using methoxide ion as the nucleophile, established the following order of ease of displacement: $SMe_2^+ > NMe_3^+ > F > NO_2 > Cl$. In the reactions to be discussed, advantage is taken of this

(1) P. Friedländer and E. Lenk, *Ber.*, **45**, 2083 (1912).
(2) L. F. Fieser and R. G. Kennelly, *J. Amer. Chem. Soc.*, **57**, 1611 (1935).
(3) K. Fries, H. Heering, E. Hemmecke, and G. Siebert, *Ann.*, **527**, 83 (1937).
(4) F. G. Bordwell and C. J. Albisetti, Jr., *J. Amer. Chem. Soc.*, **70**, 1955 (1948).
(5) J. Siće and M. Mednick, *ibid.*, **75**, 1628 (1953).
(6) D. G. Bew and G. R. Clemo, *J. Chem. Soc.*, 1314 (1953).
(7) A. Ruwet and M. Renson, *Bull. Soc. Chim. Belg.*, **79**, 75 (1970).
(8) E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 39 (1956).
(9) R. M. Chakrabarti, N. B. Chapman, and K. Clarke, *Tetrahedron*, **25**, 2781 (1969).
(10) A. Ruwet and M. Renson, *Bull. Soc. Chim. Belg.*, **79**, 593 (1970).
(11) P. Friedländer and A. Laske, *Ann.*, **351**, 412 (1907).
(12) D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *Tetrahedron Lett.*, 1075 (1971).
(13) A. Reissert, *Ber.*, **61**, 1680 (1928).
(14) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Amer. Chem. Soc.*, **79**, 385 (1957).
(15) B. A. Bolto and J. Miller, *Aust. J. Chem.*, **9**, 74 (1956).

displacement lability of a nitro function, which is ortho to either a cyano or carboxaldehyde function.

When an *o*-nitrobenzonitrile[16] was allowed to react with an equivalent amount of methyl thioglycolate and excess potassium hydroxide in aqueous DMF at ice-bath temperature, the product obtained was the corresponding methyl 3-aminobenzo[*b*]thiophene-2-carboxylate (Scheme I). The product was formed by thiol

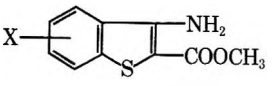
SCHEME I



anion displacement of the activated nitro function followed by base-catalyzed cyclization of the type earlier discussed. The reaction conditions and yields are summarized in Table I. When *o*-chlorobenzo-

TABLE I

METHYL 3-AMINOBENZO[*b*]THIOPHENE-2-CARBOXYLATES[a]



X[b]	Mp, °C	Yield, %	Crystn solvent[c]	Temp, °C	Time, hr
H	110–111	72	A	0	0.5
4-Cl	111–112	84	B	0	1
6-Cl	151–152	72	B	0	1
4-OCH_3	147–148	35	B	0	0.5
4-NO_2	132–133	67	B	0	0.5
6-NO_2	229–231	47	B	0	0.5
6-CF_3	126–127	69	C	0	0.5
4-NO_2, 6-CF_3	189–191	80	B	0	5 min
4-NO_2, 6-CH_3	148–149	55	B	0	0.5

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds: Ed. [b] Registry numbers are, respectively, 35212-85-2, 35212-86-3, 35212-87-4, 35212-88-5, 35212-89-6, 35212-90-9, 35212-91-0, 35212-92-1, and 35212-93-2. [c] A, alcohol–water; B, alcohol; C, methylcyclohexane.

nitrile was utilized as starting material in the reaction, it was recovered unchanged even after two days at room temperature.

Similarly, when an *o*-nitrobenzaldehyde was allowed to react with an equivalent amount of methyl thioglycolate and excess potassium carbonate in DMF at various temperatures, the product obtained was the corresponding methyl benzo[*b*]thiophene-2-carboxylate (Scheme II). The reaction conditions and yields are summarized in Table II. Yields of both tables are based on crystallized products.

These reactions represent but two examples wherein activated nitro functions can be utilized in the synthesis of heterocycles and uniquely substituted benzenes.

(16) *o*-Nitrobenzonitriles are readily prepared from 1-chloro-2-nitrobenzenes by reaction with cuprous cyanide and from *o*-nitroanilines by diazotization and displacement with cyanide ion.

SCHEME II

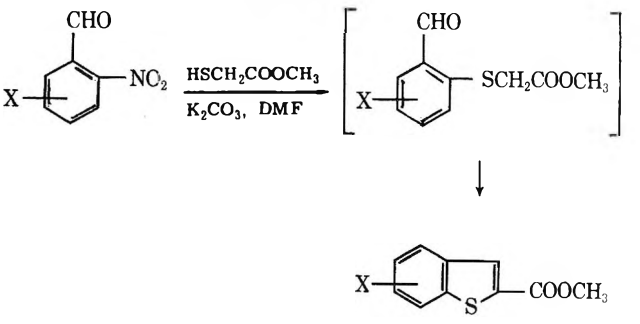
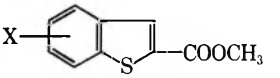


TABLE II

METHYL BENZO[*b*]THIOPHENE-2-CARBOXYLATES[a]



X[b]	Mp, °C	Yield, %	Crystn solvent[c]	Temp, °C; time, hr
H	72–73[d]	52	A	0, 0.5; 25, 20
4-Cl	89–90	70	B	0, 0.5; 25, 16
5-Cl	109–110	49	B	0, 0.5; 25, 21
4-NO_2	152–154	16	B	0, 3.5
6-NO_2	207–209	16	B	0, 2; 25, 1
5,6-diOMe	158–159	16	B	100, 18

[a] Satisfactory analytical values (±0.3% for C, H and N, S or Cl) were reported for all compounds: Ed. [b] Registry numbers are, respectively, 22913-24-2, 35212-95-4, 35212-96-5, 34084-87-2, 34084-88-3, 35212-99-8. [c] A, alcohol–H_2O; B, alcohol. [d] Lit. mp 72–73°: R. Weissgerber and O. Kruber, *Ber.*, **53**, 1551 (1920).

Further examples will be the subject of future communications from this laboratory.

Experimental Section[17]

Materials.—*o*-Nitrobenzonitrile, 6-chloro-2-nitrobenzonitrile, 4-chloro-2-nitrobenzonitrile, and all substituted *o*-nitrobenzaldehydes were obtained from the Aldrich Chemical Co. 2-Nitro-6-methoxybenzonitrile,[18] α,α,α-trifluoro-2-nitro-*p*-tolunitrile,[19] and 2,4-dinitrobenzonitrile[20] were prepared by procedures described in the literature.

General Procedure for Methyl 3-Aminobenzo[*b*]thiophene-2-carboxylates.—To a cold solution (ice bath) containing 30 mmol of the substituted *o*-nitrobenzonitrile and 30 mmol of methyl thioglycolate in 60 ml of DMF was added dropwise a solution of 3 g of potassium hydroxide in 15 ml of water. The mixture was stirred in the cold for the time shown in Table I and poured into ice water. The solid crude product was collected and crystallized from the appropriate solvent (Table I).

General Procedure for Methyl Benzo[*b*]thiophene-2-carboxylates.—To a cold solution (ice bath) containing 30 mmol of the substituted *o*-nitrobenzaldehyde and 5 g of anhydrous potassium carbonate in 60 ml of DMF was slowly added 30 mmol of methyl thioglycolate. The mixture was stirred in the cold for 0.5 hr and at the temperature and for the time period shown in Table II. The mixture was then poured into ice water, and the solid was collected and crystallized from the appropriate solvent (Table II).

2,6-Dinitrobenzonitrile.—A solution containing 25 g of 1-chloro-2,6-dinitrobenzene (0.123 mol) and 20 g of cuprous cyanide (0.222 mol) in 150 ml of *N*,*N*-dimethylacetamide was stirred and heated at 140° for 1 hr. The mixture was cooled and poured into ice water. The solid product was collected, dried, and triturated twice with 400 ml of hot ethyl acetate.

(17) Melting points were determined on a Mel-Temp apparatus and are uncorrected.

(18) A. Russell and W. G. Tebbens, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 293.

(19) M. Hauptschein, E. A. Nodiff, and A. J. Saggiomo, *J. Amer. Chem. Soc.*, **76**, 1051 (1954).

(20) P. Cohn and P. Friedländer, *Ber.*, **35**, 1265 (1902).

Filtration, removal of the solvent, and crystallization from alcohol yielded 12.7 g of product, mp 149–151° (lit.[21] 145°).

Anal. Calcd for $C_7H_3N_3O_4$: C, 43.54; H, 1.57; N, 21.76. Found: C, 43.46; H, 1.50; N, 21.74.

2,6-Dinitro-*p*-tolunitrile.—A solution containing 18 g of 4-chloro-3,5-dinitrotoluene (0.083 mol) and 15 g of cuprous cyanide (0.167 mol) in 150 ml of *N*,*N*-dimethylacetamide was stirred and heated at 130–135° for 1 hr. The mixture was cooled and poured into ice water. The crude product was collected by filtration, dried, and triturated with 500 ml of hot ethyl acetate. Filtration, removal of the solvent, and crystallization from alcohol yielded 10.9 g of product, mp 105–107° (lit.[22] 103°).

Anal. Calcd for $C_8H_5N_3O_4$: C, 46.39; H, 2.43; N, 20.29. Found: C, 46.32; H, 2.39; N, 20.01.

α,α,α-Trifluoro-2,6-dinitro-*p*-tolunitrile.—A solution containing 95 g of 4-chloro-3,5-dinitrobenzotrifluoride[23] (0.35 mol) and 35 g of cuprous cyanide (0.39 mol) in 200 ml of DMF was heated at 100° for 3.5 hr. The mixture was cooled and poured into ice water. The crude product was collected, dried, and triturated with hot ethyl acetate. Filtration, removal of the solvent, and crystallization from benzene yielded 60 g of product, mp 94–96°.

Anal. Calcd for $C_8H_2F_3N_3O_4$: C, 36.80; H, 0.77; N, 16.09. Found: C, 37.02; H, 0.91; N, 16.37.

(21) S. Reich, *Ber.*, **45**, 804 (1912).
(22) A. Claus and C. Beysen, *Ann.*, **266**, 223 (1891).
(23) L. M. Yagupol'skii and V. S. Mospan, *Ukr. Khim. Zh.*, **21**, 81 (1955); *Chem. Abstr.*, **49**, 8866 (1955).

Registry No.—2,6-Dinitrobenzonitrile, 35213-00-4; 2,6-dinitro-*p*-tolunitrile, 35213-01-5; α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile, 35213-02-6.

Acknowledgments.—The author wishes to thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

The 1,2-Dithiolium Cation. XI.[1a] Polycyclic Dithiole and "No-Bond Resonance" Compounds[1b]

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Received April 18, 1972

The first known tricyclic 1,2-dithiolium salts **11**, **12**, and **13** have been prepared. The preparation of polycyclic thiothiophthene derivatives from these and related compounds is discussed.

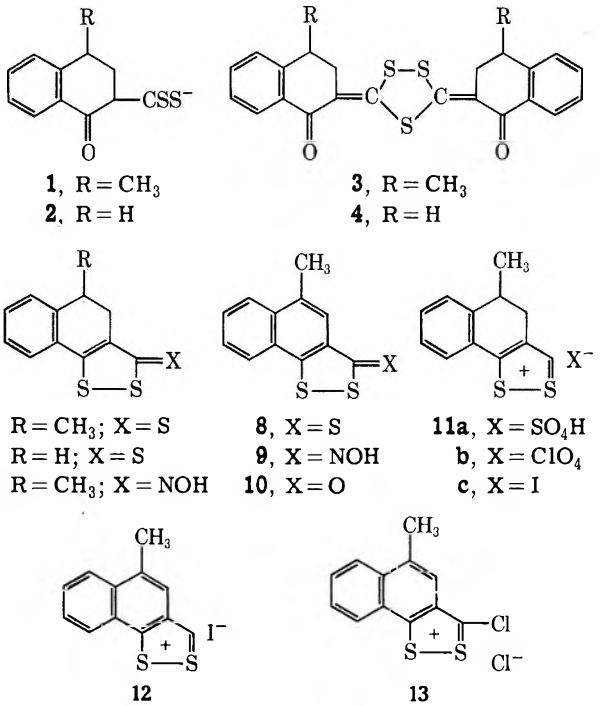
Recent investigations on the thiothiophthene "no-bond resonance" system have been facilitated by discoveries of attractive preparative methods based on condensation reactions of 1,2-dithiolium salts or other dithioles.[2] The present paper describes the preparation of certain bicyclic and tricyclic dithioles and the conversion of some of them to polycyclic thiothiophthene derivatives.

The investigation began with the application to 4-methyl-1-tetralone of the Thuillier–Vialle synthesis[3] of 1,2-dithiole-3-thiones. After base-catalyzed addition of carbon disulfide to give the dithiocarboxylic acid salt **1**, isolation from solution was effected by hypoiodite oxidation rather than the more usual procedures of acidification or alkylation. Analysis and molecular weight determination showed that the product thus obtained was the trithiolane **3**; it reacted smoothly with phosphorus pentasulfide to give the 1,2-dithiole-3-thione **5**, which was aromatized to **8** by sulfur at 190°.

Tetralone reacted similarly to give **2**, **4**, and **6**, but in somewhat lower yield; these were not investigated further.

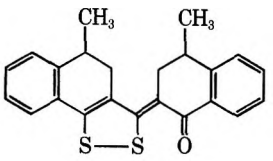
Although **5** and **8** are of course closely related, they belong to different families of dithiolethiones ("trithiones"), the aryl and benzo substituted, which differ in their behavior toward peracetic acid. The former are rapidly converted to high yields of aryl-1,2-dithiolium salts,[4] while the latter give poorly defined oxidation products which are not saltlike. Benzo-1,2-dithiolium salts are, in fact, obtainable only by an entirely different and circuitous method.[5] It is therefore of some interest that peracetic acid converts both **5** and **8** to the tricyclic dithiolium salts **11** and **12**, respectively. The latter was, to be sure, obtained in only modest yield and an impure state.

Hydroxylamine reacts with both **5** and **8**, giving oximes **7** and **9**, respectively, but mercuric acetate desulfuration succeeded only with **8**, giving **10**.

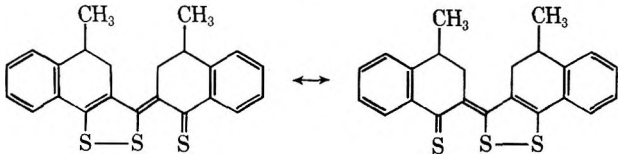


(1) (a) For paper IX, see E. Klingsberg, *Syn.*, 29 (1972). (b) Presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 1972.
(2) E. Klingsberg, *Quart. Rev.*, **23**, 537 (1969).
(3) A. Thuillier and J. Vialle, *Bull. Soc. Chim. Fr.*, 1398 (1959).
(4) E. Klingsberg, *J. Amer. Chem. Soc.*, **83**, 2934 (1961).
(5) A. Lüttringhaus, M. Mohr, and N. Engelhard, *Ann.*, **661**, 84 (1963).

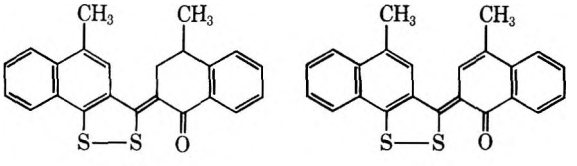
Following a known method[6] for converting dithiolium salts to thiothiophthenes, **11a** was condensed with 4-methyltetralone to give **14**, which reacted with P_2S_5 to give the polycyclic thiothiophthene **15**. Attempts to dehydrogenate this to a completely aromatic system were unsuccessful.



14



15

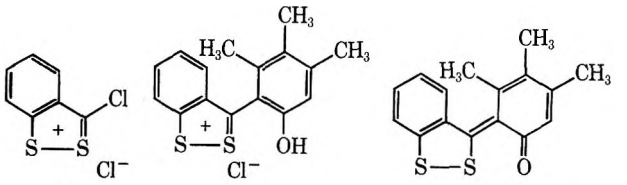


16 **17**

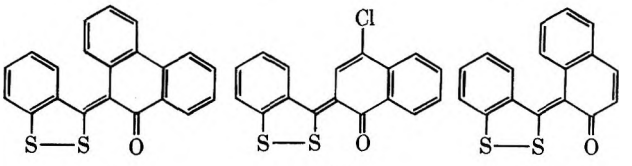
Like benzo-1,2-dithiole-3-thione, **8** reacted with sulfur dichloride to give a chlorodithiolium chloride **13**, which condensed with 4-methyl-1-tetralone to give **16** and with 4-methyl-1-naphthol to give **17**. The latter proved resistant to P_2S_5, again blocking the way to the fully aromatic system.

Similar results were given by a series of compounds prepared from 3-chloro-4,5-benzo-1,2-dithiolium chloride **18**.[7] Like 3-chloro-5-phenyl-1,2-dithiolium perchlorate,[8] **18** condensed readily with a series of phenolic compounds constituted for ortho substitution. The products, isolable as dithiolium salts such as **19**, were readily converted to pseudobases **20**–**23**. Reaction with P_2S_5 gave uniformly discouraging results. On the other hand, the partially saturated thiothiophthenes such as **28**, obtainable from **18** by condensation with cyclic ketones to dithioles **24**–**27** followed by P_2S_5 treatment, resisted attempts at aromatization. Similar difficulties have been encountered in the 3-phenyl-1,2-dithiole series.[9]

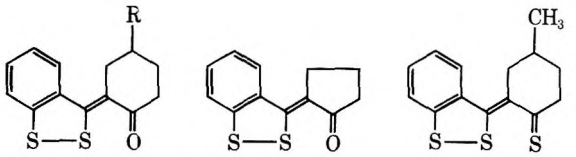
An unsuccessful attempt to devise a convenient synthesis for the little known 2-mercapto-1-naphthoic acid **29**, which would be a useful intermediate for the synthesis of naphthodithiole derivatives, began with the preparation of naphtho[2,1-*b*]thiophene-1,2-dione (**30**) from 2-naphthalenethiol and oxalyl chloride, a reaction that seems to have been reported only in the patent literature.[10] Good results are given by fusion at 170°; no catalyst is necessary. The product is readily isolated from the reaction mixture in 70% yield by virtue of its alkali solubility to give the sodium salt **31**, which regenerates **30** on acidification. The alkali-



18 **19** **20**



21 **22** **23**

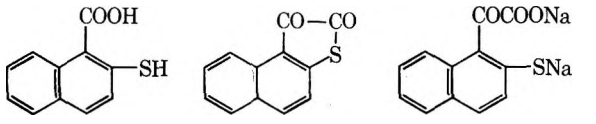


24, R = Me
25, R = Me_3C
26, R = H

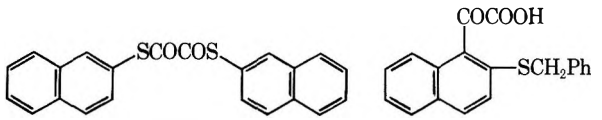
27 **28**

insoluble product consists of smaller yields of the hitherto unknown oxalic dithiol ester **32**.

No way could be found to eliminate a carbon atom from **30** or **31**, which are surprisingly stable. Prolonged boiling has no effect on **31**, and oxidation and decarboxylation experiments were unsuccessful. Benzylation of **31** gives **33**, which is converted to **30** by thionyl chloride.



29 **30** **31**



32 **33**

Experimental Section[11]

Trithiolane 3.—A 1.7 *M* solution of sodium *tert*-amylate was prepared by refluxing a mixture of 30.0 g of sodium ribbon and 88.0 g of *tert*-amyl alcohol in 500 ml of benzene for 24 hr. After filtration through glass wool to remove excess sodium, 259 ml (0.44 mol of sodium *tert*-amylate) of the solution was stirred in an ice bath while 32.0 g (0.20 mol) of 4-methyl-1-tetralone dissolved in 13.3 ml (0.22 mol) of carbon disulfide was added dropwise. A thick yellow slurry formed. After completion of addition, stirring was continued for 0.5 hr, followed by addition of 200 ml of water. The red aqueous layer was separated, and the benzene layer was washed twice with 200-ml portions of water. To the combined aqueous extracts was added, dropwise, 50.8 g (0.20 mol) of iodine dissolved in dilute sodium hydroxide. The copious yellow precipitate was filtered, washed free of base with water, and air dried, yield 28.3 g (65%), mp 195–200°. Crystallization from 360 ml of nitroethane yielded 17.7 g of bright orange crystals, mp 205–207°.

Anal. Calcd for $C_{24}H_{20}O_2S_3$: C, 66.0; H, 4.6; S, 22.0. Found: C, 65.8; H, 4.5; S, 22.0.

Results were similar when the reaction was performed on a much larger scale.

(6) E. Klingsberg, *J. Amer. Chem. Soc.*, **85**, 3244 (1963).
(7) J. Faust and R. Mayer, *Ann.*, **688**, 150 (1965).
(8) G. A. Reynolds, *J. Org. Chem.*, **33**, 3352 (1968).
(9) R. Pinel, Y. Mollier, and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 856 (1967).
(10) German Patent 402,994 (1924); *Friedl.*, **14**, 474 (1924).

(11) Melting points are corrected.

Trithiolane **4** was prepared similarly. α-Tetralone (29.2 g, 0.20 mol) dissolved in 12.1 ml (0.20 mol) of carbon disulfide was dripped into 0.40 mol of sodium *tert*-amylate in benzene. After iodine treatment, a yield of 28.1 g (68%) of yellow solid, mp 225–226°, was obtained. Chlorobenzene gave orange crystals, mp 243–243.5°.

Anal. Calcd for $C_{22}H_{16}O_2S_3$: C, 64.6; H, 3.9; S, 23.5. Found: C, 64.4; H, 3.8; S, 23.3.

4,5-Dihydro-5-methyl-3*H*-naphtho[1,2-*c*]-1,2-dithiole-3-thione (5).—To a refluxing solution of 14.1 g (0.033 mol) of **3** in 200 ml of pyridine was added 22.5 g (0.101 mol) of P_2S_5. The mixture was refluxed 2.5 hr, cooled, diluted with ice water, chilled, and filtered, yield 11.8 g (71%) of deep orange solid, mp 105–107°. The compound crystallized from hexane with unchanged melting point.

Anal. Calcd for $C_{12}H_{10}S_3$: C, 57.6; H, 4.0; S, 38.4. Found: C, 57.6; H, 4.0; S, 38.5.

The dithiolethione **6** was prepared from **4** by refluxing with P_2S_5 for 1 hr in toluene, followed by filtration and evaporation. The gummy orange product was crystallized successively from methylcyclohexane and methanol, giving an orange product, mp 92–92.5°.

Anal. Calcd for $C_{11}H_8S_3$: C, 56.0; H, 3.4; S, 40.6. Found: C, 55.7; H, 3.7; S, 40.3.

5-Methyl-3*H*-naphtho[1,2-*c*]-1,2-dithiole-3-thione (8).—A mixture of 6.0 g (0.024 mol) of **5** and 1.58 g (0.048 g-atom) of sulfur was fused at 190° for 16 hr. The product was ground and crystallized from 50 ml of toluene to give 4.3 g (71%) of deep orange needles, mp 160–162°.

Anal. Calcd for $C_{12}H_8S_3$: C, 58.1; H, 3.2; S, 38.7. Found: C, 58.2; H, 3.1; S, 39.1.

5-Methyl-3*H*-naphtho[1,2-*c*]-1,2-dithiol-3-one Oxime (9).—A mixture of 0.50 g (2.0 mmol) of **8**, 0.20 g (2.9 mmol) of hydroxylamine hydrochloride, and 0.40 g (2.9 mmol) of sodium acetate trihydrate was stirred and refluxed in 50 ml of ethanol for 3 hr, slowly turning clear. Cooling and filtration gave 0.48 g (96%) of yellow product, mp 228–230°. Crystallization from dilute ethanol gave pale yellow product, melting point unchanged.

Anal. Calcd for $C_{12}H_9NOS_2$: C, 58.4; H, 3.6; N, 5.7; S, 25.9. Found: C, 58.6; H, 3.6; N, 5.5; S, 26.1.

Under similar conditions, **5** was converted in 65 hr of refluxing to a 76% yield of impure oxime **7**, mp 136–150°. Crystallization from methanol or hexane gave pale yellow product, mp 157–159°. Slow decomposition occurred on storage at room temperature.

Anal. Calcd for $C_{12}H_{11}NOS_2$: C, 57.9; H, 4.4; N, 5.6; S, 25.7. Found: C, 57.6; H, 4.4; N, 5.3; S, 26.0.

5-Methyl-3*H*-naphtho[1,2-*c*]-1,2-dithiol-3-one (10).—A suspension of 2.5 g (0.010 mol) of **8** in 200 ml of warm acetone was added to a solution of 4.0 g (0.013 mol) of mercuric acetate in 100 ml of acetic acid. The mixture was stirred at room temperature for 48 hr and then filtered to give a pale yellow solution. Dilution with water gave 1.75 g (76%) of pale yellow product, mp 126.5–127.5°. Crystallization from methylcyclohexane raised the melting point to 128–128.5°.

Anal. Calcd for $C_{12}H_8OS_2$: C, 62.1; H, 3.4; S, 27.6. Found: C, 61.9; H, 3.6; S, 27.5.

4,5-Dihydro-5-methylnaphtho[1,2-*c*]-1,2-dithiolium Hydrogen Sulfate (11a).—A solution of 24.0 g (0.096 mol) of **5** in 200 ml of acetone was immersed in an ice bath, and 54.0 g (0.288 mol) of 40% peracetic acid was added dropwise over a 2-hr period. Stirring was continued for 1 hr after addition was complete; this was followed by filtering and washing with cold acetone, to yield 25.8 g (85%) of bright yellow, water-soluble solid, mp 162–164°. It slowly decomposed on storage.

Anal. Calcd for $C_{12}H_{12}O_4S_3$: C, 45.6; H, 3.8; S, 30.4. Found: C, 45.8; H, 4.0; S, 30.6.

The corresponding perchlorate (**11b**) was prepared from **11a** in aqueous solution and crystallized from acetic acid or ethanol, mp 187.5–188.5°.

Anal. Calcd for $C_{12}H_{11}ClO_4S_2$: C, 45.3; H, 3.5; Cl, 11.1; S, 20.1. Found: C, 45.3; H, 3.4; Cl, 11.0; S, 20.2.

The orange iodide (**11c**) was crystallized from ethanol, mp 190–192° dec.

Anal. Calcd for $C_{12}H_{11}IS_2$: C, 41.6; H, 3.2; I, 36.7; S, 18.5. Found: C, 41.6; H, 3.2; I, 36.2; S, 18.2.

5-Methylnaphtho[1,2-*c*]-1,2-dithiolium Iodide (12).—A mixture of 1.24 g (5.0 mmol) of **8** and 1.7 g (15 mmol) of 30% hydrogen peroxide in 50 ml of acetic acid was stirred overnight at room temperature and then freed of solid by filtration. Addition of a little HI dissolved in acetic acid gave a brown precipitate, which was filtered, washed with ether, and further purified by trituration in benzene. The impure orange iodide weighed 0.65 g (38%) and melted at 104–107° dec.

Anal. Calcd for $C_{12}H_9IS_2$: I, 36.9; S, 18.6. Found: I, 34.5; S, 17.3.

Complete purification was not achieved and the product decomposed on storage.

Preparation of 14 from 11a.—A mixture of 15.9 g (0.050 mol) of **11a** and 6.4 g (0.040 mol) of 4-methyl-1-tetralone in 150 ml of ethanol was refluxed for 4 hr, cooled, and filtered, yield 6.9 g (46%) of red-brown solid. Crystallization from 300 ml of methylcyclohexane gave 3.8 g of bronze crystals, mp 176–178°. Additional crystallizations from methylcyclohexane and nitromethane gave bronze needles, mp 181–182°.

Anal. Calcd for $C_{23}H_{20}OS_2$: C, 73.5; H, 5.3; S, 17.0. Found: C, 73.4; H, 5.4; S, 17.0.

Conversion of 14 to 15.—To a refluxing solution of 3.8 g (0.010 mol) of **14** in 60 ml of chlorobenzene was added 3.3 g (0.015 mol) of P_2S_5. The mixture was stirred and refluxed for 0.5 hr, cooled to room temperature, and filtered. The filtrate was evaporated, yielding 4.1 g of slightly gummy purple product. Extraction in a Soxhlet apparatus with hexane gave 3.0 g of purple solid which was then stirred in dilute alkali for several hours, filtered, washed, and dried, yield 2.4 g (61.5%) of deep purple solid, mp 222–224°. Toluene gave deep purple crystals, mp 232–233.5°.

Anal. Calcd for $C_{23}H_{20}S_3$: C, 70.4; H, 5.1; S, 24.5. Found: C, 70.3; H, 5.3; S, 24.1.

Preparation of 3-Chloro-5-methylnaphtho[1,2-*c*]-1,2-dithiolium Chloride (13) and Conversion to 16.—Sulfur dichloride (3.0 ml) was added through the condenser to a stirred refluxing solution of 3.0 g (0.012 mol) of **8** in 90 ml of toluene. After 0.5 hr the product was cooled, filtered, and washed with benzene to yield 2.9 g (0.010 mol) of **13** as an orange solid. This was added to a solution of 1.7 g (0.011 mol) of 4-methyl-1-tetralone in 15 ml of toluene and stirred at reflux for 5.5 hr. Evaporation gave a red gum which was dissolved in toluene and chromatographed on a column of alumina. Elution with hexane followed by 75% benzene–25% methylcyclohexane gave 1.3 g (31%) of **16** as orange crystals, mp 170–171°. Crystallization from toluene or nitroethane raised the melting point to 173.5–175°.

Anal. Calcd for $C_{23}H_{18}OS_2$: C, 73.8; H, 4.8; S, 17.0. Found: C, 73.4; H, 5.1; S, 17.1.

Preparation of 17 from 13.—The chlorodithiolium chloride **13** (6.8 g, 0.027 mol) was added to a solution of 3.6 g (0.023 mol) of 4-methyl-1-naphthol in 90 ml of dry acetonitrile. After 24 hr of stirring at room temperature, the product was filtered and crystallized from 300 ml of butyl acetate to yield 2.8 g (33%) of purple needles, mp 215–216° dec.

Anal. Calcd for $C_{23}H_{16}OS_2$: C, 74.3; H, 4.3; S, 17.2. Found: C, 74.0; H, 4.2; S, 17.1.

3-Chlorobenzo-1,2-dithiolium Chloride (18).—To a stirred refluxing solution of 6.0 g (0.033 mol) of benzo-1,2-dithiole-3-thione[12] in 60 ml of benzene, 6.0 ml (9.7 g, 0.094 mol) of sulfur dichloride was carefully added, in portions, through the condenser. The mixture was stirred at reflux for 0.5 hr, cooled, and filtered. The yellow product was washed with carbon disulfide and transferred to a tared flask. After removal of traces of solvent by gentle warming, the yield was 6.5–7.0 g (87–94%). Results were similar on a large scale. It should be protected from moisture (which rapidly converts it to benzo-1,2-dithiol-3-one) and used as soon as possible.[7]

3-(2-Hydroxy-4,5,6-trimethylphenyl)benzo-1,2-dithiolium Chloride (19).—A mixture of 11.0 g (0.049 mol) of **18** and 6.8 g (0.050 mol) of 3,4,5-trimethylphenol in 125 ml of acetonitrile, sealed with a $CaCl_2$ tube to exclude moisture, was stirred at room temperature for 3.5 hr and then filtered. The yield of orange product, mp 244–245°, was 9.2 g (58%). It crystallized from acetic acid with unchanged melting point.

Anal. Calcd for $C_{16}H_{15}ClOS_2$: C, 59.6; H, 4.6; Cl, 11.0; S, 19.9. Found: C, 59.2; H, 4.6; Cl, 11.0; S, 19.4.

This was converted by dilute pyridine to the violet pseudobase **20** and crystallized from nitromethane followed by methylcyclohexane, mp 161–163°.

Anal. Calcd for $C_{16}H_{14}OS_2$: C, 67.2; H, 4.9; S, 22.4. Found: C, 67.2; H, 4.8; S, 22.1.

Pseudobase **21** was prepared by stirring 7.0 g (0.031 mol) of **18** and 5.0 g (0.026 mol) of 9-phenanthrol in 100 ml of acetonitrile

(12) E. Klingsberg and A. M. Schreiber, *J. Amer. Chem. Soc.*, **84**, 2941 (1962).

for 2 hr. The product was filtered, digested in dilute NaOH, filtered, washed, and dried, yielding 8.5 g (96%) of purple product, mp 202–203°. Crystallization from acetic acid, butyl acetate, or methylcyclohexane raised the melting point to 207–207.5°.

Anal. Calcd for $C_{21}H_{12}OS_2$: C, 73.3; H, 3.5; S, 18.6. Found: C, 73.4; H, 3.3; S, 18.4.

Pseudobase **22**, prepared similarly from 4-chloro-1-naphthol, crystallized from nitromethane as purple needles, mp 211.5–212°.

Anal. Calcd for $C_{17}H_9OS_2Cl$: C, 62.2; H, 2.7; Cl, 10.8; S, 19.5. Found: C, 62.1; H, 2.7; Cl, 10.7; S, 19.2.

Pseudobase **23**, prepared from 2-naphthol, contained a chlorinated by-product that was eliminated by chromatography of a methanol or nitromethane solution over alumina. The product was readily eluted, a reddish impurity being retained, and crystallized from methanol as purple needles, mp 162.5–163°.

Anal. Calcd for $C_{17}H_{10}OS_2$: C, 69.4; H, 3.4; S, 21.8. Found: C, 69.8; H, 3.2; S, 21.2.

2-(Benzo-1,2-dithiol-3-ylidene)-4-methylcyclohexanone (24).—A mixture of 22.0 g (0.099 mol) of **18** and 15.0 ml (13.7 g, 0.124 mol) of 4-methylcyclohexanone in 75 ml of toluene was stirred at reflux for 50 min, filtered hot, cooled, and chilled in Dry Ice–acetone, yielding 9.7 g (38%) of red-brown solid, mp 122–126°. Crystallization from 55 ml of acetic acid gave 7.5 g of red solid, mp 130–131.5°.

Anal. Calcd for $C_{14}H_{14}OS_2$: C, 64.1; H, 5.3; S, 24.4. Found: C, 64.1; H, 5.3; S, 24.6.

4-*tert*-Butylcyclohexanone gave yellow-red **25**, mp 164.5–165.5° (ethanol or methylcyclohexane).

Anal. Calcd for $C_{17}H_{20}OS_2$: C, 67.1; H, 6.6; S, 21.0. Found: C, 66.9; H, 6.5; S, 20.8.

Cyclohexanone gave orange-red **26**, mp 114.5–115° (hexane).

Anal. Calcd for $C_{13}H_{12}OS_2$: C, 62.7; H, 4.8; S, 25.8. Found: C, 62.7; H, 4.7; S, 25.7.

Cyclopentanone gave brown **27**, mp 149–151° (methylcyclohexane).

Anal. Calcd for $C_{12}H_{10}OS_2$: C, 61.5; H, 4.3; S, 27.3. Found: C, 61.2; H, 4.1; S, 27.2.

Thiothiophthene 28.—Phosphorus pentasulfide (4.50 g, 0.020 mol) was added to a refluxing solution of 4.18 g (0.016 mol) of **24** in 120 ml of toluene. The mixture was refluxed 1.5 hr, cooled, and filtered. The resulting olive-green solid was washed to a clear run-off with petroleum ether (bp 30–60°), dried, and stirred overnight in dilute alkali. Filtering, washing thoroughly with water, and drying gave 4.0 g of purple solid, mp 128–131°. Crystallization from methylcyclohexane or ethanol gave purple needles, mp 149.5–150°.

Anal. Calcd for $C_{14}H_{14}S_3$: C, 60.5; H, 5.0; S, 34.5. Found: C, 60.5; H, 5.1; S, 34.7.

Naphtho[2,1-*b*]thiophene-1,2-dione (30).—A mixture of 30.0 g (0.19 mol) of 2-naphthalenethiol and 45 ml (67 g, 0.53 mol) of oxalyl chloride was heated under reflux for 3 hr in an oil bath at 110–120°. The condenser was then set for distillation and heating continued for 1 hr at 165–175°. The product was cooled, ground, and subjected to prolonged or repeated digestion at room temperature with 1 *N* NaOH, which left undissolved 8.4 g (24%) of crude 2-naphthyl dithioloxalate (**32**), mp 170–200°. Crystallization from 280 ml of trichloroethylene gave 5.2 g (15%), mp 225–227°. It could also be crystallized from toluene or butyl acetate.

Anal. Calcd for $C_{22}H_{14}O_2S_2$: C, 70.6; H, 3.7; S, 17.1. Found: C, 70.2; H, 3.8; S, 17.2.

Acidification of the orange NaOH solution gave 28.0 g (70%) of red-orange **30**, mp 156–158°. A specimen crystallized from butyl acetate or methylcyclohexane melted at 158–159° (lit.[10] mp 153°).

Anal. Calcd for $C_{12}H_6O_2S$: C, 67.3; H, 2.8; S, 14.9. Found: C, 67.1; H, 2.9; S, 14.7.

2-Benzylthio-1-naphthaleneglyoxylic Acid 33.—To a boiling solution of 2.14 g (0.0100 mol) of **30** in 20 ml of 5 *N* NaOH, 20 ml of water, and 20 ml of ethanol, was added 1.50 ml (1.65 g, 0.0130 mol) of benzyl chloride. The solution turned from orange to pale yellow in 1–2 min and was then cooled and acidified. An oil formed and slowly changed to 3.2 g (100%) of yellow crystals, mp 110–113°. Crystallization from toluene or methylcyclohexane raised the melting point to 115–118°.

Anal. Calcd for $C_{19}H_{14}O_3S$: C, 70.8; H, 4.3; S, 9.9. Found: C, 70.5; H, 4.2; S, 9.7.

Refluxing for 1 hr with thionyl chloride in benzene, both of which were then evaporated, gave **30**.

Registry No.—**3**, 35051-21-9; **4**, 35051-22-0; **5**, 35051-23-1; **6**, 35051-24-2; **7**, 35051-25-3; **8**, 35051-26-4; **9**, 35051-27-5; **10**, 35051-28-6; **11a**, 35051-29-7; **11b**, 35051-30-0; **11c**, 35051-31-1; **12**, 35051-32-2; **14**, 35051-33-3; **15**, 35096-47-0; **16**, 32003-89-7; **17**, 34180-78-4; **19**, 35051-36-6; **20**, 32741-87-0; **21**, 34294-68-3; **22**, 34192-52-4; **23**, 34192-54-6; **24**, 32003-88-6; **25**, 32041-16-0; **26**, 32003-84-2; **27**, 32003-83-1; **28**, 35051-45-7; **30**, 35051-46-8; **32**, 35051-47-9; **33**, 35051-48-0.

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Kinetics of the Chromic Acid Oxidation of Deoxybenzoin[1]

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The kinetics of the chromic acid oxidation of deoxybenzoin has been examined in 91% acetic acid. The rate law is given by $v = k_1k_2[\text{ketone}][Cr^{VI}][H^+]^2/(k_{-1}[H^+] + k_2[Cr^{VI}])$ where k_1 was found to be equal to the rate of enolization. Benzoin was shown to be the intermediate in the reaction, and the source of the products, benzil, benzaldehyde, and benzoic acid. Substituent effects on the oxidation reaction and on enolization were found to be the same. When the concentration of chromium(VI) was maintained at a low level during the course of the reaction, bidesyl became a significant product. This suggests the formation of the desyl radical *via* a reaction involving an intermediate oxidation state of chromium.

The oxidation of ketones frequently provides a useful synthetic route to α-hydroxy ketones, α diketones, and carboxylic acids. As part of a continuing investigation of the mechanisms of chromic acid oxidations, we have studied the oxidation of deoxybenzoin. This is a convenient substrate in that the reaction site is localized by the flanking phenyl rings thus minimizing secondary reactions. Further, the compound provides an opportunity to examine substituent effects.

The chromic acid oxidation of ketones has received previous study. Umeda and Tarama[3] as well as Best, Littler, and Waters[4] have investigated the kinetics of the oxidation of cyclohexanone and found the rate to

(1) This investigation was supported by a grant from the National Science Foundation.

(2) Taken in part from the Ph.D. Thesis of O. Aniline, 1968.

(3) K. Umeda and K. Tarama, *Nippon Kagaka Zasshi*, **83**, 1216 (1962).

(4) P. A. Best, J. S. Littler, and W. A. Waters, *J. Chem. Soc.*, 822 (1962).

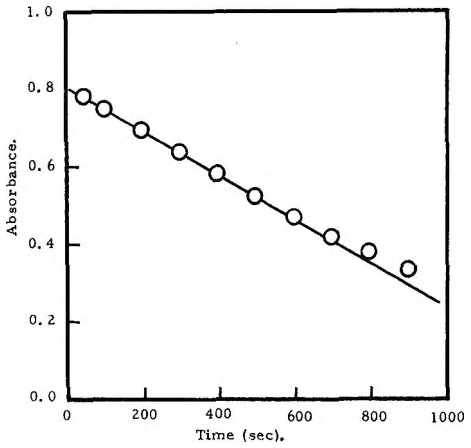

Figure 1.—Zero-order plot for the chromic acid oxidation of deoxybenzion.

have a first-order dependence on the concentrations of ketone, chromium(VI), and hydrogen ion. The latter workers investigated kinetic isotope effects in the system and interpreted these results in terms of an enol intermediate.

Strong evidence for an enol intermediate was provided by Roček and Riehl[5] who found that the oxidation of α-chlorocyclohexanone became independent of the concentration of chromium(VI) when the concentration of the oxidant was high. The limiting rate was close to the rate of enolization as measured by the rate of bromination.

Results

The stoichiometry of the chromic acid oxidation of deoxybenzoin might reasonably be expected to correspond to any of eq 1–3. When deoxybenzoin was allowed to react with chromium(VI) in 91% acetic acid in the presence of 1 *M* perchloric acid, and the products were determined gas chromatographically, it was found that 11% of the deoxybenzoin was consumed *via* reaction 1, 41% *via* reaction 2, and 48% *via* reaction 3. It is not unlikely that, in the actual reaction, process 2 arises *via* process 1 followed by oxidation of benzaldehyde. If that were the case, the oxidation of deoxybenzoin would proceed 52% *via* reaction 1 and 48% *via* reaction 3.

$$3C_6H_5CH_2\overset{O}{\overset{\|}{C}}C_6H_5 + 4HCrO_4^- + 16H^+ \longrightarrow 3C_6H_5CHO + 3C_6H_5CO_2H + 4Cr^{3+} + 10H_2O \quad (1)$$

$$C_6H_5CH_2\overset{O}{\overset{\|}{C}}C_6H_5 + 2HCrO_4^- + 8H^+ \longrightarrow 2C_6H_5CO_2H + 2Cr^{3+} + 5H_2O \quad (2)$$

$$3C_6H_5CH_2\overset{O}{\overset{\|}{C}}C_6H_5 + 4HCrO_4^- + 16H^+ \longrightarrow 3C_6H_5\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}C_6H_5 + 4Cr^{3+} + 13H_2O \quad (3)$$

The products also were analyzed *via* isotope dilution using deoxybenzoin-*carbonyl*-^{14}C as the reactant. In this case, 56% of the reaction proceeded *via* reaction 1 and 44% *via* reaction 3. The results *via* the two methods are in good agreement.

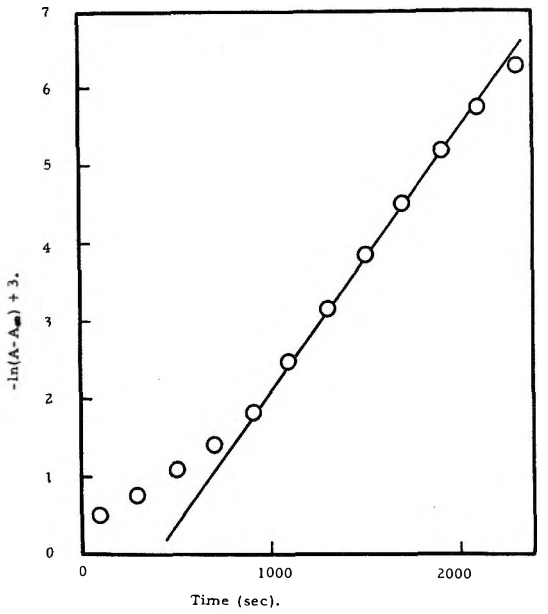

Figure 2.—First-order plot for the chromic acid oxidation of deoxybenzoin.

Another possible reaction is the one following.

$$6C_6H_5CH_2\overset{O}{\overset{\|}{C}}C_6H_5 + 2HCrO_4^- + 8H^+ \longrightarrow 3(C_6H_5CH_2\overset{O}{\overset{\|}{C}}CHC_6H_5)_2 + 2Cr^{3+} + 8H_2O$$

Under the normal experimental conditions, no significant quantity of bidesyl is formed. However, when the reaction was carried out by the slow addition of chromium(VI) to the reaction mixture, 6% of the deoxybenzoin was converted to dibenzyl, as determined *via* isotope distillation. When a fivefold excess of manganous ion was added to the reaction mixture, the formation of benzil was decreased. However, the formation of bidesyl was not affected.

The kinetics of the reaction were studied spectrophotometrically at 340–420 mμ using degassed solutions to avoid interference by oxygen. An excess of deoxybenzoin was employed. Under these conditions, the disappearance of chromium(VI) appeared to be zero order through the first 50% of the reaction (Figure 1). The first-order plot had initial curvature followed by a relatively linear portion (Figure 2).

The slopes of the zero-order plots were dependent on the initial chromium(VI) concentration, and, thus, the apparent zero-order behavior results from a kinetic complication. This was identified as follows. To convert the apparent zero-order rate constants to units comparable with the first-order rate constants derived from the latter part of the reaction, they were divided by the chromium(VI) concentration giving the data summarized in Table I. The ratio of the first-order constants (k_f) to this latter quantity (hereafter referred to as k_i) was essentially constant, with a value of 2.2 ± 0.1.

The behavior observed in this case is characteristic of processes in which an intermediate builds up in concentration during the earlier part of the reaction and

(5) J. Roček and A. Riehl, *J. Org. Chem.*, **32**, 3569 (1967); *J. Amer. Chem. Soc.*, **89**, 6691 (1967).

TABLE I

EFFECT OF DEOXYBENZOIN CONCENTRATION ON THE RATE OF CHROMIC ACID OXIDATION[a]

Deoxybenzoin, M	$k_i \times 10^3$,[b] sec^{-1}	$k_f \times 10^3$,[c] sec^{-1}	k_f/k_i	$k_i/([DSB] \times 10^3)$, l. mol^{-1} sec^{-1}
0.200	1.190	2.75	2.3	6.0
0.160	0.921	2.05	2.2	5.8
0.120	0.702	1.68	2.4	5.9
0.100	0.567	1.24	2.2	5.7
0.080	0.474	1.02	2.2	5.9
0.060	0.338	0.703	2.1	5.6
0.040	0.211	0.481	2.1	5.3
0.020	0.110			5.5
			2.2 ± 0.1	5.7 ± 0.2

[a] $[Cr^{VI}] = 2.28 \times 10^{-3}$ M; $[HClO_4] = 0.412$ M; $T = 30.0°$; 380 mμ. [b] k_i is the initial first-order rate constant obtained by dividing the apparent zero-order constant by $[Cr^{VI}]$. [c] k_f is the first-order rate constant observed in the later stages of the reaction.

then reaches a steady state. When the steady state has been reached, the reaction will show normal first-order behavior with a rate constant twice the initial rate constant. A reasonable possibility for such an intermediate is benzoin, which could further be oxidized to give the set of observed products. The kinetic scheme would be

$$C_6H_5CH_2\overset{O}{\overset{\|}{C}}C_6H_5 + HCrO_4^- + H^+ \xrightarrow{k_a} C_6H_5\overset{O}{\overset{\|}{C}}HCC_6H_5 \quad (\text{OH})$$

$$C_6H_5\overset{O}{\overset{\|}{C}}HCC_6H_5 + HCrO_4^- + H^+ \xrightarrow{k_b} C_6H_5\overset{O}{\overset{\|}{C}}\overset{O}{\overset{\|}{C}}C_6H_5 + C_6H_5\overset{O}{\overset{\|}{C}}H + C_6H_5CO_2H \quad (\text{OH})$$

If $k_b \gg k_a$, the observed rate constant after the steady state has been reached would be $2k_a$, whereas the initial rate constant would be k_a.

This explanation was tested by determining the rate of oxidation of benzoin ($k = 1.78$ l. mol^{-1} sec^{-1}, 0.3 M $HClO_4$, 0.0115 M benzoin, and 2.44×10^{-3} M Cr^{VI}) and calculating the change in absorbance with time for the oxidation of deoxybenzoin using the above kinetic scheme. A comparison of calculated and observed absorbance values is given in Figure 3 and it can be seen that good agreement is obtained.

When benzoin was oxidized in the presence of a two-fold excess of chromic acid and the products analyzed by vpc, it was found that 48% of the reactant was converted to benzil while the rest led to cleavage products. The agreement with the deoxybenzoin product study again indicates that benzoin is an intermediate, and indicates that k_i is the appropriate rate constant for use in the following discussion.

The initial first-order rate constants for the oxidation of deoxybenzoin divided by the ketone concentration gave a constant second-order rate coefficient (Table I) showing the reaction to have a first-order dependence on the ketone concentration. The effect of acid concentration on the rate of oxidation also was examined (Table II) and a plot of the logarithms of the rate constants against H_0 gave a linear relationship with a slope of 1.20. This is quite similar to that found for the

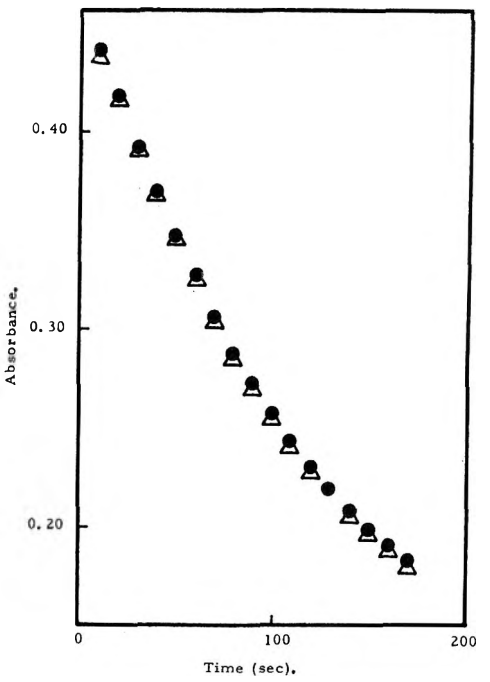

Figure 3.—Calculated (Δ) and observed (●) absorbance values for the chromic acid oxidation of deoxybenzoin.

TABLE II

EFFECT OF ACID CONCENTRATION ON THE RATE OF OXIDATION OF DEOXYBENZOIN[a]

$[HClO_4]$, M	$k_1 \times 10^3$, sec^{-1}	H_0
0.050	0.14	+0.055
0.100	0.37	−0.270
0.150	0.67	−0.460
0.200	0.96	−0.600
0.250	1.34	−0.730
0.300	1.79	−0.830

[a] [Deoxybenzoin] = 0.200 M; $[Cr^{VI}] = 2.51 \times 10^{-3}$ M; $T = 30.0°$; 390 mμ.

oxidation of benzaldehyde (1.07)[6] and of diphenylmethane (1.25)[7] and is equivalent to a first-order dependence on the acid concentration.

The effect of chromium(VI) concentration on the rate of reaction also was studied. As the concentration was increased in the range 0.00171–0.0193 M, the apparent zero-order portion of the reaction increased in duration and the initial slopes of the first-order rate plots decreased by an amount greater than that which could be accounted for by the acid chromate–dichromate equilibrium.[8]

The decrease in rate coefficient might result from a process such as

$$\text{deoxybenzoin} + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{enol} + H^+$$

$$\text{enol} + Cr^{VI} + H^+ \xrightarrow{k_2} \text{products}$$

This would be in accord with the observation of Roček and Riehl in their study of the chromic acid oxidation

(6) K. B. Wiberg and T. Mill, *J. Amer. Chem. Soc.*, **80**, 3022 (1958).
(7) K. B. Wiberg and R. J. Evans, *Tetrahedron*, **8**, 313 (1960).
(8) The oxidation of alcohols and of related compounds have a kinetic dependence on the acid chromate ion rather than total chromic acid (*cf.* K. B. Wiberg, "Oxidation in Organic Chemistry," Part A, Academic Press, New York, N. Y., 1965, p 159 ff). In view of the later conclusions concerning the nature of the oxidation step, it seemed appropriate to assume that only $HCrO_4^-$ is involved in the rate expression in the present case also.

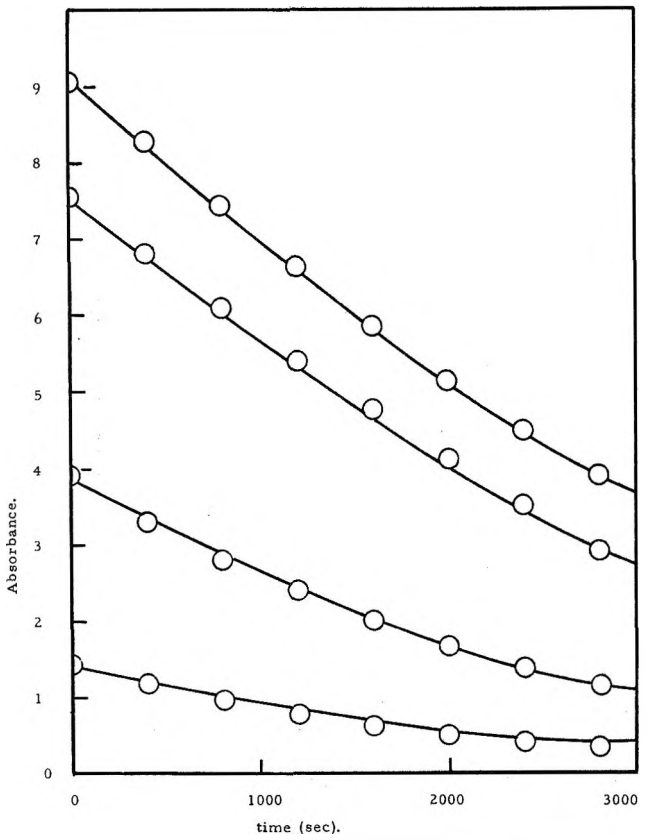

Figure 4.—Absorbance *vs.* time curves for four representative chromic acid concentrations (0.0193 *M*, 0.0171 *M*, 0.0113 *M*, and 0.0060 *M* from top to bottom). The circles are experimental points and the lines are values calculated as described in the text. [Deoxybenzoin] = 0.161 *M*; [$HClO_4$] = 0.309 *M*; *T* = 30.0°; 420 mμ. A 1-cm cell was used for the lower concentrations, and a 0.2-cm cell was used for the higher concentrations.

of several aliphatic ketones.[5] The rate law for such a process would be

$$-d[Cr^{VI}]/dt = k_1k_2[\text{ketone}][Cr^{VI}][H^+]^2/(k_{-1}[H^+] + k_2[Cr^{VI}])$$

Thus, when $k_2[Cr^{VI}] \gg k_{-1}[H^+]$, the rate constant should no longer depend on the concentration of oxidant. Because of the complexity of the system in which benzoin is an intermediate which only slowly reaches a steady state, and in which the absorbancy index of chromium(VI) is a function of the chromium(VI) concentration, the above rate law was tested by numerical integration of the rate expressions in Scheme I which apply to the case of a constant hydrogen ion concentration (*i.e.*, the dependence on acid concentration is absorbed into the rate constants).[9]

The rate of enolization of deoxybenzoin was determined by measuring the acid-catalyzed rate of bromination in 91% acetic acid. Using a 0.309 *M* perchloric acid, the rate constant was 1.72×10^{-5} sec^{-1} (the zero-order rate constant divided by the ketone concentration). This value was used as the initial approximation of k_a.[10] As long as $k_{-a} \gg k_a$, only the

SCHEME I

$$\text{deoxybenzoin} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \text{enol}$$

$$2HCrO_4^- \overset{K}{\rightleftharpoons} Cr_2O_7^{2-} (+H_2O)$$

$$\text{enol} + HCrO_4^- \xrightarrow{k_b} \text{benzoin} + Cr^{III}$$

$$\text{benzoin} + HCrO_4^- \xrightarrow{k_c} \text{products} + Cr^{III}$$

$$d[\text{ketone}]/dt = -k_a[\text{ketone}] + k_{-a}[\text{enol}]$$

$$d[\text{enol}]/dt = k_a[\text{ketone}] + k_{-a}[\text{enol}] - k_b[\text{enol}][HCrO_4^-]$$

$$d[\text{benzoin}]/dt = k_b[\text{enol}][HCrO_4^-] - k_c[\text{benzoin}][HCrO_4^-]$$

$$d[Cr^{VI}]/dt = k_b[\text{enol}][HCrO_4^-] + k_c[\text{benzoin}][HCrO_4^-]$$

$$[HCrO_4^-] = (\sqrt{1 + 8K[Cr^{VI}]} - 1)/4K \qquad K = 25^6$$

$$A = 1.77 \times 10^5[Cr^{VI}]^3 + 1.33 \times 10^4[Cr^{VI}]^2 + 153[Cr^{VI}] + 30[Cr^{III}]$$

ratio of k_b to k_{-a} is of significance in determining the rate of disappearance of chromic acid. The value of k_{-a} which was used (0.3)[11] was the largest which could conveniently be used in the numerical integration program. The value of k_c was found to be 1.78 l. mol^{-1} sec^{-1} (see above), and a value of k_b ~40 was estimated from a plot of initial rates against the chromic acid concentration. Both k_a and k_b were adjusted so as to give a good fit to the experimental data (Figure 4 shows the results of four typical calculations; a total of ten chromic acid concentrations were used). The values of the rate constants follow: $k_a = 1.5 \times 10^{-5}$ and $k_b = 44$. The value of k_b, as indicated above, depends on k_{-a} and, since the k_{-a} used is a minimum value, the true k_b is presumably greater than 45 l. mol^{-1} sec^{-1}. The rate of oxidation of the enol is therefore considerably greater than that for benzoin. This is in agreement with the results of Roček and Riehl.[5] At the highest chromic acid concentration (0.0193 *M*) the enol concentration was 35% of its equilibrium value making enolization largely rate determining, whereas at the lowest chromic acid concentration (0.00171 *M*) the enol concentration was 73% of its equilibrium value.

Substitution of the methylene protons in deoxybenzoin by deuterium caused a marked retardation of the rate of chromic acid oxidation. The ratio of the initial first-order constants obtained from the zero-order plots was 4.5. Similarly, the bromination of deoxybenzoin and desoxybenzoin-d_2 showed a kinetic isotopic effect of 4.0. Again, the results are in satisfactory agreement.

The effect of substituents on the rates of oxidation and enolization were determined giving the data summarized in Tables III and IV. The 4-methoxy and 4-ethoxy derivatives led to side reactions in both types of reactions (probably attack at the aromatic ring)[12] and could not be included in the study. When the substituent was attached to the benzoyl ring, a small negative ρ value was found for both oxidation (−0.42) and

(9) The rate expressions are simplified in that the oxidation by chromium(V) or chromium(IV) is ignored. It is known that these species will come to their steady-state concentrations rapidly under the reaction conditions, and their effect will then appear largely in the stoichiometry rather than in the kinetics of the process. The four-order Runge-Kutta procedure was used in the numerical integration.

(10) Depending on the details of the stoichiometry involving the chromium species of intermediate valence, the apparent rate of enolization for the oxidation process could range from 0.67 to 2.00 times the true rate of enolization.[5]

(11) The keto–enol equilibrium constant for cyclohexanone has been determined by R. P. Bell and P. W. Smith [*J. Chem. Soc. B*, 241 (1966)] to be 4.1×10^{-6}. If the constant were the same for deoxybenzoin, k_{-a} would be 4.2. It would not be surprizing if the constant were somewhat larger for deoxybenzoin. Using $k_{-a} = 0.3$, satisfactory results were obtained in the numerical integration using a step size of 2 sec.

(12) S. G. Brandenberger, L. W. Maas, and I. Dvoretzky, *J. Amer. Chem. Soc.*, **83**, 2146 (1961).

TABLE III

RATES OF CHROMIC ACID OXIDATION OF DEOXYBENZOINS[a]

Substituent	$k \times 10^5$, sec^{-1}	k_{rel}
A. Benzyl Ring[b]		
H	0.93	1.00
p-Cl	1.03	1.10
p-NO_2	1.11	1.19
m-CF_3	0.58	0.62
p-CH_3	1.05	1.13
B. Benzoyl Ring[c]		
H	0.57	1.10
p-C_2H_5O	0.74	1.30
p-CH_3	0.61	1.07
p-Cl	0.49	0.86

[a] [Deoxybenzoin] = 3×10^{-2} *M*; [$HClO_4$] = 0.309 *M*; *T* = 30.0°; 420 mμ. [b] [Cr^{VI}] = 3.97×10^{-3} *M*. [c] [Cr^{VI}] = 2.29×10^{-3} *M*.

TABLE IV

RATES OF ENOLIZATION OF DEOXYBENZOINS[a]

Substituents	$k \times 10^5$, sec^{-1}	k_{rel}
A. Benzyl Ring		
H	1.72	1.00
p-Cl	2.05	1.19
p-NO_2	2.59	1.50
m-CF_3	1.26	0.73
p-CH_3	2.99	1.16
B. Benzoyl Ring		
H	1.72	1.00
p-C_2H_5O	2.84	1.65
p-CH_3	2.09	1.21
p-Cl	0.83	0.48

[a] [Deoxybenzoin] = 3×10^{-2} *M*; [Br_2] = 3×10^{-3} *M*; [$HClO_4$] = 0.309 *M*; *T* = 30.0°; 450 mμ.

enolization (−1.0).[13] On the other hand, when a para substituent was attached to the benzyl ring, both electron-releasing and -attracting groups accelerate the reaction. The 3-trifluoromethyl group retarded both oxidation and enolization. Clearly, no correlation with σ could be obtained. However, the effect of substituents on oxidation and on enolization were quite similar (Figure 5).

Discussion

The kinetic data require that the enol be an intermediate in the oxidation and that benzoin be the first-formed product. Reaction 5 may occur either by formation of the chromium(VI) ester of the enol followed by attack of water at the α carbon, or by attack of chromium(VI) on the double bond. The chromic acid oxidation of isopropenyl acetate has been found to be quite slow, whereas its reaction with bromine is quite rapid. This leads us to believe that the attack by chromium(VI) is not at the double bond. Thus, we favor reaction 6. As a result of the initial oxidation step, chromium(VI) is formed. It is now known that chromium(VI) is an active oxidant in the chromic acid oxidation of alcohols.[14] Thus, it would not be surprising if it were also to react with deoxybenzoin with the formation of the desyl radical.

Under the usual reaction conditions in which the concentration of chromium(VI) is reasonably high during most of the reaction, the desyl radical would be expected to be readily oxidized to benzoin. However, if the concentration of chromium(VI) is maintained low *via* slow addition during the course of the reaction, there should be a good opportunity for the coupling of desyl radicals leading to bidesyl. The latter is found (6%) under these conditions and is absent under the more usual reaction conditions. It would be possible to generate bidesyl by an alternate route (such as by attack of a desyl cation on the enol) but this seems rather unlikely. Thus, the second reaction appears to be that shown in eq 7–9 where reactions 8 and 9 are competitive. We cannot specify the mode of reaction of chromium(V), although it would not be surprising if it were to react in a fashion similar to chromium(VI). The fact that manganese(II) does not suppress the formation of bidesyl suggests that manganese(III) also effects the oxidation of deoxybenzoin to the desyl radical. This type of reaction has ample precedent.[15]

The oxidation of benzoin occurs at a rate 500 times as great as that of deoxybenzoin and is comparable with that of isopropyl alcohol. The reaction is almost certainly a typical alcohol oxidation in which the esterification of the hydroxy group is the first step. The formation of major amounts of cleavage products is ex-

(13) A similar value of ρ was found for the enolization of acetophenone: D. P. Evans, V. G. Morgan, and H. B. Watson, *J. Chem. Soc.*, 1167 (1935).

(14) J. Roček and A. E. Radkowsky, *J. Amer. Chem. Soc.*, **90**, 2986 (1968); K. B. Wiberg and S. K. Mukherjee, *ibid.*, **93**, 2543 (1971).

(15) W. A. Waters and J. S. Littler, "Oxidation in Organic Chemistry," K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, p 185 ff.

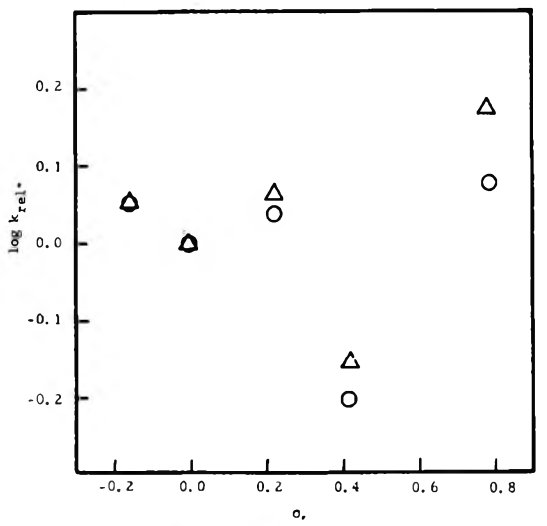

Figure 5.—Effect of substituents on the chromic acid oxidation (○) and enolization (△) of deoxybenzoin.

pected since this is the normal course of the reaction when a group which is able to bear a positive charge is attached to the alcohol carbon.[16] The normal product, benzil, is probably formed *via* oxidation by chromium(VI) whereas the cleavage products would be expected to arise *via* oxidation by the intermediate oxidation states of chromium. In view of the recent results of Roček and Rahman[17] on the chromium(VI) oxidation of alcohols, it seems clear that at least part of the cleavage results from oxidation by chromium(VI).

Experimental Section

Materials.—Reagent grade glacial acetic acid was purified by treatment with chromic acid as previously described.[6] Reagent grade sodium dichromate hydrate was dried under vacuum at 100° over phosphorus pentoxide. Sodium perchlorate (G. F. Smith) was recrystallized from water and dried at 140° for 24 hr. Manganous perchlorate hexahydrate (G. F. Smith) was used directly without purification or drying. Reagent grade 70% perchloric acid was analyzed by titration with standard sodium hydroxide solution.

Deoxybenzoin (Eastman Kodak) was recrystallized twice from methanol and sublimed. 4-Methyl-, 4-chloro-, and 4-nitrodeoxybenzoin were prepared by the Friedel–Crafts reaction between benzene and the corresponding acyl chlorides using aluminum chloride as the catalyst. In all cases, the melting points agreed with the literature values. 4′-Methyl-, 4′-chloro-, and 4′-ethoxydeoxybenzoin were prepared in a similar fashion using phenylacetyl chloride and the appropriate reactant. Again, the melting points agreed with the literature values. All of the deoxybenzoins were sublimed before use.

Deoxybenzoin-*carbonyl*-^{14}C.—Potassium cyanide-^{14}C (50 μCi) was dissolved in 100 ml of water containing 115 g (1.77 mol) of potassium cyanide. A solution of 200 g of benzyl chloride (1.58 mol) in 240 ml of ethanol was added dropwise to the heated cyanide solution over 30 min. After heating to reflux for 2.5 hr, the reaction mixture was cooled and filtered. Distillation gave 131 g (71%) of benzyl cyanide-^{14}C, bp 108–111° (13 mm). The benzyl cyanide was hydrolyzed to phenylacetic acid and converted to deoxybenzoin. The activity of the product was 1121 dpm/mg.

Deoxybenzoin-α,α-d_2.—A mixture of 8.0 g of deoxybenzoin, 150 ml of anhydrous ether and 30 g of acetic acid-*d* was treated with 1 drop of bromine and heated to reflux for 48 hr. The solvents were removed using a rotary evaporator and the procedure was repeated. The product was recrystallized twice from benzene–heptane and sublimed. The nmr spectrum indicated 96% deuterium incorporation.

3-Trifluoromethyldeoxybenzoin.—3-Trifluoromethylphenylacetyl chloride was prepared by the addition of thionyl chloride to 3-trifluoromethylphenylacetic acid (PCR), and had bp 94–96° (15 mm). A solution of diphenylcadmium was prepared using the Grignard reagent formed from 1.5 g of magnesium turnings and 10.0 g of bromobenzene in 200 ml of dry ether, by the addition of 5.7 g of anhydrous cadmium chloride. Most of the ether was removed by distillation and 200 ml of benzene was added. To the diphenylcadmium solution was added 10 g of the acid chloride in 20 ml of benzene. The flask was heated with stirring for 3 hr. Following the usual work-up, the product was isolated by distillation giving 7.0 g (53%) of the ketone, bp 109–111° (0.3 mm). Final purification was effected by preparative vpc (20% neopentyl glycol sebacate on Chromsorb W).

Anal. Calcd for $C_{15}H_{11}F_3O$: C, 68.2; H, 4.2. Found: C, 68.1, 68.2; H, 4.2, 4.2.

Kinetic Measurements.—The disappearance of chromium(VI) was followed spectrometrically at 380–420 mμ. One solution contained sodium dichromate, sodium perchlorate, and perchloric acid in 91% acetic acid. The other solution contained deoxybenzoin in 91% acetic acid. Both solutions were made up a short time before the kinetic experiment. The solutions were degassed separately in two legs of a U cell attached to a spectrometer cell. The solutions were brought to the reaction temperature and were mixed at time zero by inverting the cell. The cell was placed in a spectrometer (Cary Model 15 or Beckman DU) and the transmittance was measured as a function of time.

The rates of enolization were determined in a similar fashion except that bromine replaced sodium dichromate and 450 mμ was used.

Product Analysis.—The products formed in the oxidation of deoxybenzoin were determined both by vpc analysis and by isotope dilution. In the former case the reaction was carried out in a fashion similar to the kinetic experiments except that benzophenone was included as an internal standard. After complete reaction, the reaction solution was treated with water and extracted with benzene. Benzoic acid was extracted from the benzene using sodium carbonate and was isolated by acidification. The amount of benzoic acid formed was determined by weighing after thorough drying. The amounts of unreacted deoxybenzoin and of benzil and benzaldehyde were determined by vpc by comparison of the areas for these compounds with that of benzophenone. Starting with 5.0 mmol of deoxybenzoin and 5.4 mmol of sodium dichromate there was obtained 1.8 mmol of deoxybenzoin, 2.5 mmol of benzoic acid, 1.3 mmol of benzil, 0.3 mmol of benzaldehyde, and 0.1 mmol of benzoin acetate.

The isotope dilution experiment was carried out under conditions similar to the kinetic experiments except that 2.0 g of deoxybenzoin-^{14}C was the reactant. To the reaction product mixture was added 1.0 g of benzoic acid, 1.0 g of benzil, and 0.5 g of bidesyl along with water and benzene. Benzoic acid was isolated from the benzene solution as described above. The benzene solution was treated with heptane and concentrated whereupon crystals of bidesyl began to form. The bidesyl was separated by filtration and recrystallized from 10:1 benzene–heptane.

The filtrate was concentrated to 5 ml and was separated into its components by vpc on a 20% neopentyl glycol sebacate column. The benzil was recrystallized from methanol and dried under vacuum. The activities of the benzoic acid, bidesyl, and benzil were determined by liquid scintillation counting in toluene containing PPO and POPOP. Correction for quenching was effected by adding a known amount of deoxybenzoin-^{14}C and recounting.

In each case the activity of the bidesyl was the same as the background (~40 dpm). In a typical experiment, 1.80 mmol of benzil was formed along with 4.82 mmol of benzoic acid.

Slow Addition of Chromium(VI) to Deoxybenzoin-^{14}C.—To a solution of 2.06 g (10.5 mmol) of deoxybenzoin-^{14}C in 50 ml of 1 *M* perchloric acid in 91% acetic acid was added dropwise with stirring at 85° a solution of 1.5 g of sodium dichromate (11.4 mmol) of 50 ml of 1 *M* perchloric acid in 91% acetic acid. The amount of bidesyl was determined by adding 0.5 g of unlabeled material followed by work-up as described above. Analysis of the bidesyl indicated that 0.3 mmol of bidesyl was formed in the reaction which corresponds to 0.6 mmol of deoxybenzoin. Thus, 6% of the reactant was converted into this product.

(16) J. J. Cawley and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 1771 (1963).

(17) M. Rahman and J. Roček, *ibid.*, **93**, 5455, 5462 (1971).

Oxidation of Benzoin.—The oxidation of 1.04 g (4.9 mmol) of benzoin with 1.35 g (10.3 mmol) of sodium dichromate was effected in the presence of benzophenone as an internal standard. After work-up as described above, the amount of benzil was determined by comparison of its vpc trace area with that of benzophenone. No benzaldehyde was found using this excess of chromium(VI). The products were benzil (2.42 mmol, 48%) and benzoic acid (5.37 mmol, 52%).

Registry No.—Chromic acid, 7738-94-5; deoxybenzoin, 451-40-1; 3-trifluoromethyl deoxybenzoin, 30934-66-8.

Oxymercuration–Demercuration of 6-Methylenebicyclo[3.1.1]heptane and 5-Methylenebicyclo[2.1.1]hexane[1]

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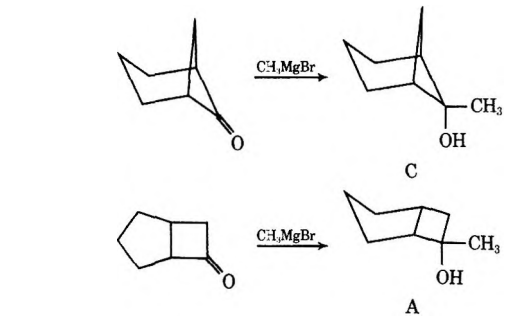
Oxymercuration followed by borohydride reduction has been applied to 6-methylenebicyclo[3.1.1]heptane (I) and 5-methylbicyclo[2.1.1]hexane (II). The reaction of I led to 22% of 6-methylbicyclo[3.1.1]heptan-6-ols, 67% of 6-methylbicyclo[3.2.0]heptan-6-ols, 4% of 2-methylnorbornan-2-ol, and 6% of 2-methylenecycloheptanol. The rearrangements are analogous to those found in the solvolytic reactions of 6-substituted bicyclo[3.1.1]heptanes. The reaction of II led to 44% 2-methylenecyclohexanol, 28% of 3-methylenecyclohexanol, and 28% of 3-methylcyclohex-3-en-1-ol. An examination of the nmr spectrum of the reaction solution as a function of time indicated that a cyclopropane derivative was first formed and that this rearranged further to olefinic compounds. Corresponding product studies showed that the cyclopropane derivative, on reduction, gave 4-methylenecyclohexanol, whereas the other products were derived from the olefinic intermediates.

The oxymercuration of bicyclic olefins followed by *in situ* borohydride reduction of the organomercurial intermediate has been found to be a useful route to alcohols.[3] The reaction leads in effect to Markovnikov hydration, and generally gives little or no rearrangement. Because the reaction might provide a convenient route to alcohols which are epimeric with those formed by Grignard reagent addition to the corresponding ketones, the reaction has been explored with the strained methylenecyclobutane type compounds, 6-methylenebicyclo[3.1.1]heptane (I) and 5-methylenebicyclo[2.1.1]hexane (II).

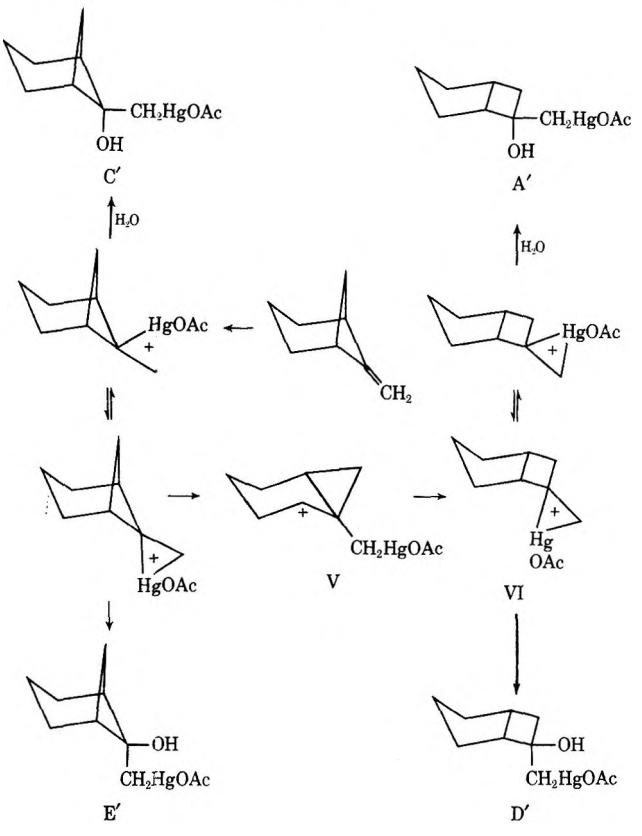
The reaction of I with mercuric acetate in aqueous tetrahydrofuran occurred readily and sodium borohydride reduction was essentially instantaneous. However, instead of producing only one alcohol, a mixture of six alcohols was obtained. They could be separated by gas chromatography, giving A (32%), B (4%), C (20%), D (36%), E (2%), and F (6%). The alcohols A–E all had methyl singlets in their nmr spectra at τ 8.6–8.8, indicating they were tertiary alcohols. The infrared spectrum of F showed bands at 1625 and 850 cm^{-1}, suggesting an exocyclic double bond.

The alcohol C was found to be *endo*-6-methylbicyclo[3.1.1]heptan-6-ol by comparison with the nmr spectrum of an authentic sample prepared by the addition of the methyl Grignard reagent to bicyclo[3.1.1]heptan-6-one. The assignment of configuration is based on analogy with the lithium aluminum hydride reduction of the ketone, which gives 98% of *endo*-bicyclo[3.1.1]-heptan-6-ol.[4]

Mechanistic considerations suggested that one of the alcohols might be 6-methylbicyclo[3.2.0]heptan-6-ol. The endo isomer was prepared by the addition of the



SCHEME I



(1) This investigation was supported by Public Health Service Grant GM12800 from the National Institute of General Medical Studies.

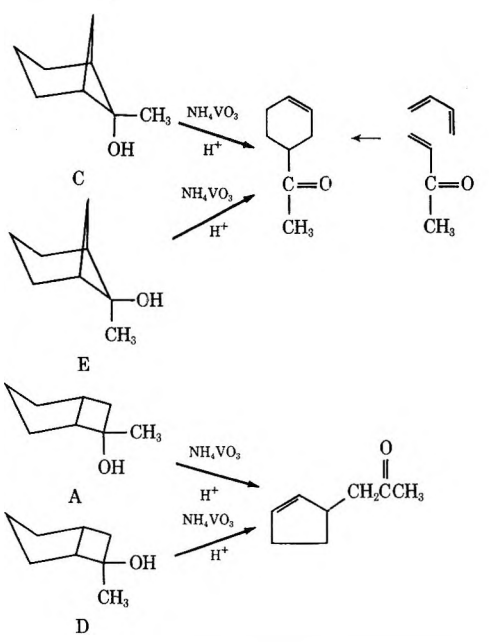
(2) Taken from part of the Ph.D. thesis of Wan-fang Chen, 1971.

(3) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967); H. C. Brown and W. J. Hammer, *ibid.*, **89**, 1525 (1967); H. C. Brown, J. H. Kawakawi, and S. Ikegamin, *ibid.*, **89**, 1526 (1967).

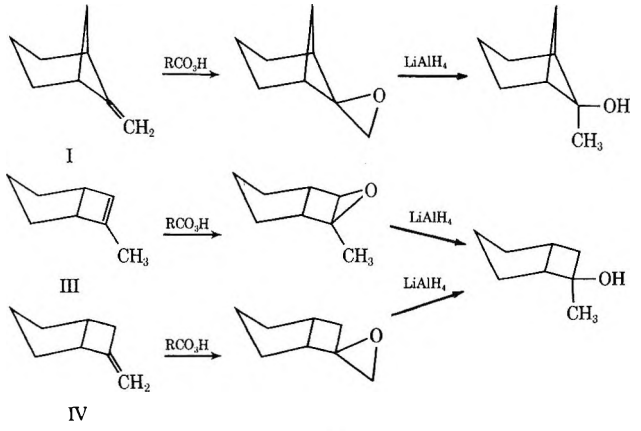
(4) K. B. Wiberg and B. A. Hess, Jr., *ibid.*, **89**, 3015 (1967).

methyl Grignard reagent to bicyclo[3.2.0]heptanone, and was found to be identical with A. Again, the assignment of configuration is based on analogy with the lithium hydride reduction of bicyclo[3.2.0]heptanone, which gives 90% of the endo isomer.[5]

The spectra of E and D were similar to those of C and A, respectively, suggesting that they might be the other members of the epimeric pairs. This was confirmed using vanadium(V) oxidation, which is known to lead to cleavage of tertiary alcohols.[6] The results are shown below.

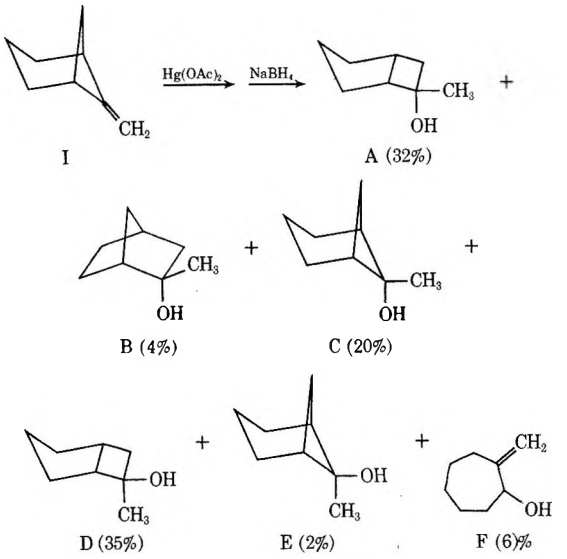


In each case, both isomers gave the same ketonic product, which was identified by comparison with an authentic sample. The alcohols E and D also were prepared by the following methods.



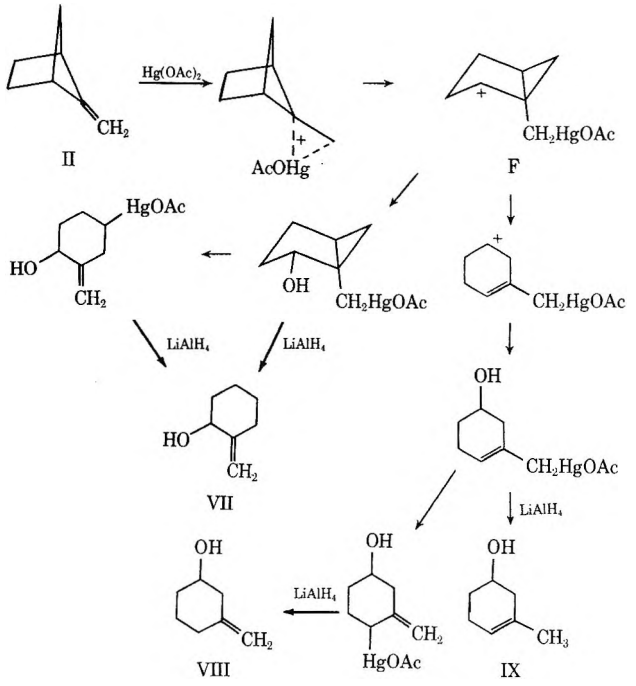
The preparations of the olefins III and IV are described in the Experimental Section.

The alcohol F had an nmr spectrum very similar to that of 2-methylenecyclohexanol except for two more protons in the τ 8.0–8.8 region. Thus, it appears to be 2-methylenecycloheptanol. The alcohol B had an nmr spectrum corresponding to that of 5-methyl-*endo*-bicyclo[2.1.1]heptan-5-ol, formed by the addition of the methyl Grignard reagent to norbornanone. The course of the oxymercuration–demercuration of I may then be described as



The addition of mercuric acetate to olefins appears to involve initially the addition of $HgOAc^+$ to give a bridged ion.[7] This may be attacked by water to give C′ and E′, from which C and E are derived. A rearrangement corresponding to that found in the solvolysis of *endo*-bicyclo[3.1.1]heptyl-6 tosylate[4] would then give a bicyclo[3.1.0]heptyl cation (V) which may further rearrange to the bicyclo[3.2.0]heptyl-6 cation (VI) from which A′ and D′ are formed (Scheme I).

In order to gain further information on the nature of the reaction, 5-methylenebicyclo[2.2.1]hexane (II) was used as the reactant. The products of the reaction were 2-methylenecyclohexanol (VII) (44%), 3-methylenecyclohexanol (VIII) (28%), and 3-methylcyclohex-3-en-1-ol (IX) (28%). These results may be accommodated as follows.



(5) F. F. Nelson, Ph.D. Thesis, University of Wisconsin, 1960.
(6) J. R. Jones and W. A. Waters, *J. Chem. Soc.*, 2772 (1960).

(7) *Cf.* W. Kitching, *Organometal. Chem. Rev.*, **3**, 61 (1968); it should be noted that H. C. Brown and K.-T. Liu, *J. Amer. Chem. Soc.*, **93**, 7335 (1971), have presented evidence which they interpret as disfavoring this type of intermediate.

The results raise two questions. First, why are no unrearranged alcohols formed, whereas significant amounts of such products were found with 6-methylbicyclo[3.1.1]heptane? Second, why does the product have predominantly the less stable exocyclic double bond when its precursor presumably had an endocyclic double bond?

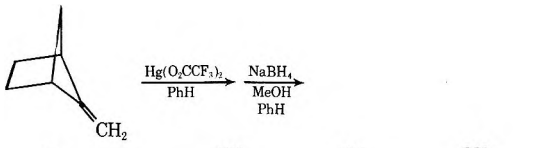
Additional information concerning the course of the reaction was obtained *via* an nmr study of the reaction of mercuric trifluoroacetate[8] with II in benzene solution. The signal from the original olefin protons disappeared completely by the time the first spectrum was taken (5 min). Cyclopropyl protons and olefinic protons were found at τ 9–10 and 4.5–6, respectively. As time went on, the cyclopropyl protons began to disappear and were replaced by olefinic protons (Table I).

TABLE I

CHANGE IN NMR SPECTRUM DURING THE REACTION OF MERCURIC TRIFLUOROACETATE WITH 5-METHYLENEBICYCLO[2.1.1]HEXANE

Reaction time	Number of protons		
	τ 4.5–6	τ 7.5–9	τ 9–10
5–75 min	1.3	7.4	1.3
24 hr	1.7	7.6	0.7
40 hr	1.74	7.86	0.4
60 hr	1.8	7.92	0.28
132 hr	1.92	7.94	0.14

The products from the mercuric trifluoroacetate reaction were determined by adding the benzene solution to sodium borohydride in methanol. The results were



	VII	VIII	IX
(a) 70°	16%	70%	14%
(b) 0°	71%	29%	0%

When the reaction was carried out at 0° for a short time before quenching with sodium borohydride, 4-methylenecyclohexanol was the major product, and no 3-methylcyclohex-3-en-1-ol was formed. When the reaction was carried out at 70° (corresponding to the longer reaction times in Table I), 3-methylenecyclohexanol became the major product and some IX was also formed.

It is clear from these results that VII is formed from a precursor containing a cyclopropane ring and that VIII and IX are formed from further rearranged species. The lack of unrearranged alcohols probably results from the driving force for strain relief which leads to rapid rearrangement to the cyclopropylcarbinyl cation, F. The alcohols VIII and IX are not formed from the same intermediate, but rather appear to be formed from two separate intermediates, one of which is derived from the other.

(8) H. C. Brown, M.-H. Rei, and K.-T. Liu, *J. Amer. Chem. Soc.*, **92**, 1760 (1970).

Experimental Section

7-Formylbicyclo[3.2.1]octan-6-one.—With ice-bath cooling, 62 g (0.5 mol) of bicyclo[3.2.1]octan-6-one[9] was dropped into a suspension of 54 g of sodium methoxide in 60 g of methyl formate and 100 ml of anhydrous ether. The mixture was stirred overnight at room temperature. It was then cooled and 20 ml of ice–water was added. The ether layer was separated and the aqueous layer was washed once with ether. The aqueous layer was acidified with 60 g of acetic acid and 100 ml of water and extracted with three 300-ml portions of ether. The combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed using a rotary evaporator, and the residue was distilled giving 53 g (70%) of 7-formylbicyclo[3.2.1]octan-6-one, bp 80° (0.5 mm).

7-Diazobicyclo[3.2.1]octan-6-one.—To a solution of 53 g (0.35 mol) of 7-formylbicyclo[3.2.1]octan-6-one and 70 g of triethylamine in 345 ml of ethylene chloride was added dropwise 70 g of *p*-toluenesulfonyl azide. The reaction mixture was stirred at room temperature overnight. The yellow solution was washed with a solution of 21 g of potassium hydroxide and 200 ml of water. The aqueous solution was separated and washed with three 80-ml portions of methylene chloride. The methylene chloride solutions were combined, washed with saturated sodium chloride solution, and dried over magnesium sulfate. The solvent was removed using a rotary evaporator, giving 30 g (58%) of 7-diazobicyclo[3.2.1]octan-6-one, which was used without further purification. The diazoketone was converted to bicyclo[3.1.1]-heptane-6-carbonyl chloride as described previously.[9]

***N,N*-Dimethylbicyclo[3.1.1]heptane-6-carboxamide.**—To a stirred and cooled mixture of 55 g of 25% dimethylamine and 150 ml of ether was added 20.1 g (0.13 mol) of bicyclo[3.1.1]heptane-6-carbonyl chloride. The solution was stirred for 8 hr after the addition was completed. The mixture was then diluted with 150 ml of water and extracted with four 50-ml portions of ether. After drying the ether was removed by distillation. The residue was distilled, giving 18.8 g (89%) of the amide, bp 121–122° (15 mm).

6-Dimethylaminomethylbicyclo[3.1.1]heptane.—To a stirred slurry of 15 g of lithium aluminum hydride and 100 ml of anhydrous ether was added a solution of 18.8 g (0.11 mol) of *N,N*-dimethylbicyclo[3.1.1]heptane-6-carboxamide in 200 ml of anhydrous ether. After the addition, the mixture was stirred for 24 hr at room temperature. It was then cooled in an ice bath, 50 ml of cold water was added cautiously, and it was stirred vigorously for 2 hr. After filtering by suction the salt was washed with three 50-ml portions of ether. The ether fractions were combined and dried over magnesium sulfate. The ether was distilled using a 30 in. Helipack column and the residue was distilled to give 15.5 g (90%) of the amine, bp 69° (10 mm).

6-Dimethylaminomethylbicyclo[3.1.1]heptane *N*-Oxide.—To a cooled and stirred solution of 15.5 g (0.1 mol) of 6-dimethylaminomethylbicyclo[3.1.1]heptane in 120 ml of methanol was added dropwise 57 g of 30% hydrogen peroxide. After the reaction mixture was stirred for 24 hr, 10 g of 30% hydrogen peroxide was added. The reaction mixture was then stirred for another 20 hr. A small amount of platinum black in water was added and the solution was stirred for 4 hr until no further oxygen was involved. The solvent was removed under reduced pressure, giving a residue which solidified to a waxlike paste (17.8 g, 97%) of the crude *N*-oxide.

6-Methylenebicyclo[3.1.1]heptane.—6-Dimethylaminomethylbicyclo[3.1.1]heptane *N*-oxide (17.8 g, 0.11 mol) was heated to 190° in a 15-ml round-bottom flask fitted with two successive Dry Ice–acetone traps at a pressure of 5 mm. After 10 hr the reaction mixture was completely pyrolyzed. The collection traps contained two liquid phases. After an addition of 150 ml of olefin-free pentane, the reaction mixture was washed successively with 100-ml portions of 1 *N* hydrochloric acid, two 50-ml portions of saturated sodium carbonate solution, 50 ml of water, and 50 ml of saturated sodium chloride solution. After drying over anhydrous potassium carbonate, pentane was removed using a 30-in. Helipack column. The residue was distilled carefully to give 7.9 g (70%) of the olefin, bp 92° (150 mm). The infrared spectrum had a C=C band at 1670 cm^{-1}. The nmr spectrum had bands at τ 5.4 (2 H, s), 6.7–7.0 (2 H, broad singlet), 7.8–8.8 (8 H, multiplet).

(9) K. B. Wiberg and B. A. Hess, Jr., *J. Org. Chem.*, **31**, 2250 (1966).

Anal. Calcd for C_8H_{12}: C, 88.8; H, 11.2. Found: C, 88.6; H, 11.1.

Bicyclo[3.1.1]heptan-6-one.—A mixture of 1.5 g (0.014 mol) of 6-methylenebicyclo[3.1.1]heptane and 2 ml of pyridine in 20 ml of methylene chloride was placed in the flask with an ozone inlet and the outlet attached to a 5% potassium iodide solution. The mixture was cooled at −80° in a Dry Ice–acetone bath. A stream of ozone was bubbled into the mixture until the potassium iodide solution turned from pale yellow to dark brown. The mixture was then allowed to warm to room temperature. The solvent was removed using a rotary evaporator and the residue was extracted with three 50-ml portions of ether. The combined ether solution was then washed successively with dilute acid, water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. After drying over anhydrous potassium carbonate, the ether was removed using a 30-in. Helipack column to give 0.8 g (53%) of the ketone. Vpc analysis indicated only one component. The infrared spectrum showed a peak at 1780 cm^{-1} (C=O) and the nmr spectrum had bands at τ 6.8–7.1 (2 H, broad singlet), 7.4–7.8 (4 H, multiplet), 7.9–8.5 (4 H, multiplet). The product was identical with that previously prepared *via* a different method.[4]

6-Methyl-*endo*-bicyclo[3.1.1]heptan-6-ol.—Methyl bromide was bubbled into a mixture of 0.5 g of magnesium turnings and 25 ml of anhydrous ether until the magnesium had dissolved. The reaction mixture was heated to reflux for 30 min to remove the excess methyl bromide. It was then cooled to 0° and 0.8 g (7 mmol) of bicyclo[3.1.1]heptan-6-one in 15 ml of anhydrous ether was added dropwise. After the addition, the solution was stirred overnight and then the magnesium salt was decomposed by adding 5 ml of ice–water and 15 ml of saturated ammonium chloride solution. The ether layer was separated, and the water layer was saturated with sodium chloride and extracted with two 20-ml portions of ether. The ether layers were combined and dried over magnesium sulfate and the solvent was removed using a rotary evaporator. The residue was distilled at 150° (0.3 mm), giving 0.8 g (87%) of the alcohol. The nmr spectrum had bands at τ 8.6 (3 H, s) and 7.67–8.9 (10 H, multiplet).

Anal. Calcd for $C_8H_{14}O$: C, 76.1; H, 11.2. Found: C, 75.9, 76.1; H, 11.3, 11.2.

The 3,5-dinitrobenzoate was prepared and after recrystallization from hexane it had mp 117–118.5°.

6-Methyl-*exo*-bicyclo[3.1.1]heptan-6-ol.—A mixture of 1.62 g (0.015 mol) of 6-methylenebicyclo[3.1.1]heptane and 1.5 g of sodium carbonate in 20 ml of methylene chloride was cooled in an ice–water bath and 4 g of *m*-chloroperbenzoic acid in 25 ml of methylene chloride was added dropwise. After stirring overnight, the solution was cooled to 0° and sodium sulfite was added to destroy the excess perbenzoic acid. The reaction mixture was diluted with 50 ml of water and the methylene chloride later was separated. The aqueous layer was washed with 20-ml portions of methylene chloride. The methylene chloride solutions were combined and washed with sodium bicarbonate solution, water, and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the excess methylene chloride was removed, giving 1.7 g of crude epoxide. This was purified by vpc using a 10 ft × 0.375 in. Silicon oil column at 140°, giving 0.92 g (50%) of the pure epoxide, retention time 17 min. The nmr spectrum had bands at τ 7.49 (2 H, s) and 7.5–8.7 (10 H, multiplet).

Anal. Calcd for $C_8H_{12}O$: C, 77.4; H, 9.7. Found: C, 77.2, 77.2; H, 10.0, 9.8.

A solution of 0.92 g (7.4 mmol) of the epoxide and 20 ml of anhydrous ether was added to a stirred slurry of lithium aluminum hydride and 40 ml of anhydrous ether. The reaction mixture was worked up in the usual fashion, giving 0.75 g (81%) of the tertiary alcohol. The nmr spectrum had bands at τ 8.82 (3 H, s) and 7.73–8.84 (10 H, multiplet).

Anal. Calcd for $C_8H_{14}O$: C, 76.1; H, 11.2. Found: C, 76.1, 75.9; H, 11.0, 11.2.

The dinitrobenzoate was prepared and after recrystallization from hexane it had mp 165–166°.

6-Methyl-*endo*-bicyclo[3.2.0]heptan-6-ol.—The reaction of 1.1 g (0.01 mol) of bicyclo[3.2.0]heptan-6-one with methylmagnesium bromide was carried out as described above. Distillation at 150° (0.3 mm) gave 1.0 g (81%) of 6-methyl-*endo*-bicyclo[3.2.0]heptan-6-ol. Its nmr spectrum had bands at τ 8.7 (3 H, s) and 7.33–9.07 (10 H, multiplet).

Anal. Calcd for $C_8H_{14}O$: C, 76.1; H, 11.2. Found: C, 75.9, 76.1; H, 11.3, 11.2.

The 3,5-dinitrobenzoate was prepared. After recrystallization from hexane it had mp 126–127°.

6-Methylbicyclo[3.2.0]hept-6-ene.—6-Bicyclo[3.1.0]hexyl methyl ketone (1.24 g, 0.01 mol) was converted to the tosylhydrazone with 1.86 g (0.01 mol) of *p*-toluenesulfonhydrazide in 10 ml of 60% aqueous methanol. After recrystallization from methanol, it had mp 123–125°. The tosylhydrazone was converted to the sodium salt using the procedure of Friedman and Schechter[10] and was pyrolyzed at 160°. The product was analyzed by vpc using a 10 ft × 0.375 in. silicon oil column at 100°. Besides the solvent, diglyme, only 0.4 g (28%) of a product with retention time 10 min was obtained. The nmr spectrum had bands at τ 4.58 (broad singlets), two bridgehead hydrogens at 7.01 and 7.12, and nine methylene hydrogens at 8.1–8.8.

6-Methyl-*exo*-bicyclo[3.2.0]heptan-6-ol.—6-Methylbicyclo[3.2.0]heptene-6 (0.4 g, 3.7 mmol) was converted to the epoxide with 1.5 g of *m*-chloroperbenzoic acid as described above. Reduction was affected using 0.2 g of lithium aluminum hydride in 40 ml of ether, giving 0.2 g (88%) of the tertiary alcohol. The nmr spectrum had bands at τ 8.92 (3 H, singlet) and 6.92–8.85 (10 H, multiplet).

Anal. Calcd for $C_8H_{14}O$: C, 76.1; H, 11.2. Found: C, 76.0, 76.1; H, 11.3, 11.4.

6-Methylenebicyclo[3.2.0]heptane.—A solution of 0.05 mol of *n*-butyllithium in about 150 ml of ether was stirred under nitrogen, and 0.5 mol of crystalline methyltriphenylphosphonium bromide was added over a 5-min period. After the solution was stirred for 4 hr at room temperature, 5 g (0.045 mol) of bicyclo[3.2.0]heptan-6-one was added dropwise. The solution became colorless and the white precipitate separated. The mixture was heated to reflux overnight and cooled, and the precipitate was removed by filtration. The ether solution was washed with water and then dried. The ether was distilled through a 30-in. Helipack column and the residue was purified by vpc using a 10 ft × 0.375 in. silicon oil column to give 0.8 g (16%) of 6-methylenebicyclo[3.2.0]heptane, retention time 11 min. The ir spectrum showed C=C absorption at 1640 and 880 cm^{-1}. The nmr spectrum had bands at τ 5.33 (2 H, m) and 6.62–8.7 (10 H, m).

6-Methyl-*exo*-bicyclo[3.2.0]heptan-6-ol.—6-Methylenebicyclo[3.2.0]heptane (0.8 g, 0.074 mol) was converted to the epoxide with 3 g of *m*-chloroperbenzoic acid as was described above, giving 0.41 g (44%) of the epoxide. The lithium aluminum hydride reduction of 0.4 g of the epoxide gave 0.32 g (77%) of 6-methyl-*exo*-bicyclo[3.2.0]heptan-6-ol. The product was identical with that described above.

The alcohol was converted to the 3,5-dinitrobenzoate, which after recrystallization from hexane had mp 115–116°.

Vanadium(V) Oxidation of 6-Methyl-*endo*-bicyclo[3.1.1]heptan-6-ol.—A solution of 1 g of concentrated sulfuric acid in 10 ml of water was added dropwise to a mixture of 0.25 g (0.02 mol) of 6-methyl-*endo*-bicyclo[3.1.1]heptan-6-ol, 0.47 g (0.04 mol) of ammonium vanadate, and 30 ml of water. The reaction mixture was stirred overnight and then extracted with three 40-ml portions of ether. The solution was dried over magnesium sulfate, ether was removed, and the residue was analyzed by vpc using a 20 ft × 0.375 in. DEGS column at 150°. Only one product, retention time 22 min, was found. It was shown to be 3-cyclohexenyl methyl ketone by comparison with an authentic sample.

The reaction also was carried out using the exo isomer, and the same product was found.

Vanadium(V) Oxidation of 6-Methyl-*endo*-bicyclo[3.2.0]heptan-6-ol.—The oxidation of 6-methyl-*endo*-bicyclo[3.2.0]heptan-6-ol was effected using the above procedure. The only product, retention time 37 min, was identified as 2-cyclopentenyl-1-acetone by comparison with an authentic sample.

5-Methylenebicyclo[2.1.1]hexane.—To a stirred slurry of 3.2 g of lithium aluminum hydride in 100 ml of anhydrous ether was added a solution of 12.5 g (0.082 mol) of *N,N*-dimethylbicyclo[2.1.1]hexane-6-carboxamide[11] in 150 ml of dry ether. After stirring for 24 hr, the mixture was cooled in an ice bath and treated with 50 ml of cold water. The ether solution was separated by filtration, dried over magnesium sulfate, and distilled, giving 10.5 g (93%) of 5-dimethylaminobicyclo[2.1.1]hexane, bp 46–47° (8 mm). To a cooled and stirred solution of the amine in 120 ml of methanol was added dropwise 52 g of 30% hydrogen

(10) L. Friedman and H. Schechter, *J. Amer. Chem. Soc.*, **83**, 3159 (1961).

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

peroxide. After 24 hr, an additional 10 g of hydrogen peroxide was added. Twenty hours later it was treated with platinum black in water. Removal of the solvent gave 11 g (94%) of the *N*-oxide. The latter was heated in a 50-ml flask to 180° (5 mm) and the product was collected in two successive Dry Ice–acetone traps. It was taken up in 150 ml of olefin-free pentane, and the pentane solution was washed with 100 ml of 1 *N* hydrochloric acid, two 50-ml portions of sodium bicarbonate solution, and water. After drying over potassium carbonate, distillation gave 4 g (60%) of 5-methylenebicyclo[2.1.1]hexane, bp 70–72° (100 mm). The nmr spectrum had bands at τ 5.78 (2 H, s), 7.17 (2 H, s), 8.28–9.2 (6 H, m).

Anal. Calcd for C_7H_{10}: C, 89.3; H, 10.7. Found: C, 89.2; H, 10.6.

Oxymercuration–Demercuration of 6-Methylenebicyclo[3.1.1]heptane.—To a stirred mixture of 9.57 g (0.03 mol) of mercuric acetate, 30 ml of water, and 30 ml of tetrahydrofuran was added 3.24 g (0.03 mol) of 6-methylenebicyclo[3.1.1]heptane. The solution became colorless and clear in 28 sec. After the solution was stirred for an additional 5 min at room temperature, 30 ml of 3 *M* sodium hydroxide was added followed by 30 ml of 3 *M* sodium borohydride in 3 *M* sodium hydroxide. The reduction appeared to be instantaneous. The aqueous layer was saturated with sodium chloride, and the organic layer was separated. The aqueous solution was extracted with ether. The combined organic solution was dried over magnesium sulfate, concentrated using a rotary evaporator, and separated into its components by vpc using a 28 ft × 0.375 in. 20% Carbowax column at 140°. The products were 6-methyl-*endo*-bicyclo[3.2.0]heptan-6-ol (32%, 35 min); 2-methylbicyclo[2.2.1]heptan-2-ol (4%, 40 min); 6-methyl-*endo*-bicyclo[3.1.1]heptan-6-ol (20%, 45 min); 6-methyl-*exo*-bicyclo[3.2.0]heptan-6-ol (35%, 50 min); 6-methyl-*exo*-bicyclo[3.1.1]heptan-6-ol (2%, 58 min); and 2-methylenecycloheptanol (6%, 80 min).

Oxymercuration–Demercuration of 5-Methylenebicyclo[2.1.1]hexane.—To a mixture of 3.2 g (0.01 mol) of mercuric acetate, 10 ml of water, and 10 ml of tetrahydrofuran was added 0.94 g (0.01 mol) of 5-methylenebicyclo[2.2.1]hexane. The solution became clear and colorless in 32 sec. Reduction with sodium borohydride (10 ml of 0.5 *M*) and subsequent work was effected as described above giving 2-methylenecyclohexanol (44%, 17.7 min, 220-in. TCEP column at 110°), 3-methylenecyclohexanol (28%, 18.7 min), and 3-methyl-Δ^3-cyclohexanol (28%, 21.5 min).

Nmr Study of the Reaction of Mercuric Trifluoroacetate with 5-Methylenebicyclo[2.1.1]hexane in Benzene Solution.—A 2 *M* solution of 5-methylenebicyclo[2.1.1]hexane in benzene (solution A) and a 2 *M* solution of mercuric trifluoroacetate in benzene (solution B) was prepared. Equal volumes of the two solutions were mixed in an nmr tube and spectra were taken 5 min, 20 min, 45 min, 75 min, 24 hr, 40 hr, 60 hr, and 132 hr after mixing. The signal of the original olefinic protons (τ 5.78) had completely disappeared in 5 min and cyclopropyl protons (τ 9–10), new olefinic protons and the proton α to the trifluoroacetyl group (τ 4.5–6) were found. As time went on the cyclopropyl proton bands diminished and were replaced with olefinic protons.

The reaction also was carried out on a preparative scale. To a solution of 0.94 g (0.01 mol) of 5-methylenebicyclo[2.1.1]hexane in 5 ml of benzene was added a solution of 4.35 g (0.01 mol) of mercuric trifluoroacetate in 5 ml of benzene. The reaction was quite exothermic and the temperature increased to 70°. After the solution had cooled to room temperature, a solution of 0.9 g of sodium borohydride in 10 ml of 1:1 benzene-methanol was added. The mixture was filtered, concentrated using a rotary evaporator, and analyzed by vpc using a 220-in. TCEP capillary column at 110°. The products were 2-methylenecyclohexanol (16%), 3-methylenecyclohexanol (70%), and 3-methyl-Δ^3-cyclohexanol (14%). The reaction was repeated with the temperature controlled at 0° throughout. The products were 2-methylenecyclohexanol (71%) and 3-methylenecyclohexanol (29%).

Registry No.—I, 35324-39-1; II, 28366-41-8; 7-formylbicyclo[3.2.1]octan-6-one, 35324-41-5; *N,N*-dimethylbicyclo[3.1.1]heptane-6-carboxamide, 35324-42-6; 6-dimethylaminomethylbicyclo[3.1.1]heptane, 35378-27-9; 6-methyl-*endo*-bicyclo[3.1.1]heptan-6-ol, 35378-28-0; 6-methyl-*endo*-bicyclo[3.1.1]heptan-6-ol 3,5-dinitrobenzoate, 35378-29-1; 6,8-epoxybicyclo[3.1.1]heptene-6, 35323-95-6; 6-methyl-*exo*-bicyclo[3.1.1]heptan-6-ol, 35323-96-7; 6-methyl-*exo*-bicyclo[3.1.1]heptan-6-ol 3,5-dinitrobenzoate, 35323-97-8; 6-methyl-*endo*-bicyclo[3.2.0]heptan-6-ol, 13837-37-1; 6-methyl-*endo*-bicyclo[3.2.0]heptan-6-ol 3,5-dinitrobenzoate, 35323-99-0; 6-methyl-*exo*-bicyclo[3.2.0]heptan-6-ol, 35324-00-6; 6-methyl-*exo*-bicyclo[3.2.0]heptan-6-ol 3,5-dinitrobenzoate, 35324-01-7.

Bridged Polycyclic Compounds. LXXIII. Nitrous Acid Deaminations of Some Isomeric Aminodibenzobicyclooctadienes[1]

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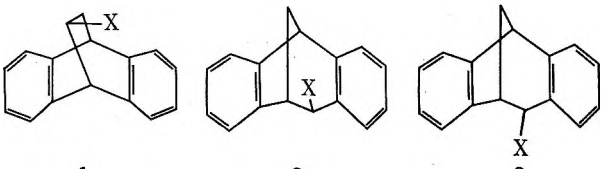
Reaction of 7-aminodibenzobicyclo[2.2.2]octadiene (**1a**) and *exo*- and *endo*-2-aminodibenzobicyclo[3.2.1]octadienes (**2a** and **3a**) with nitrous acid in glacial acetic acid leads primarily to dibenzobicyclo[3.2.1]octadien-*exo*-2-ol (**2c**) and the corresponding acetate (**2d**). Changes in product ratios with solvent composition suggest that the relatively large amount of alcohol product results partly from an intramolecular reaction pathway, involving the diazohydroxide intermediate.

Quantitative differences in product-forming pathways in amine deaminations, compared with halide or sulfonate solvolyses, have been described by many workers.[2] However, the inherent difficulty of using product-distribution studies to determine the roles of diazonium ions and carbonium ions with varying structures and under widely different conditions has led to proposals of a variety of intermediate species in the product-determining steps of the amine–nitrous acid and related reactions. Only recently has a comprehensive theory begun to emerge, which can account for the many "unusual" products in the amine–nitrous acid reaction.[2b-d]

The large body of data concerning solvolytic pathways in the dibenzobicyclooctadienyl system led us to a comparative study of the amine–nitrous acid reaction in this system. Cationic intermediates produced by solvolysis of dibenzobicyclo[2.2.2]octadienyl substrates

(1) (a) Paper LXXII: S. J. Cristol, A. L. Noreen, and G. W. Nachtigall, *J. Amer. Chem. Soc.*, **94**, 0000 (1972). (b) This work was reported at the 18th National Organic Symposium of the American Chemical Society, Columbus, Ohio, June 1963.

(2) (a) H. Zollinger, "Azo and Diazo Chemistry," Interscience, New York, N. Y., 1951, pp 123–136; (b) R. A. M. O'Ferrall, *Advan. Phys. Org. Chem.*, **5**, 362 (1967); (c) E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, pp 440–483; (d) L. Friedman in "Carbonium Ions," Vol. II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley–Interscience, New York, N. Y., 1970, pp 655–713.



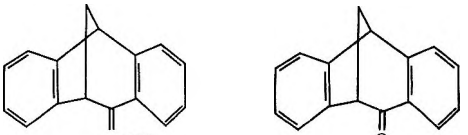
1 2 3

a, X = NH_2 **d**, X = OAc
b, X = OTs **e**, X = NH_3^+, $^-$OTs
c, X = OH **f**, X = ONO

(1) almost invariably lead to rearranged [3.2.1] exo C-2 products (2) through kinetic control,[3,4] where it has been shown that the usual order of thermodynamic stability is [3.2.1] exo C-2 derivative (2) < [3.2.1] endo C-2 derivative (3) < [2.2.2] derivative (1).[4e] Following the same pattern, reaction of amines **1a–3a** and their *p*-toluenesulfonate salts with nitrous acid in acetic acid led completely to dibenzobicyclo[3.2.1]-octadiene products substituted at C-2.

Synthesis of the Amines.—Compound **1a** was prepared by the method of Wawzonek and Hallum.[5] Lithium aluminum hydride reduction of 2-oximinodibenzobicyclo[3.2.1]octadiene (**4**) led primarily to the endo amine **3a**. The exo amine **2a** was obtained in good yield by solvolysis of dibenzobicyclo[2.2.2]octadien-7-yl *p*-toluenesulfonate (**1b**) in liquid ammonia at 100° in a sealed tube. Since the amines **2a** and **3a** proved to be difficult to purify, their *p*-toluenesulfonate salts were isolated, purified, and subsequently used in the deaminations. The *N*-acetyl derivatives of **2a** and **3a** were also prepared and characterized.

Structural assignments of the amines **2a** and **3a** were made on the basis of analogies in their modes of synthesis and reaction. Solvolyses of dibenzobicyclo[2.2.2]-octadien-7-yl derivatives are known to give exclusively or preponderantly dibenzobicyclo[3.2.1]octadien-*exo*-2-yl derivatives.[3,4a,d,f] Therefore the amine produced by ammonolysis of **1b** may confidently be assigned structure **2a**. On the other hand, lithium aluminum hydride reduction of dibenzobicyclo[3.2.1]octadien-2-one (**5**) is known to give predominantly endo 2-alcohol **3c**;[4d] so the endo 2-amine **3a** was anticipated from the corresponding reduction of the oxime **4**. A pmr spectral analysis[6] of



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amine **1a** was consistent with the structure assignment presented here.

Deamination Results in Glacial Acetic Acid.—Deamination of the amine **1a** and the *p*-toluenesulfonates of amines **1a–3a** in glacial acetic acid led to dibenzobicyclo[3.2.1]octadien-*exo*-2-ol (**2c**) and exo 2-acetate **2d** in high yield. The *p*-toluenesulfonate salt of amine **1a** was shown to give a product mixture identical with that produced in the deaminations of the free amine **1a** and its hydrochloride salt. With **3e** a small amount of the endo 2-alcohol **3c** was isolated as well. The exo 2-nitrite **2f** and dibenzobicyclo[3.2.1]octadien-2-one (**5**) formed a small percentage of the products. All alcohol and acetate products were shown to be stable under reaction conditions. No substituted dibenzobicyclo[2.2.2]octadienes or dibenzobicyclo[2.2.2]octatriene was found in the product mixture.

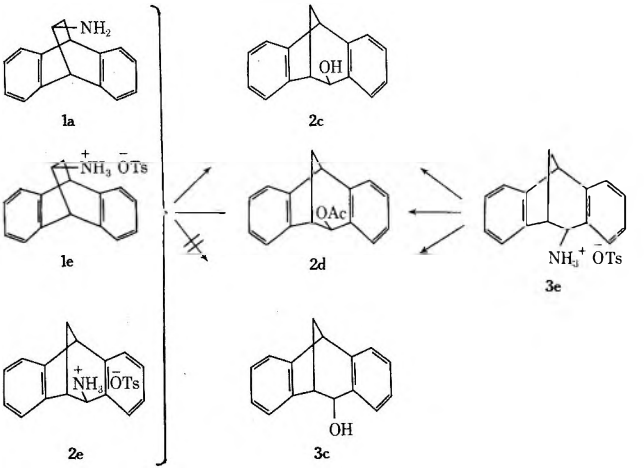
TABLE I
YIELDS OF DEAMINATION PRODUCTS[a,b]

Amine	Exo acetate 2d, %	Exo ol 2c, %	Endo ol 3c, %	Nitrite 2f, %	Ketone 5, %
1a[c]	80	19		<1	0.2
1e	76	24			
2e	76	24			
3e	87	9	3	~1	Trace
1a[d]	75	25			

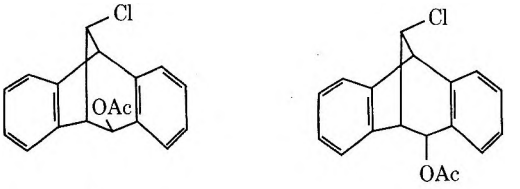
[a] Analysis by quantitative differential infrared method. [b] Using an amine–nitrous acid ratio of 1:7 to 1:10 to ensure complete reaction of the amines. [c] Based upon column chromatographic isolation. [d] Using an amine–nitrous acid ratio of 1:1.

Yields of the various deamination products from reactions in glacial acetic acid are shown in Table I, which is followed by a diagrammatic summary of these reactions (Scheme I).

SCHEME I



Structure Proof of the Deamination Products.—The exo 2-alcohol **2c** and exo 2-acetate **2d** could be interconverted by treatment with an acetic anhydride–pyridine solution and by hydride cleavage. The configuration at C-2 was based upon the known syn–exo acetoxy chloride **6** and syn–endo acetoxy chloride **7**.[4a,b] Reduction of **6** with sodium biphenyl produced the exo alcohol **2c** while the analogous reduction of **7** gave endo alcohol **3c**.[4c] Both alcohols were oxidized to the same ketone **5**. The chemical evidence presented here



6 7

(3) W. R. Vaughan and A. C. Schoenthaler, *J. Amer. Chem. Soc.*, **80**, 1956 (1958).

(4) (a) S. J. Cristol and R. K. Bly, *ibid.*, **82**, 6155 (1960); (b) S. J. Cristol, R. P. Arganbright, and D. D. Tanner, *J. Org. Chem.*, **28**, 1374 (1963); (c) S. J. Cristol and D. D. Tanner, *J. Amer. Chem. Soc.*, **86**, 3122 (1964); (d) S. J. Cristol, F. P. Parungo, and D. E. Plorde, *ibid.*, **87**, 2870 (1965); (e) S. J. Cristol, F. P. Parungo, D. E. Plorde, and K. Schwarzenbach, *ibid.*, **87**, 2879 (1965); (f) S. J. Cristol, R. Caple, R. M. Sequeira, and L. O. Smith, Jr., *ibid.*, **87**, 5679 (1965).

(5) S. Wawzonek and J. V. Hallum, *J. Org. Chem.*, **18**, 288 (1953).

(6) S. J. Cristol, T. W. Russell, J. R. Mohrig, and D. E. Plorde, *ibid.*, **31**, 581 (1966).

for the structure of the exo alcohol **2c** and exo acetate **2d** has also been substantiated by proton magnetic resonance studies.[7]

Deamination of the Amines in Water–Acetic Acid Mixtures.—The high yields of alcohol from the deamination of amines **1a** and **2a** in acetic acid were reproducible in a number of separate experiments. Although a small amount of water is present when an amine is deaminated in anhydrous acetic acid, due to the production of water in the deamination process itself and to the competitive decomposition of nitrous acid, the water can comprise no more than 4% of the solvent when a tenfold excess of sodium nitrite is used under our reaction conditions.

$$RNH_2 + HNO_2 + CH_3CO_2H \longrightarrow CH_3CO_2R + N_2 + 2H_2O$$

$$3HNO_2 \longrightarrow 2NO + HNO_3 + H_2O$$

In order to test if the high alcohol/acetate ratio was sharply dependent upon the percentage of water in the bulk solvent, the deamination of amine **1a** was effected in four different solvent mixtures (Table II). Proton

TABLE II

PER CENT ALCOHOL PRODUCTS FROM DEAMINATIONS IN ACETIC ACID–WATER MIXTURES

Amine	Solvent composition,[a] % water	Alcohol products,[b,c] %
1a	0	24
1a	11	29
1a	25	35
1a	50	52
3e	0	12[d,e]
3e	3	12[d,f]

[a] Mole per cent of added water. [b] By pmr integration of C-2 protons. [c] Based on 2-alcohol and 2-acetate comprising 100% of product. [d] By quantitative differential infrared analysis. [e] A mixture of alcohols **2c** and **3c**, see Table I. [f] 10% **2c** and 2% **3c**.

magnetic resonance spectral analysis showed only a small gradual increase in the mole percentage of exo alcohol **2c** in the product of the nitrous acid deamination of the [2.2.2] amine **1a** when 0, 11, and 25 mol % water were present in the acetic acid solvent. Even deamination of **1a** in the presence of 50 mol % water in the acetic acid solvent increased the proportion of the exo alcohol **2c** to only 50%. Similarly, the product yields were exactly the same for the deamination of endo amine salt **3e** in glacial acetic acid and in the presence of a tenfold mole excess of water in the acetic acid deamination medium. This remarkable lack of solvent sensitivity in the proportion of alcohol in the product leads us to propose that much of the alcohol found in the deamination product results directly from an intramolecular reaction of the diazohydroxide intermediate.

An alternative source for the large amount of alcohol product could have been the nitrite esters sometimes formed in deamination reactions. These esters, if unstable under work-up procedures, could possibly have yielded large amounts of the corresponding alcohols. However, control experiments strongly suggest that this was not the situation here. The exo 2-nitrite **2f** was prepared by the reaction of the exo 2-ol **2c** with nitrosyl chloride in pyridine. The resulting nitrite was subjected to deamination conditions in anhydrous acetic acid. Although indeed 60% of nitrite **2f** was unstable to work-up conditions, the amount of ketone **5**[8] formed in the nitrite decomposition (1.5%) showed that the amount of alcohol formed by this pathway in the deamination could not be more than 14 ± 3%, since only 0.2 ± 0.05% ketone was formed in the amine–nitrous acid reaction. Undoubtedly this 14% represents a maximum percentage of alcohol formed by this route, since the calculation assumes complete destruction of the nitrite under work-up conditions. That the hydrolysis of nitrite esters could not have been an important source of the large amounts of alcohol products in deamination reactions was also demonstrated by the isolation of 25% exo alcohol **2c** in the presence of a limited amount of sodium nitrite (see Table I). No evidence could be found for the presence of any nitrite in this product mixture.

A second alternative is that a small amount of water might be far better able to compete with the bulk acetic acid for combination with the carbonium ion intermediate. This postulate was tested by solvolysis of dibenzobicyclo[2.2.2]octadien-7-yl tosylate in a 3.7 mol % water–96.3 mol % acetic acid mixture. This solvent mixture contained the maximum amount of water that could be produced by the decomposition of nitrous acid (*vide supra*). The product was again composed completely of rearranged [3.2.1] products, with 13% of the exo alcohol and 87% of the exo acetate found. Neither endo acetate nor endo alcohol was formed. This exo alcohol should again represent a maximum amount of alcohol in the deamination product, since the ratio of alcohol to acetate in the product does not change when as little as an equimolar quantity of sodium nitrite was used in the deamination. The decomposition of nitrous acid in this experiment would produce far less than 1 mol % water.

The differences in the products resulting from reaction of exo amine **2a** and endo amine **3a** with sodium nitrite in acetic acid are also consistent with the intervention of an intramolecular pathway leading to much of the alcohol product. Whereas both the [2.2.2] amine and exo [3.2.1] amine gave only exo products, the endo amine produced, in addition to the exo alcohol and acetate, a small amount (3%) of the endo alcohol **3c**. However, no endo acetate was found, although all alcohol and acetate products were shown to be stable under reaction conditions. It does not seem likely that this endo alcohol results from reaction of an intermediate carbonium ion and the bulk solvent, but rather it arises directly from the diazohydroxide intermediate, without intervention of the bulk solvent.

Discussion

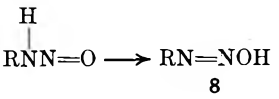
The high proportion of exo 2-ol **2c** resulting from nitrous acid deamination of **1a**, **1e**, and **2e** and our stereochemical results can be understood most easily in terms of ion-pair phenomena. This concept of the importance of ion-pair phenomena in the amine–nitrous acid reaction and the closely related nitrosamide decomposition in relatively nonpolar solvents, such as

(7) S. J. Cristol, J. R. Mohrig, and D. E. Plorde, *J. Org. Chem.*, **30**, 1956 (1965).

(8) Experiments with 4,4′-dimethoxybenzhydrol suggest that in some cases direct air oxidation of the alcohol may be responsible for the small amounts of ketone formed under deamination conditions.

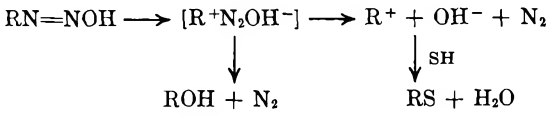
acetic acid, has been considered by a number of investigators.[2,9-19]

The available evidence suggests that deamination proceeds through an unstable diazohydroxide (**8**),[2,16-18]



possibly the syn diazohydroxide. Dissociation would lead to the diazonium cation, which by loss of N_2 would ultimately give stable products.

In our results, it is clear that the diazonium ion loses N_2 before the hydroxide gegenion can diffuse away.[20,21]

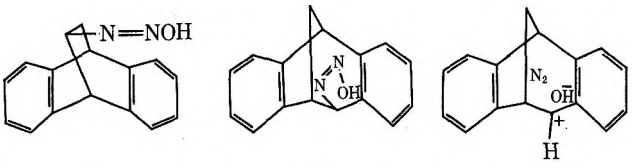


The timing of C–N *vs.* N–O bond breaking depends upon the nature of the organic group, R. If R is better able to stabilize a positive charge, the C–N bond is more easily cleaved.[22]

Indeed, it has now become quite clear that the importance of ion-pair phenomena as manifested by retention of configuration of substitution products and high amounts of alcohol products in nonpolar solvents in the deamination process is related to the stability of the incipient carbonium ion resulting from loss of molecular nitrogen.[2,9-19] These ion-pair phenomena seem important only with more stable carbonium ion systems in which the alkanediazonium ion is either bypassed as an intermediate species or has an extremely short lifetime. A wide range of "relatively stable" carbonium ions exists, from 4-octyl[10] to 2-phenyl-2-butyl.[9d] Probably, then, ion pairs leading to intramolecular deamination products are but one important part of a total view of amine deamination reactions. White has suggested the importance of vibrationally excited ion pairs in these reactions.[9c]

An Sn2 pathway would not be favorable for the diazohydroxide decomposition in the present case[24] because approach of solvent to the back of the developing carbonium ion would be blocked by the bulky carbon skeleton. Also, the ring system does not allow for ready inversion of the attacked carbon atom.

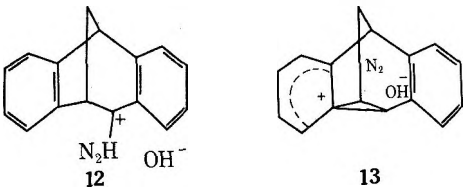
Amines **1a** and **2a** gave identical product distributions, suggesting common intermediates, while **3a** gave a different product distribution, presumably from one or more different intermediates. In the ion-pair representation, we would have (most simply) **11** as the final intermediate from **9** and **10**, leading directly to **2c**. Any



9 **10** **11**

acetate from solvolysis would also be exclusively exo (**2d**), as was found to be the case (Table I).

An ion-pair pathway is also consistent with the formation of endo alcohol **3c** with concurrent absence of endo acetate **3d** in the deamination of the *p*-toluenesulfonate salt of endo amine **3e**. The initially formed benzyl cation–hydroxide ion pair **12** from the endo diazohydroxide would have hydroxide ion at a position favorable for attack at the endo side of the carbonium ion, if coordination can occur before hydroxide migrates to the exo position. The predominant formation of exo alcohol and acetate from endo precursor once again demonstrates the marked preference for exo attack on the dibenzobicyclo[3.2.1]octadien-2-yl cation. There is the additional possibility of an Sn2 reaction leading to a portion of the exo acetate product. It is difficult to assess the relative important of attack by water in the bulk solvent and an intramolecular inversion pathway[2c] in the formation of exo alcohol from **12**.



12 **13**

It has been suggested[4b,e] that the benzyl cation is the most probable product-forming species in the carbonium ion chemistry of the dibenzobicyclo[3.2.1]-octadien-2-yl system, with stereoelectronic control accounting for the preponderance of exo products.[25] The importance of exo attack is also consistent with the lower torsional strain[26] and therefore greater stabilities of the transition states leading to exo products. The data also agree with the idea that the endo diazohydroxide leads initially to **12**, while **9** and **10** give the pheno-

(9) (a) E. H. White and C. A. Aufdermarsh, Jr., *J. Amer. Chem. Soc.*, **83**, 1179 (1961); (b) E. H. White and F. W. Bachelor, *Tetrahedron Lett.*, 77 (1965); (c) E. H. White and C. A. Elliger, *J. Amer. Chem. Soc.*, **89**, 165 (1967); (d) E. H. White and J. E. Stuber, *ibid.*, **85**, 2168 (1963).

(10) (a) M. C. Whiting, *Chem. Brit.*, 482 (1966); (b) H. Maskill, R. M. Southam, and M. C. Whiting, *Chem. Commun.*, 496 (1965).

(11) H. Felkin, *C. R. Acad. Sci.*, **236**, 298 (1953).

(12) R. Huisgen and C. Rüchardt, *Justus Liebigs Ann. Chem.*, **601**, 21 (1956).

(13) T. Cohen and E. Jankowski, *J. Amer. Chem. Soc.*, **86**, 4217 (1964).

(14) H. Tanida, T. Tsuji, and T. Irie, *J. Org. Chem.*, **31**, 3941 (1966).

(15) J. H. Bayless, A. T. Jurewicz, and L. Friedman, *J. Amer. Chem. Soc.*, **90**, 4466 (1968).

(16) J. G. Traynham and M. T. Yang, *ibid.*, **87**, 2394 (1965).

(17) M. Chérest, H. Felkin, J. Sicher, F. Šipoš, and M. Tichý, *J. Chem. Soc.*, 2513 (1965).

(18) (a) R. A. Moss and S. M. Lane, *J. Amer. Chem. Soc.*, **89**, 5655 (1967); (b) R. A. Moss and G. H. Temme, III, *Tetrahedron Lett.*, 3219 (1968).

(19) C. W. Shoppee, J. G. Feher, R. M. Hall, R. E. Lack, and L. Tarasoff, Jr., *J. Chem. Soc. C*, 2211 (1968).

(20) Proton transfer from the solvent (SH) could precede the dissociation of cation–hydroxide ion pairs.

(21) Moss has suggested[18a] that in alkaline diazotate hydrolyses the leaving group N=NOH has considerable integrity.

(22) As the stability of the cation R^+ increases, the breaking of the N–O and C–N bonds can become more synchronous.[23] As this occurs, more alcohol product can be directly formed through an intramolecular pathway. This may account for our data on the yields of alcohol from deamination of benzylic amines in glacial acetic acid: $C_6H_5CH_2NH_2$ (1.1% ROH, 1.0% aldehyde, 97.4% ROAc), $(C_6H_5)_2CHNH_2$ (7% ROH, 5% ketone, 88% ROAc), $(p\text{-}CH_3OC_6H_4)_2CHNH_2$ (8% ROH, 92% ROAc), $(C_6H_5)_3CNH_2$ (>95% ROH, <5% ROAc).

(23) For the dependence of concerted two-bond cleavage upon the nature of R, see J. L. Kice, R. A. Bartsch, M. A. Dankleff, and S. L. Schwartz, *J. Amer. Chem. Soc.*, **87**, 1734 (1965).

(24) However, for cases where direct displacement on diazohydroxide or diazonium ion intermediates has been proposed, see (a) J. A. Berson and D. A. Ben-Efraim, *ibid.*, **81**, 4094 (1959); (b) J. A. Berson and A. Remanick, *ibid.*, **86**, 1749 (1964); (c) R. D. Guthrie, *ibid.*, **89**, 6718 (1967); (d) ref 14–16; (e) W. J. Albery, J. E. C. Hutchins, R. M. Hyde, and R. H. Johnson, *J. Chem. Soc. B*, 219 (1968).

(25) However, see (a) H. Tanida, H. Ishitobi, and T. Irie, *J. Amer. Chem. Soc.*, **90**, 2688 (1968); (b) H. C. Brown and G. L. Tritle, *ibid.*, **90**, 2689 (1968); (c) M. C. Kochansky, Ph.D. Thesis, University of Colorado, 1971.

(26) (a) P. v. R. Schleyer, *ibid.*, **89**, 699 (1967); (b) *ibid.*, **89**, 701 (1967).

nium ion–hydroxide ion pair **13**, resulting in exo products.[25c]

Experimental Section

General Deamination Procedure.—The amine or ammonium compound was dissolved in anhydrous acetic acid (Baker and Adamson, distilled from boron triacetate, 0.01% water by Karl Fischer titration) in a round-bottom flask equipped with a condenser, a drying tube, and a magnetic stirring bar. Solid sodium nitrite was added at 18° from an erlenmeyer flask attached to the reaction vessel by means of a rubber sleeve. The solution was then allowed to warm to room temperature and subsequently stirred for 3–4 hr more. Multiple extractions of the reaction mixture with pentane were followed by water and sodium bicarbonate washings of the combined pentane extract. The pentane was removed by rotary evaporation after the solution had been dried ($MgSO_4$). The oily residue was held at 1 Torr until the product had a constant weight. The exo and endo alcohols **2c** and **3c** and acetates **2d** and **3d** were found to be stable to the acetic acid–nitrous acid reaction conditions and isolation procedures, using infrared analysis.

Nitrous Acid Deamination of 7-Aminodibenzobicyclo[2.2.2]octadiene (1a).—A 3.18-g (46.1 mmol) sample of sodium nitrite was slowly added to a solution of 1.02 g (4.61 mmol) of **1a**[5] in 36 ml of acetic acid over a 2-hr period. The crude oily product weighed 1.10 g.

Conversion of the Deamination Mixture from 1a to Dibenzobicyclo[3.2.1]octadien-*exo*-2-ol (2c).—A 1.25-g sample of the deamination mixture dissolved in anhydrous ether was added dropwise to a vigorously stirred suspension of 220 mg (5.8 mmol) of lithium aluminum hydride in 40 ml of anhydrous ether. Slow addition of water and acidification with 12 *M* hydrochloric acid solution, followed by separation and extraction of the aqueous layer with petroleum ether (bp 60–70°), washing of the ether–petroleum ether solution with 5% sodium bicarbonate solution, drying ($MgSO_4$), and removal of the solvent, gave 1.10 g (100%) of crude **2c**. Crystallization from petroleum ether gave 825 mg (75%), mp 119–119.5°.

Anal.[27] Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.33; H, 6.12.

Preparation of 2d from 2c.—A 256-mg (1.15 mmol) sample of the exo alcohol **2c**, dissolved in a mixture of 10 ml of acetic anhydride and 2 ml of pyridine, was heated at reflux for 1 hr, cooled, and then poured into 100 ml of water and 100 ml of petroleum ether. The aqueous layer was extracted again with petroleum ether. The two organic extracts were combined, extracted with water, dried, and evaporated under vacuum. The acetate **2d** was crystallized from methanol–water. The first crop, mp 85–85.5° (softening at 83–85°), weighed 242 mg (80%). An infrared spectrum of the crude product was identical with the infrared spectrum of the exo acetate **2d** prepared from the deamination mixture of the amine **1a**. In an analogous experiment, **2d** was crystallized by allowing the crude oil to sit in the refrigerator overnight. Upon recrystallization from methanol–water the acetate **2d**, mp 75–77°, was obtained. The two crystal modifications gave identical infrared spectra in carbon disulfide solution.

Anal. Calcd for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10. Found: C, 81.55; H, 6.23.

Preparation of Dibenzobicyclo[3.2.1]octadien-2-one (5).—A 193-mg (0.87 mmol) sample of the exo alcohol **2c** was heated at 55–60° for 72 hr with 672 mg (4.25 mmol) of potassium permanganate in a solution made from 13 ml of benzene, 8 g of *tert*-butyl alcohol, and 2 ml of water. After destruction of excess permanganate with ethanol, the manganese dioxide was allowed to coagulate and the mixture was filtered; evaporation of the solvent under vacuum gave the crude ketone. Recrystallization from petroleum ether gave 96 mg (51%) of a white solid, mp 114–114.5°. An infrared spectrum taken in carbon disulfide solution (0.03 *M*) showed the carbonyl absorption at 5.87 μ whereas the carbonyl absorption in a KBr pellet was 5.89 μ.

Anal. Calcd for $C_{16}H_{12}O$: C, 87.24; H, 5.49. Found: C, 87.41; H, 5.72.

Preparation of Dibenzobicyclo[3.2.1]octadien-*exo*-2-ol Nitrite (2f).—Our procedure followed those of Barton and Kornblum.[28] Nitrosyl chloride was passed into a solution of exo alcohol **2c** (1.02 g, 4.6 mmol) in 11 ml of anhydrous pyridine (purged with nitrogen) at −20 to −30° for 20 min. The reaction mixture was poured into 50 ml of water and 50 ml of petroleum ether. After separation, the aqueous layer was further extracted with petroleum ether. The petroleum ether extracts were combined and washed with dilute HCl and then water. The solution of the nitrite **2f** was dried ($MgSO_4$) and evaporated to dryness (reduced pressure). Infrared analysis of the crude oily product (1.16 g, 100% yield) showed the characteristic intense 6.1-μ absorption of a nitrite ester. There was no evidence for an O–H stretching absorption or for carbonyl absorption. The crude nitrite **2f** was not crystallized, since it proved to be extremely soluble in all organic solvents. In methanol–water mixtures the nitrite was converted to the exo alcohol **2c**.

Treatment of Exo Nitrite 2f under Deamination Conditions.—Sodium nitrite (2.80 g) was added to a solution of 1.13 g of the crude exo nitrite in 36 ml of dry acetic acid at 20–22°. After 4.5 hr, the reaction mixture was poured into 200 ml of water, extracted with ether, and then worked up in the usual way. An infrared spectrum of the crude product (1.05 g) showed a very large nitrite absorption at 6.1 μ. A 192-mg sample of the crude product was chromatographed on an alumina column (activity I[29] neutral alumina) using carbon tetrachloride and then chloroform (distilled from phosphorus pentoxide). The recovered material (159 mg) was composed of 36–42% nitrite **2f**, approximately 60% exo alcohol **2c**, and 1.5% ketone **5**. A 857-mg sample of the crude product was hydrolyzed to the exo alcohol **2c** in a mixture of 40 ml of 95% ethanol, 10 ml of water, and 10 ml of a 3% hydrochloric acid solution, at 25° for 30 min. Water was added to the solution, and an ether extraction was performed. The product was worked up in the usual manner, resulting in an oily solid weighing 783 mg (103% yield). A synthetic mixture composed of 1.3 mol % of the ketone **5** and 98.7 mol % of the exo alcohol **2c** in carbon disulfide had the same infrared spectrum as did the product.

Dibenzobicyclo[2.2.2]octadien-7-ol *p*-toluenesulfonate (1b) was prepared from a 998-mg (5.3 mmol) sample of *p*-toluenesulfonyl chloride and 1.05 g (4.75 mmol) of alcohol **1c**[5] in 3.5 ml of pyridine. The usual work-up gave 1.64 g (92%) of crude product, from which 1.00 g of **1b**, mp 105–107° dec, was obtained by recrystallization from petroleum ether.

Anal. Calcd for $C_{23}H_{20}SO_3$: C, 73.38; H, 5.36; S, 8.52. Found: C, 73.10; H, 5.69; S, 8.62.

Preparation of the Hydrochloride of 7-Aminodibenzobicyclo[2.2.2]octadiene.—Dry hydrogen chloride was bubbled into a solution of 8.06 g of the amine **1a** in 500 ml of petroleum ether. Filtration gave 8.84 g (94%) of amine hydrochloride, mp 264–267° dec, after recrystallization from water.

Anal. Calcd for $C_{16}H_{18}NClO$ (the monohydrate): C, 69.68; H, 6.58; N, 5.08; Cl, 12.86. Found: C, 69.99; H, 6.51; N, 5.13; Cl, 13.09.

Preparation of Dibenzobicyclo[2.2.2]octadien-7-ylammonium *p*-Toluenesulfonate (1e).—A solution of 1.00 g (4.52 mmol) of amine **1a**, 870 mg (4.57 mmol) of *p*-toluenesulfonic acid monohydrate, and 80 ml of distilled water was distilled until crystals began to reappear. Upon addition of water and cooling, 1.36 g (76%) of **1e** resulted. After drying at 110° for 5 hr, **1e** melted at 285–289°. Repeated crystallizations from hot water gave mp 288–290°. A mixture melting point with exo salt **2e**, mp 288–290°, was depressed to 265–270°.

Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89. Found: 69.65; H, 6.26.

Preparation of Dibenzobicyclo[3.2.1]octadien-*exo*-2-ylammonium *p*-Toluenesulfonate (2e).—*p*-Toluenesulfonate **1b** (1.93 g, 5.13 mmol) was sealed in a Carius tube with 50 ml of anhydrous ammonia and heated at 105–110° for 36 hr. The reaction mixture was cooled and the excess ammonia was evaporated. The residue was dissolved in ether, washed with saturated sodium bicarbonate solution and water, dried ($MgSO_4$), and treated with an excess of dry hydrogen chloride dissolved in dry ether. A white solid, 1.18 g (89%), was collected, mp above 300°. The solid was placed in 5% potassium hydroxide solution and extracted with ether. The combined organic layers were washed

(27) All analyses were run by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(28) (a) D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, **82**, 2640 (1960); (b) N. Kornblum and E. P. Oliveto, *ibid.*, **69**, 465 (1947).

(29) H. Brockmann and H. Schodder, *Chem. Ber.*, **74B**, 73 (1941).

with water and dried ($MgSO_4$) and the solvent was removed to give an intractable oil, which could not be crystallized from Skellysolve B or from methanol–water. The oil was reconverted to the amine hydrochloride and purified by means of the *p*-toluenesulfonate salt by crystallization from a water solution containing an equimolar amount of *p*-toluenesulfonic acid monohydrate. After drying at 110° for 2 hr, **2e** melted at 288–290° dec.

Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89. Found: C, 70.43; H, 5.98.

***N*-Dibenzobicyclo[3.2.1]octadien-*exo*-2-ylacetamide** was prepared from 103 mg (0.40 mmol) of the hydrochloride of **2a** and 3 ml of acetic anhydride in 6 ml of dry pyridine. After 19 hr at room temperature, the solution was poured into 150 ml of water, precipitating 51 mg (49%) of solid. Recrystallization from Skellysolve B–chloroform (95:5) gave white crystals, mp 194–196°.

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.09; H, 6.51. Found: C, 81.93; H, 6.41.

Preparation of 2-Oximinodibenzobicyclo[3.2.1]octadiene (4).—A solution of 1.14 g (5.16 mmol) of the ketone **5**, 2.5 g (36 mmol) of hydroxylamine hydrochloride, 10 g (179 mmol) of potassium hydroxide, and 50 ml of 95% ethanol was heated under reflux for 2 hr and then poured into 650 ml of water. Recrystallization of the air-dried precipitate (900 mg, 74%) from methanol gave **4**, mp 239–240°.

Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57. Found: C, 81.47; H, 5.58.

Preparation of Dibenzobicyclo[3.2.1]octadien-*endo*-2-ylammonium *p*-Toluenesulfonate (3e).—A solution of 1.90 g (8.06 mmol) of oxime **4** in 150 ml of purified tetrahydrofuran was added dropwise to a stirred mixture of 1.20 g (31.6 mmol) of lithium aluminum hydride in 150 ml of tetrahydrofuran. The solution was heated at reflux for 24 hr. Then 30 ml of ethyl acetate was added (caution!). The mixture was evaporated almost to dryness. Methanol (10 ml) was added, then 200 ml of water. The ether solution obtained from three 100-ml extractions was washed with water, dried ($MgSO_4$), and concentrated to 50 ml. Addition of hydrogen chloride dissolved in dry ether gave 1.77 g (85%) of **3a** hydrochloride. Final purification was done *via* the *p*-toluenesulfonate in the usual way. Recrystallization from water and drying at 94° (1 Torr) for 4.5 hr gave **3e**, mp 232–234°. A mixture melting point with the exo salt **2e**, mp 288–290°, was 222–227°.

Anal. Calcd for $C_{23}H_{23}NO_3S \cdot H_2O$: C, 67.13; H, 6.12. Found: C, 67.33; H, 6.12.

***N*-Dibenzobicyclo[3.2.1]octadien-*endo*-2-ylacetamide** was prepared by the procedure used for the preparation of **2a** acetamide. Recrystallization of the precipitate (330 mg, 79%) gave the endo acetamide, mp 183.5–184.5°.

Anal. Calcd for $C_{18}H_{17}NO$: C, 82.09; H, 6.51. Found: C, 81.97; H, 6.50.

Analytical Infrared Procedure.—A differential technique was used,[30] in which mixtures of unknown composition were compared to synthetic mixtures of known composition at the same concentrations. Purified isooctane and carbon disulfide were suitably transparent solvents (0.1 *M* solutions) for this infrared region. For the dibenzobicyclo[3.2.1]octadiene 2-substituted compounds, characteristic absorption maxima were, for ketone **5**, 14.3 and 14.5 μ; endo alcohol **3c**, 14.1 and 16.2 μ; exo alcohol **2c**, 15.7 μ; and exo acetate **2d**, 19.25 μ. Both exo and endo 2-ols had a common peak at 16.65 μ which was very useful for determining total alcohol concentration in a mixture. The product analysis was accurate to ±2%.

Deamination of 1a. Variation I.—Sodium nitrite (8.66 g, 125 mmol) was added to a stirred solution of amine **1a** (7.3 g, 33 mmol) in 100 ml of anhydrous acetic acid over a 1.5-hr period. The crude product, from the usual work-up procedure, was chromatographed on 65 g of activity I[29] neutral alumina. The 14 collected fractions, eluted with purified CCl_4 and then $CHCl_3$, were evaporated under vacuum and the compounds were identified by infrared spectra run on neat samples. The deamination produced 80 mol % of exo acetate **2d**, 19 mol % of exo alcohol **2c**, and 0.2 ± 0.05 mol % of ketone **5**. The ketone per cent was calculated by a quantitative infrared procedure using the 2.78-μ peak of **2c** and that at 5.87 μ for **5**. The ketone composed 10 ± 2% of one fraction which weighed 160 mg. The total recovered eluted products, when converted to the exo alcohol, weighed 7.18 g (98% yield).

Deamination of 1a. Variation II.—Using the same general procedure as before, a 1.02-g (4.61 mmol) sample of **1a** was dissolved in 36 ml of dry acetic acid. To this stirred solution was added 318 mg (4.61 mmol) of sodium nitrite in portions over a 40-min period. The crude product weighed 442 mg. The aqueous reaction mixture was then made strongly basic with a 6 *M* potassium hydroxide solution and extracted with ether. The ether solution was washed thoroughly with water, dried ($MgSO_4$), and evaporated. By this procedure, 558 mg of the amine **1a**, mp 101.5–104°, was isolated. The differential infrared analysis method (*vide supra*) showed that the deamination product was composed of 25% of **2c** and 75% of **2d**. Absence of any absorption at 6.1 μ showed that no nitrite **2f** was present.

Deamination of 1a. Variation III.—In this series of experiments **1a** was treated with sodium nitrite in acetic acid with varying amounts of water present. The product composition was determined by integration of proton magnetic resonance spectra, using the endo proton on C-2 of the **2c**, **2d**, and **2f** present in the crude product mixture dissolved in $CDCl_3$.[7] A Jeol C60-HL spectrometer was used for the analysis. The doublet present at τ 3.77 was taken as indicating the presence of **2f**. Seven pmr integrations were made on the spectrum of each product mixture. Analytical results recorded in Table II were precise to better than ±1%. The composition of a known mixture of **2c** and **2d** could be determined to within 1% of the actual value. In each product mixture 12 ± 2 mol % **2f** was indicated. Thus, the deamination of **1a** in glacial acetic acid, shown as giving 24% **2c** in Table II, led to 21% alcohol **2c**, 66% acetate **2d**, and 13% nitrite **2f**.

Deamination of 1e.—A solution of **1e** (187 mg, 0.48 mmol), which had been dried for 1 hr at 150°, in 10 ml of dry acetic acid was treated with 320 mg (4.64 mmol) of sodium nitrite over a 10-min period. Differential infrared analysis of the product showed the presence of 24 mol % of **2c** and 70 mol % of **2d**. Comparison of peak height at 6.15 μ with the peak height of a sample of known concentration suggested the presence of about 1% **2f**.

Deamination of 2e.—A solution of 124 mg (0.315 mmol) of this salt (dried for 1 hr at 150°) in 8.0 ml of acetic acid was treated with 200 mg (3.18 mmol) of sodium nitrite under the usual conditions. Work-up gave 67 mg of yellow oil. Differential infrared analysis demonstrated the presence of 24 mol % of [3.2.1] alcohol. Infrared peak positions indicated that the alcohol was exo, and that the rest of the product was exo acetate **2d**. A small amount of nitrite (1–2%) was present.

Deamination of 3e.—The monohydrate of **3e** (241 mg, 0.585 mmol) was converted to **3e** by addition and distillation of benzene (100 ml). Glacial acetic acid (12 ml) was added and the solution was treated as usual with 400 mg (5.80 mmol) of sodium nitrite. The yellow, oily product weighed 151 mg. Differential infrared analysis showed the *total* alcohol content (using only the exo epimer in the synthetic mixture) to be 12 mol %. Chromatography of 126 mg of the deamination product on 5.0 g of activity I alumina[29] in carbon tetrachloride and then chloroform gave 115 mg (88 mol %) of **2d**, containing about 1% of nitrite, and 13.3 mg (12 mol %) of [3.2.1] alcohols. Differential infrared analysis showed the content of this total alcohol portion to be 24% **3c** and 76% **2c**. A duplicate experiment, beginning with 100 mg of **3e**, gave a total [3.2.1] 2-ols content of 12 mol %, which was 21% **3c** and 79% **2c**.

Deamination of 3e in the Presence of Added Water.—A mixture of 100 mg (0.24 mmol) of the monohydrate of **3e**, 47.3 mg (2.63 mmol) of distilled water, and 5.0 ml of glacial acetic acid was treated with 175 mg (2.54 mmol) of sodium nitrite under the usual conditions. Differential infrared analysis of the oily product, 54 mg, gave the total [3.2.1] alcohol content to be 12%. The alcohols were separated from the acetate by chromatography (*vide supra*) and shown by differential analysis to contain 18 ± 6% **3c** and 82 ± 6% **2c**.

Solvolysis of Dibenzobicyclo[2.2.2]octadien-7-ol *p*-Toluenesulfonate (1b) in Acetic Acid.—A solution of **1b** (102 mg, 0.271 mmol) and 26.1 mg (0.318 mmol) of anhydrous sodium acetate in 2.18 ml (38.1 mmol) of dry acetic acid/0.026 ml (1.44 mmol) of distilled water was stirred at room temperature for 359 hr. Ether extraction of a 1.0-ml sample in 20 ml of water and the usual work-up followed. The remaining reaction mixture was

(30) (a) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis," 3rd ed, Macmillan, New York, N. Y., 1952, p 632; (b) using a Perkin-Elmer Model 137 infrared spectrophotometer fitted with potassium bromide optics.

stirred at room temperature for a complete reaction time of 432 hr. Normal isolation procedures, using pentane extraction, were used. Product composition of these two solvolysis fractions was determined by differential infrared analysis. The former contained 11 mol % of **2c**, 84.5 mol % of **2d**, and 4.5 mol % of **1b**. Similarly, the product of the solvolysis reaction (after 432 hr) contained 15 mol % of **2c**, 83 mol % of **2d**, and 2 mol % of **1b**.

Registry No.—**1a** HCl, 35079-81-3; **1b**, 2975-83-9; **1e**, 35079-83-5; **2c**, 837-65-0; **2d**, 35079-85-7; **2e**, 35079-86-8; **2f**, 35079-87-9; **3e**, 35079-88-0; **4**, 2969-43-9; **5**, 2198-06-3; *N*-dibenzobicyclo[3.2.1]octadien-*exo*-2-ylacetamide, 35079-91-5; *N*-dibenzobicyclo[3.2.1]octadien-*endo*-2-ylacetamide, 35079-92-6.

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Synthesis of 1,2-Dialkylcyclopropenes, Methyl Malvalate, and Methyl Sterculate[1a]

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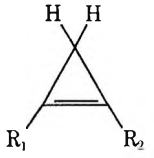
Dipropyl-, dipentyl-, dihexyl-, diheptyl-, and dioctylcyclopropene and methyl malvalate and sterculate have all been synthesized. Ethyl diazoacetate is decomposed in the presence of the appropriate alkyne, followed by hydrolysis to yield a 1,2-disubstituted 3-cyclopropenecarboxylic acid. Exposure to perchloric acid results in decarbonylation to a cyclopropenium ion, which is reduced by sodium borohydride to a 1,2-disubstituted cyclopropene. The absence of any 1,3-disubstituted cyclopropene in the product is consistent with theory. Spectroscopic data is presented. The cyclopropenethiol reaction is discussed.

The 1,2-disubstituted cyclopropene function occurs in the fatty acid chain of lipids from certain plants belonging to the order Malvales, cottonseed oil being the most common. These cyclopropenoid fatty acids have recently been the subject of intense investigation and are held responsible for numerous physiological disorders in farm and laboratory animals.[1]

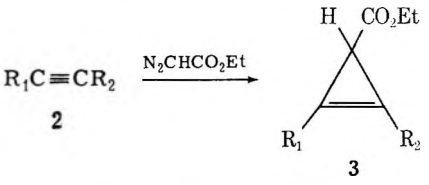
Results

We have developed a synthesis to produce 1,2-disubstituted cyclopropenes (**1**) in quantities for biological testing and feedings. Gensler and coworkers[2] have reported a comparable route to **1f** and **1g**.



1a, $R_1 = R_2 =$ propyl
b, $R_1 = R_2 =$ pentyl
c, $R_1 = R_2 =$ hexyl
d, $R_1 = R_2 =$ heptyl
e, $R_1 = R_2 =$ octyl
f, $R_1 =$ octyl, $R_2 = -(CH_2)_6CO_2Me$ (methyl malvalate)
g, $R_1 =$ octyl, $R_2 = -(CH_2)_7CO_2Me$ (methyl sterculate)

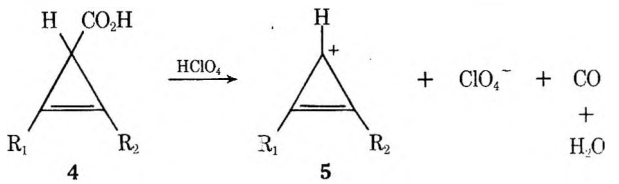
Ethyl diazoacetate, in the presence of a copper catalyst, adds to disubstituted acetylenes (**2**) yielding 1,2-disubstituted cyclopropene-3-carboxylates (**3**).[3] In the



present investigation, alkynes are 40–50% converted to the corresponding cyclopropene by an equal molar amount of diazoacetate. About 90–95% of the unreacted acetylenic compound can be recovered, reflecting the rather high selectivity of the carboxylcarbene. Other workers[2] report a 60–70% conversion for this identical reaction.

All the resulting 1,2-dialkyl-3-carboxylcyclopropenes can be purified by high vacuum distillation (5×10^{-2} mm), with the exception of one, methyl 9,10-(carboxymethano)-9-octadecenate (**3g**), the precursor for sterculate (**1g**). However, unreacted methyl stearolate (**2g**) can be recovered from this latter product by vacuum distillation without significant decomposition of the desired cyclopropene, thus facilitating purification on a column.

After hydrolysis, treatment of the 1,2-disubstituted cyclopropene-3-carboxylic acid (**4**) with strong mineral



acid in acetic anhydride results in decarbonylation[4] to the corresponding cyclopropenium ion (**5**). Cyclopropenium perchlorates are less soluble and easier to purify than the fluoroborates or bromides; therefore, we chose to work with the perchlorates. Mixtures of

(1) (a) Technical Paper No. 3196, Oregon Agricultural Experiment Station; (b) A. M. Abou-Ashour and H. M. Edwards, *J. Nutr.*, **100**, 1347 (1970); (c) W. E. Donaldson and B. L. Fites, *ibid.*, **100**, 605 (1970); (d) S. V. Dande and J. F. Mead, *J. Biol. Chem.*, **245**, 1856 (1970); (e) D. J. Lee, J. H. Wales, and R. O. Sinnhuber, *J. Nat. Cancer Inst.*, **43**, 1037 (1969); (f) R. A. Phelps, *et al.*, *Poultry Sci.*, **44**, 358 (1965); (g) A. M. Miller, E. T. Sheehan, and M. G. Vavich, *Proc. Soc. Exp. Biol. Med.*, **131**, 61 (1969).

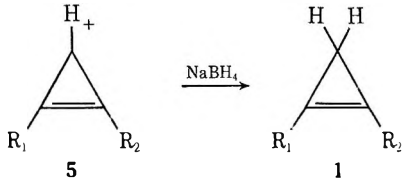
(2) (a) W. J. Gensler, *et al.*, *J. Amer. Chem. Soc.*, **91**, 2397 (1969); (b) *ibid.*, **92**, 2472 (1970); (c) *J. Org. Chem.*, **35**, 2301 (1970); (d) *Chem. Phys. Lipids*, **6**, 280 (1971).

(3) (a) I. A. D'Yakonov, *et al.*, *Zh. Org. Khim.*, **5**, 1742 (1969); *Chem. Abstr.*, **77**, 124556 (1970); (b) *Zh. Obshch. Khim.*, **29**, 3848 (1959); *Chem. Abstr.*, **54**, 195216 (1960); and references cited therein.

(4) (a) R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **83**, 2367 (1961); (b) R. Breslow, *et al.*, *ibid.*, **83**, 2375 (1961); (c) R. Breslow and P. Dowd, *ibid.*, **85**, 2729 (1963); (d) R. Breslow, H. Hover, and H. W. Chang, *ibid.*, **84**, 3168 (1962).

pentane–anhydrous ether at −20° will precipitate dipropyl-, dipentyl-, and dihexylcyclopropenium ions as solids, but in poor yields. Mixtures of chloroform–pentane precipitate all the cyclopropenium ions studied as thick, red-black oils, but in rather good yields.

Reduction[4,5] of 1,2-disubstituted cyclopropenium ions (**5**) can be accomplished with almost any hydride.



5 **1**

The problem lies in finding an unreactive solvent which will dissolve both the cyclopropenium ion and hydride at low temperatures. Seventeen per cent dimethyl ether of ethylene glycol or 20% pyridine in dimethyl sulfoxide proved to be satisfactory solvents for this reduction with sodium borohydride. The yields of **1** from decarbonylation followed by reduction are variable, but average about 55%. The reduction product consistently carries with it 4–8% of the corresponding dialkyl acetylene. When solid 1,2-dipropylcyclopropenium perchlorate was recrystallized followed by reduction, the product still contained 8% 4-octyne, demonstrating that the alkyne was not carried over from starting materials. Failure to separate the cyclopropenium perchlorate from the acetic anhydride solution before adding it to the hydride solution shifts an alkyne to cyclopropene ratio to 60% alkyne.

The products have all the chemical and spectroscopic[6] properties expected for 1,2-dialkylcyclopropenes. Synthetic malvalate and sterculate are identical in every respect with the acids isolated from natural sources. The infrared, nmr, and mass spectra of the naturally occurring esters are superimposable with those of the synthetic esters. Infrared bands attributable to the cyclopropene ring occur at 1875 and 1005 cm^{-1} for all 1,2-dialkylcyclopropenes, including methyl malvalate and sterculate.

The nmr shows a triplet centered around τ 7.66 for the two methylene groups attached to the 1 and 2 positions of the ring. The ring methylene hydrogens resonate in a single sharp peak in the area of τ 9.28–9.12, depending upon solvent. Solutions of CCl_4 and CCl_4 mixed with the polar solvents methanol or acetonitrile result in absorption farthest upfield. Adding chloroform results in a small (2 cps on a HA-100 instrument) shift downfield, while adding benzene shifts these two protons 10 cps downfield to τ 9.18. Pyridine–CCl_4 shifts the ring methylene protons farthest downfield, τ 9.12, while slightly shifting the center of the methyl triplet upfield 3 cps to the same frequency. Surprisingly, running a solution of **1a** neat also shifts the ring methylene protons downfield, to τ 9.18. Changes in chemical shift of protons on a saturated carbon have been observed in other systems and are attributed to *collision complexes.*[7]

(5) D. T. Longone and D. M. Stehouwer, *Tetrahedron Lett.*, 1017 (1970).

(6) (a) G. L. Closs in "Advances in Alicyclic Chemistry," H. Hart and G. J. Karabatsus, Ed., Academic Press, New York, N. Y., 1966, Chapter 2; (b) C. Y. Hopkins, *J. Amer. Oil Chem. Soc.*, **45**, 773 (1968).

(7) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, pp 111–113 and 246–248.

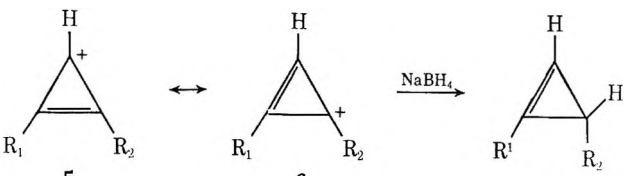
The mass spectra of all the compounds studied are consistent with the 1,2-disubstituted cyclopropene structure. All the 1,2-dialkylcyclopropenes, including methyl malvalate and sterculate, have a base peak of mass 81. Peaks with mass numbers 41, 67, and 95 are intense in all the spectra. In addition, **1e**, **1f**, and **1g** have strong peaks at mass numbers 43 and 55. Doering and Mole[8] report the parent minus one, mass 67, as the base peak for 1,2-dimethylcyclopropene and suggest that it may correspond to the 1,2-dimethylcyclopropenium ion, formed in greatest abundance by virtue of its special aromatic character. None of our spectra show any trace of a parent minus one mass peak.

All 1,2-disubstituted cyclopropenes reported here give a strong Halphen reaction.[9] However, the secondary band[9b] at 540 mμ is absent, producing more of an orange color for the synthetic compounds. Also, the synthetic compounds assay in excess of 100% compared to natural oils as standards. It is well recognized that the Halphen reaction of natural oils varies with the source and concentration of the cyclopropenoid fatty acid being tested.[9]

There are reports of a spontaneous addition of mercaptans across the strained double bond of 1,2-disubstituted cyclopropenes.[10] Raju and Reiser[11] describe the reaction as an assay method for the cyclopropenoid function in natural oils, but Coleman[9a] and Schneider[12] report that the reaction is not reproducible. We have found that, under an atmosphere of purified nitrogen, methyl mercaptan in benzene does not react with 1,2-dialkylcyclopropenes, even when a large excess of the thiol is left in contact with the olefin at room temperature for several days. Upon the introduction of oxygen, a free-radical initiator, methyl thiol rapidly adds across the double bond of **1b** to form a sulfide (thio ether) in quantitative yield.

The additions of sulfhydryl groups to olefins are well-known reactions involving acidic, nucleophilic, free radical, and photolytic catalyst.[13] It is neither surprising nor unique that they will add to cyclopropenes. We are studying the competition between sterculate and other fatty acids for thiol radicals, hoping to shed light on the reactivity of thiol radicals in biological systems.

There is a distinct possibility that reduction of **5** could lead to **7** as well as **1**. Nmr spectroscopy of the product[1] clearly shows no trace of vinylic hydrogens in



5 **6** **7**

(8) W. Doering and T. Mole, *Tetrahedron*, **10**, 65 (1960).

(9) (a) E. C. Coleman, *J. Ass. Offic. Anal. Chem.*, **53**, 1209 (1970); (b) A. V. Bailey, *et al.*, *J. Amer. Oil Chem. Soc.*, **42**, 422 (1965); (c) T. W. Hammonds, *et al.*, *Analyst*, **96**, 659 (1971).

(10) (a) H. W. Kircher, *J. Amer. Oil Chem. Soc.*, **41**, 4 (1964); (b) H. G. Reilich, *et al.*, *ibid.*, **46**, 305 (1969); (c) R. L. Ory and A. M. Altschul, *Biochem. Biophys. Res. Commun.*, **17**, 12 (1964).

(11) P. K. Raju and R. Reiser, *Lipids*, **1**, 10 (1966).

(12) E. L. Schneider, *J. Amer. Oil Chem. Soc.*, **45**, 585 (1968).

(13) (a) E. N. Prilezhaeva and M. F. Shostakovskii, *Russ. Chem. Rev.*, **32**, 399 (1963); (b) F. W. Stacey and J. F. Harris, Jr., "Organic Reactions," Vol. 13, A. C. Cope, Ed., Wiley, New York, N. Y., 1963, Chapter 4; (c) W. E. Vaughan and F. F. Rust, *J. Org. Chem.*, **7**, 472 (1942).

the area of τ 2.99 as would be expected for **7**.[14] Breslow and coworkers[4d] report three equivalent propyl groups in the nmr spectrum of tripropylcyclopropenyl perchlorate, indicating that the positive charge is evenly distributed around the ring. Also, the propyl groups in the three cations, tripropylcyclopropenyl, dipropylcyclopropenyl, and propyldiphenylcyclopropenyl perchlorate, are relatively shifted to the same extent. Differences in chemical shift between the α- and β-methylene hydrogens are very similar for the propyl groups in each of these three cations.[4d] This data supports the concept that each carbon of the cyclopropenyl cation has a similar charge structure, with essentially one-third of the charge at each ring carbon.

Our failure here to detect any **7** (less than 1%) from the reduction of **5** does not conflict with Breslow's picture of charge distribution in a cyclopropenyl perchlorate. An attacking nucleophile would certainly attack the unsubstituted position of a cyclopropenium ion more rapidly than at a position substituted with a large alkyl group. A satisfactory model to compare the relative steric effect of substituents on an organic ion during a bimolecular reaction is not available. However, bimolecular displacement reactions (SN2) have been extensively investigated and can be used to demonstrate a large rate-retarding effect when substituents are attached directly to the reacting carbon.[15] For example, methyl chloride reacts with iodide ion in acetone (a pure SN2 reaction) 180 times more rapidly than does *n*-butyl chloride. From a tabulation of some second-order displacements, methyl halides react 11 to 145 times more rapidly than their ethyl counterparts, and the few butyl halides listed react from two to four times more slowly than the ethyl compounds.[15] The bimolecular displacements of some α-substituted benzyl halides show a comparable rate-retarding effect.[15]

Competition factors, k_Y/k_o, measure the ability of a nucleophile Y to compete with water for a carbonium ion. Triphenylmethyl cation shows marked competition factors, 2.8×10^5 for azide ion in 50% aqueous acetone and 5.3×10^4 for hydroxide ion.[15] One expects an ion to become more discriminating as its stability increases. Dipropylcyclopropenium cation,[4d] $pK_{R^+} = 2.7$, is considerably more stable than triphenylmethyl cation,[16] $pK_{R^+} = -6.63$, and should show a correspondingly larger selectivity in its reactions with nucleophiles. The combination of ion selectivity with 1 and 2 substituents accounts for reduction exclusively at the 3 position.

Experimental Section

Synthesis of 1,2-Dialkylcyclopropenes and Methyl Malvalate and Sterculate.—The appropriate alkyne was placed in a flask under an atmosphere of nitrogen with a magnetic stirrer and freshly activated copper dust (approximately 4 g of copper per mole of alkyne). While the flask was immersed in an oil bath at 110–120°, an equal molar amount of ethyl diazoacetate was added slowly enough (while stirring rapidly) so that foaming did not prevent the diazoacetate from dropping directly into the liquid. After the addition was complete, unreacted alkyne was recovered by vacuum distillation followed by vacuum distillation of the ethyl 1,2-dialkyl-3-cyclopropenecarboxylate, except in the synthesis of methyl sterculate. Unreacted methyl stearolate can be recovered from its ethyl diazoacetate adduct, ethyl 1-octyl-2-(7-carbomethoxylheptyl)-3-cyclopropenecarboxylate (**3g**), by vacuum distillation, but the complex cyclopropene itself cannot be distilled without extensive thermal decomposition. The methyl stearolate–ethyl diazoacetate adduct is best separated from polydiazoacetate by column chromatography, preferably on an acid-washed alumina column eluting with pentane–ether. Table I lists the boiling points of some alkynes, their ethyl diazoacetate adducts, and the corresponding 1,2-dialkylcyclopropenes.

Table I

Distillation Temperatures and Pressures

1,2 Substituent	Acetylene temp, °C (mm)	Ethyl 3-cyclopropene carboxylate temp, °C (mm)	Cyclopropene temp, °C (mm)
Dipropyl	66 (70)	96 (0.25)[a]	
Dipentyl	55 (0.4)	100 (0.25)	
Dihexyl	68 (0.05)	122 (0.15)	73 (0.05)
Diheptyl	114 (0.1)	135 (0.13)	92 (0.04)
Dioctyl	116 (0.02)	135 (0.09)	107 (0.02)
1-Octyl-2-(7-carbomethoxyheptyl)	114 (0.025)	134 (0.025)	125 (0.03)
	128 (0.15)	159 (0.15)	
1-Octyl-2-(6-carbomethoxylhexyl)	155 (0.15)	Decomposes	136 (0.04)

[a] 3-Cyclopropenecarboxylic acid.

Ester hydrolysis was carried out with 2 equiv of 10% potassium hydroxide in 1-propanol. After heating at 100° for 2 hr under N_2, the solution was diluted, adjusted to pH 4, and extracted with ether. The extract was dried and evaporated.

Treatment of the 1,2-disubstituted 3-cyclopropenecarboxylic acid with an equal molar amount of perchloric acid in acetic anhydride (1 g of 70% perchloric acid per 10 g of cold acetic anhydride) decarbonylated it to a 1,2-disubstituted cyclopropenium perchlorate. The decarbonylation may be carried out at room temperature with the dialkyl compounds, but fatty acid percursors must be chilled to below 10°. Decarbonylation was allowed to proceed until gaseous evolution diminished. The entire cyclopropenium perchlorate–acetic anhydride solution was transferred to a large separatory funnel containing chloroform at −20°, and pentane, at the same temperature, was added until a black oil precipitates. Generally, one used 10 ml of cold chloroform for each gram of 70% perchloric acid used, and 70 ml of cold pentane was added. After the black oil was separated, which is mostly cyclopropenium perchlorate, more cold pentane was added and the separatory funnel was allowed to sit at −20° to ensure complete precipitation.

To form the hydride solution, 100 ml of dimethyl sulfoxide, 20 ml of 1,2-dimethoxyethane or 20 ml of pyridine, and 5 g of sodium borohydride were mixed under an inert atmosphere, warmed to dissolve the borohydride, and then cooled to 5–7°; lower temperatures cause sodium borohydride to precipitate. While the hydride solution was rapidly stirred, the cold black oil, 1,2-disubstituted cyclopropenium perchlorate, was slowly added. Too rapid of an addition caused formation of side products, mainly the corresponding alkyne. During the addition of fatty acids, foaming can be arrested by an immiscible layer of pentane over the hydride solution.

After dilution with a large volume of water, neutralization, and extraction with pentane, the 1,2-dialkylcyclopropenes can be distilled (see Table I for distillation data) and/or column chromatographed, eluting with pentane or hexane. The cyclopropene was always eluted before its corresponding alkyne. Acid-washed alumina only partially separated the alkynes from the desired cyclopropenes. Silica gel column gave better separation but a small per cent of the strained ring compound was lost on the column, and although gas chromatography and spectroscopic examination may show the product to be pure, it did not store well and developed a yellow color after several weeks at −20°.

Malvalic and sterculic acids should be converted to esters before further purification or storage, since they are not as stable in the acid form. Esterification may be accomplished with diazomethane or by dissolving the acid in methanol. Esterification of malvalic or sterculic acids in methanol with an acid catalyst leads to the destruction of the cyclopropene function.[17] Chromatogra-

(14) K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **83**, 1226 (1961).

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

(16) N. Deno, *J. Amer. Chem. Soc.*, **77**, 3047 (1955).

(17) J. R. Nunn, *J. Chem. Soc.*, 313 (1952).

phy of these esters was accomplished on acid-washed alumina or silica gel eluting with pentane, gradually changing to pentane–ether.

All compounds possessed the expected spectral properties as described in the text.

Alkynes. Methyl stearolate was prepared from oleic acid by a procedure similar to that reported by Butterfield and Dutton.[18] Gunstone and Hornby[19] report a procedure, which may be superior, utilizing liquid ammonia. A small molar excess of liquid bromine was added to methyl oleate in the dark until the red bromine color persisted for 1 hr. Excess bromine was removed on a vacuum evaporator. The dihalide acid was added to 30% KOH in ethylene glycol (6 mol of KOH per mole of acid) and heated at 206° under an atmosphere of nitrogen for 4 hr. Dilution, acidification, and extraction with hexane was followed by esterification in methanol–1% sulfuric acid. Vaccum distillation afforded a clear oil in 70% yield, bp 155° (0.15 mm). Spectroscopic and physical properties of acetylinic esters are rather passive. Retention on a diethylene glycol succinate column was considerably longer than for methyl oleate and a 300-ft butanediol succinate capillary column showed a single unsplit peak. Absorption in the infrared was at 2940, 2845, 1750, 1470, 1445, 1375, 1260, 1200, and 1178 cm^{-1}. The nmr showed no vinylic hydrogens and two overlapping triplets centered around τ 7.9.

Methyl 9-heptadecynoate was synthesized by the method of Ames and Covell.[20] Sodamide (52 g) and 178 g of 1-decyne were dissolved in 4.5 l. of liquid ammonia. After 1 hr, 67 g of 7-bromoheptanoic acid was dissolved in a mixture of tetrahydrofuran and glyme and slowly added. The liquid ammonia was allowed to evaporate, and dilution and acidification was followed by extraction with ether. Esterification was accomplished in methanol–1% sulfuric acid. Vacuum distillation yielded 48 g of a clean oil, bp 114° (0.025 mm). Infrared absorption appeared at 2940, 2845, 1750, 1470, 1445, 1375, 1260, 1200, and 1178 cm^{-1}. The nmr shows no vinylic hydrogens and overlapping triplets at τ 7.9. The mass spectrum shows a parent at m/e 280.

1,2-Dialkylacetylenes.—The lower homologs can be purchased from the Chemical Sample Co., Columbus, Ohio. Other alkynes were synthesized by adding the appropriate alkyl bromide to sodium acetylide in liquid ammonia. After work-up and purification the resultant 1-alkyne was added to 1 equiv of sodamide (50 g per 4 l. of NH_3) in liquid ammonia followed by addition of 1 equiv of the appropriate alkyl bromide. Distillation data is contained in Table I. Yields of the higher molecular weight alkynes are low, 50% for 9-octadecyne based on 1-decyne.

Attempts to synthesize these alkynes from the appropriate Grignard reagent and 1,4-dichloro-2-butyne (Aldrich) proved unsatisfactory.

7-Bromoheptanoic Acid.—One gram-atom of metallic sodium was dissolved in 400 ml of absolute ethanol followed by the addition of 1.05 mol of diethyl malonate. This solution was stirred for 30 min by a strong mechanical stirrer, then added to a freshly prepared solution of 1.25 mol of 1,5-dibromopentane in 100 ml of absolute ethanol. Reaction was exothermic and sodium bromide precipitated. The solution was diluted with a large volume of water and extracted with chloroform. The extract was dried and evaporated. The product was refluxed in 250 ml of acetic acid and 50 ml of sulfuric acid for 1 day, with a warm condenser allowing ethyl acetate to escape. Dilution, extraction, and distillation yielded 7-bromoheptanoic acid in 53% yield, bp 105° (0.08 mm), mp 27–30° [lit.[21] bp 140–142° (1.5 mm), mp 28–29°].

Registry No.—**1c**, 35365-52-7; **1d**, 35365-53-8; **1e**, 1089-40-3; **1f**, 5026-66-4; **1g**, 3220-60-8; **2a**, 1942-45-6; **2b**, 6975-99-1; **2c**, 35216-11-6; **2d**, 19781-86-3; **2e**, 35365-59-4; **2f**, 24471-20-3; **2g**, 1120-32-7; **3b**, 35365-62-9; **3c**, 35365-63-0; **3d**, 35365-64-1; **3e**, 35365-65-2; **3f**, 35365-66-3; **3g**, 30689-71-5; methyl 9-heptadecynoate, 25601-39-2; 3-cyclopropenecarboxylic acid 26209-00-7.

Acknowledgment.—This work was supported in part by Public Health Service Grants ES 00263 and ES 00256 from the Division of Environmental Health Sciences.

(18) R. O. Butterfield and H. J. Dutton, *J. Amer. Oil Chem. Soc.*, **45**, 635 (1968).

(19) F. D. Gunstone and G. M. Hornby, *Chem. Phys. Lipids*, **3**, 91 (1969).

(20) D. E. Ames and A. N. Covell, *J. Chem. Soc.*, 775 (1963).

(21) D. E. Ames, R. E. Bowman, and R. G. Mason, *J. Chem. Soc.*, 174 (1950).

Grignard Reagents from Bromobenzo[*h*]quinolines. 13-Substituted Derivatives of 20-Chloronaphtho[2′,1′:12,13](2,4)pyridinophane[1,2]

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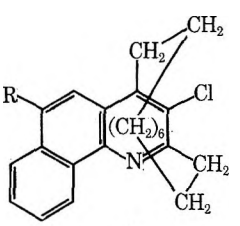
While Grignard reagents are not generally useful intermediates for synthetic conversions in quinoline systems, they are shown to be quite useful in the naphthopyridinophane series (**3**), and to a lesser, but practical extent, useful with 2-alkylbenzo[*h*]quinolines such as **9b**. The stability and utility of such Grignard reagents is not related to decreased acidity of the benzyl bridge methylene groups in **3**, since no metal exchange was noted for the dimethyl analog **9b**. Symmetrical coupling can become the major reaction of Grignard reagents in the benzo[*h*]-quinoline system, as observed for **6**. While the mechanism of this coupling is not known, the lack of coupling parallels steric hindrance at the azomethine linkage. A variety of 13-substituted derivatives of 20-chloronaphtho[2′,1′:12,13][10](2,4)pyridinophane have been prepared and one of these (**3i**) was found to be active (curative at 640 mg/kg) against *Murine Plasmodia–Plasmodium berghei*.

The initial objective of this work was to prepare certain 13-substituted derivatives of 20-chloronaphtho-[2′,1′:12,13][10](2.4)pyridinophane[3] (**3**, Table I),



3

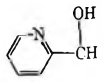
specifically the two diastereomeric[3] racemates corresponding to **3g** and **3i** which were of interest as agents against murine malaria. The replacement of aromatic bromine by functional groups of the type shown in **3g** and **3i** has been studied in detail and is usually accom-

(1) Supported by U.S. Army Medical Research Command, DADA-17-70-C-0008. This paper is contribution no. 1048 from the Army Research Program on Malaria.

(2) The methylene-bridged aromatic compounds in this study are named using the rules described by B. H. Smith in "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964. There does not exist a universally accepted method for the naming of such compounds; *cf.* F. Vogtle and P. Newmann, *Tetrahedron*, **26**, 5847 (1970). *Chemical Abstracts'* name for **3b**, for example, is 15-bromo-20-chloro-3,4,5,6,7,8,9,10,11,12-decahydro-2,13-metheno-13*H*-1-naphtho[1,2-*b*]azacyclopentadecene.

(3) (a) The pyridinophane ring is asymmetric since the methylene bridge cannot flip to the opposite face. *Cf.* W. E. Parham, R. W. Davenport, and J. B. Biasotti, *Tetrahedron Lett.*, 557 (1969); (b) W. E. Parham, R. W. Davenport, and J. K. Rinehart, *J. Org. Chem.*, **35**, 2662 (1970).

TABLE I

3	R	Mp, °C	Composition within 0.3% of calcd value for	Isolated yield	$\nu_{900-760}$, cm^{-1}
a	H	129–131	C, H, N	71% from indole	870 (m), 812 (s), 792 (s), 750 (s)
b	Br	197–198, 200–201.5[a]	C, H, N	To 91%[b] from indole	760 (s)
c	CN	231–232	C, H, N, Cl	82–100% from **3b**	900 (w), 760 (s)
d	C(=O)CH$_3$	212.5–214	C, H, N	57% from **3c** 70% from **3n**	890 (w), 880 (w), 768 (s)
e	C(=O)CH$_2$Br	207–208	C, H, N, Cl, Br	88% from **3d**	770 (m), 760 (s)
f	C(=O)CH$_2$N(C$_7$H$_{15}$)$_2$	Unstable		~100%	
g	CH(OH)CH$_2$N(C$_7$H$_{15}$)$_2$	(a) 130–131[d] (b) Oil	C, H, N, Cl C, H, N, Cl	~100%[b,d]	(a) 898 (m), 860 (s) (b) 894 (w), 880 (w), 800 (m), 762 (s)
h	C(=O)CH$_2$N(C$_4$H$_9$)$_2$	Unstable		~100%	
i	CH(OH)CH$_2$N(C$_4$H$_9$)$_2$	Mixed racemates, oil	C, H, N	80%	750 (s)
j		147–149	C, H, N	*f*	862 (s), 818 (m), 770 (s), 750 (s)
k		(a) 173–186 (b) 174–176	C, H, N	100%[e]	(a) 830 (w), 770 (m) (b) 828 (w), 785 (w), 760 (s)
l	COOH	280–282	C, H, N, Cl	33–54% from **3c** 82–100% from **3n**	790 (s), 750 (s)
m	C(=O)Cl	202–206	C, H, N	48%[g]	900 (w), 830 (m), 810 (m), 770 (s)
n	–MgBr	Not isolated			
o	–C(=O)CHBr$_2$	164	C, H, N	12%[c]	888 (w), 782 (m), 758 (m), 750 (m)

[a] After sublimation. [b] See Experimental Section. [c] By-product from **3e**. [d] Two racemic diastereomers formed in equal amounts, separated by crystallization. [e] The two diastereomeric racemates were formed in approximately equal amounts. [f] 20% as by-product in formation of **3k** when excess aldehyde is employed with **3n**. [g] From **3l** and $SOCl_2$ in benzene, $\nu_{C=O}$ 1762 cm^{-1}.

plished by a series of reactions corresponding to **3b** → **3c** → **3e** → **3f** → **3g**.[4,5]

Substituted pyridines and quinolines are conveniently prepared by reaction of the appropriate pyrrole[6] or indole[3] with reagents which effect transfer of CCl_2. We have now extended this procedure to benzo[*g*]indoles, and high yields of the benzo[*h*]quinolines **3a** (71%), **3b** (64–90%), **4** (60%), and **9b** (63%), and the related quinoline **5** (41%) were obtained by procedures similar to that shown in Scheme I.

The series of reactions outlined above, starting with **3b** leading to the two diastereomeric racemates **3g** and to the mixed racemates of **3i**, were optimized and were effected in high yields (see Experimental Section). The mixed racemates **3i**[7] was found to be curative in murine malaria at 640 mg/kg; interestingly, neither of the racemic pairs of **3g** showed activity.

In view of the significant activity observed for **3i**, we were interested in developing a shorter synthesis for ketone intermediates of type **3d** in the benzo[*h*]quinoline series and we have, accordingly, studied formation of Grignard reagents from the bromobenzo[*h*]-quinolines **3a**, **9b**, and **6**, and the bromoquinoline **5**.

Although some success has been realized by entrainment procedures for the preparation and subsequent reactions of Grignard reagents in the pyridine series,[8,9–10] Grignard reagents have not been useful intermediates for functional group interchange in the quinoline series.[10,11] This latter result is not surprising since it is known that phenylmagnesium bromide reacts slowly in ether at room temperature[12] and more rapidly[13] in ether–dioxane at room temperature to give 2-phenylquinoline. In addition, Grignard[14] and aryllithium[15] reagents react with 2- and 4-alkylquinolines, as shown in Scheme II.

In our studies with benzo[*h*]quinolines, the heterocycle, magnesium turnings, and tetrahydrofuran were heated at the reflux temperature; then a solution of 1,2-dibromoethane was added slowly over a 2-hr period.[16]

6-Bromobenzo[*h*]quinoline (6).—The quinoline **6** was treated with magnesium as described above, and the mixture was subsequently treated with carbon

(4) K. N. Campbell, C. H. Helbing, and J. F. Kerwin, *J. Amer. Chem. Soc.*, **68**, 1840 (1946).

(5) For alternative schemes see (a) R. E. Lutz, *et al.*, *ibid.*, **68**, 1813 (1946); (b) S. Winstein, *et al.*, *ibid.*, **68**, 1831 (1946); (c) K. N. Campbell and J. F. Kerwin, *ibid.*, **68**, 1837 (1946); (d) K. N. Campbell, *et al.*, *ibid.*, **68**, 1844 (1946).

(6) R. L. Jones and C. W. Rees, *J. Chem. Soc.*, 2249 (1969).

(7) Information received from Walter Reed Army Institute of Research; compound to test animal body weight.

(8) J. Overhoff and W. Proost, *Rec. Trav. Chim. Pays-Bas*, **57**, 179 (1938).

(9) H. Gilman and J. L. Towle, *ibid.*, **69**, 428 (1950).

(10) (a) J. P. Wibaut and L. G. Heeringa, *ibid.*, **74**, 1003 (1955), obtained a low yield of diphenyl-(2-quinolyl)carbinol from 2-bromoquinoline but concluded that the use of Grignard reagents in the quinoline series was not of preparative value; (b) R. F. Knott, J. Ciric, and J. G. Breckenridge, *Can. J. Chem.*, **31**, 615 (1953).

(11) Quinoline lithium reagents have been successfully used for this purpose. *Cf.* (a) A. Burger and R. N. Pinder, *J. Med. Chem.*, **11**, 267 (1968); (b) C. J. Ohnmacht, A. R. Patel, and R. E. Lutz, *ibid.*, **14**, 926 (1971).

(12) F. W. Bergstrom and S. H. McAllister, *J. Amer. Chem. Soc.*, **52**, 2847 (1930).

(13) H. Gilman and G. C. Gainer, *J. Amer. Chem. Soc.*, **71**, 2327 (1949).

(14) F. W. Bergstrom and S. H. McAllister, *J. Amer. Chem. Soc.*, **52**, 2845 (1930).

(15) K. Ziegler and H. Zeiser, *Justus Liebigs Ann. Chem.*, **485**, 174 (1931).

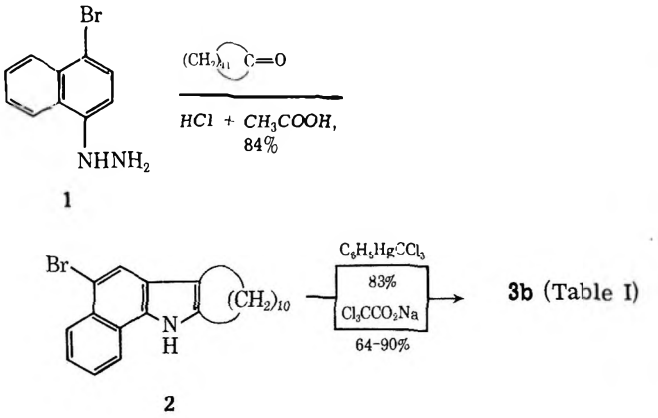
(16) The entraining reagent (1,2-dibromoethane) was not required in all cases; however, higher yields of products were obtained when it was employed, and the procedure was adopted as standard.

TABLE II

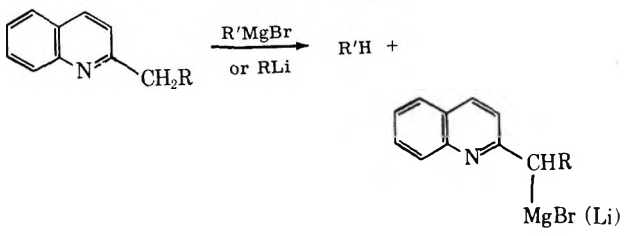
9	R	Mp, °C	Composition, within 0.3% of calcd value for	Yield, %	$\nu_{900-750}$, cm^{-1}
a	H	113–115	C, H, N	*a*	810 (s), 790 (s), 751 (s)
b	Br	224–227	C, H, N	63–77	892 (m), 851 (m), 790 (m), 760 (s)
c	COOH	332–336, dec	C, H, N	42–55[b]	900 (m), 788 (s), 750 (s)
d	D	113–115		56[c]	889 (m), 810 (m), 790 (m), 772 (s), 750 (m)
e	MgBr		Not isolated		

[a] Obtained as a by-product from all reactions of **8e**. [b] Mp 324–327°, 42% (pure) from glacial acetic. [c] 60% deuterium incorporation.

SCHEME I



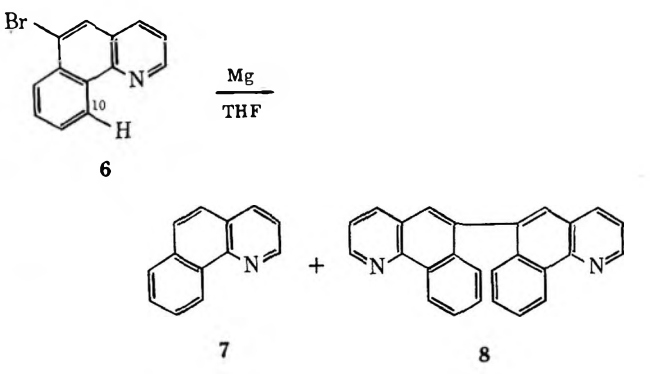
SCHEME II



dioxide and benzaldehyde. In neither case was there any evidence (ir) for the formation of carboxylic acid or alcohol. The minor product (13%) was identified as benzo[*h*]quinoline (**7**) and the major product (74%) was a dimer to which structure **8** is assigned (Scheme III). The dimer showed composition, nmr spectrum, and mass spectrum (molecular ion peak at *m/e* 356; second most intense peak at *m/e* 178) consonant with the proposed structure. Assignment of symmetric coupling at the 6 position was based on the infrared spectrum of **8**, which showed no strong peak near 810 cm^{-1}, an absorption which was observed for **7**, **3a**, and **9a**, in which there are two isolated adjacent aromatic hydrogen atoms.

The mechanism for coupling to **8** is not known; however, nucleophilic aromatic displacement of the bromine (which could be catalyzed by a complex between the nitrogen and magnesium bromide) by Grignard reagent was shown not to occur. When **6** was treated with phenylmagnesium bromide, under conditions

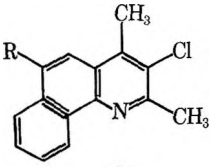
SCHEME III



where coupling to **8** was observed, only unreacted **6** (87% recovery after purification) was isolated. The lack of reactivity of **6** with phenylmagnesium bromide lends further support for the symmetric structure for **8**, since it suggests that addition of Grignard reagents across the azomethine linkage is not a significant side reaction.

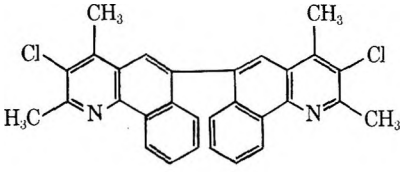
6-Bromo-3-chloro-2,4-dimethylbenzo[*h*]quinoline (9b).—5-Bromo-2,3-dimethylbenzo[*g*]indole was prepared (61% yield) from **1** and methyl ethyl ketone (Fisher synthesis) and was converted to **9b** by reaction with phenyl(trichloromethyl)mercury.

Reaction of the Grignard reagent prepared from **9b** with carbon dioxide gave a single acid **9c** (Table II)



9

(55% crude, 43% pure), 3-chloro-2,4-dimethylbenzo[*h*]quinoline (**9a**, 6%), and a dimer (~6%) to which structure ***10*** is assigned.



10

In order to determine whether any exchange had occurred of the type shown in Scheme II, the Grignard reagent from **9b** was treated with deuterium oxide and the products were separated by preparative tlc. The deuterium derivative (**9d**) was isolated in 56% yield and dimer **10** was isolated in 6% yield; the position of deuterium was established by spectral evidence. The mass spectrum showed the molecular ion peak of **9d**

(*m/e* 242) as the most intense peak with 60% deuterium incorporation. The nmr spectrum showed no deuterium incorporation in the benzylic methyl groups, but did show incorporation of deuterium in the aromatic region. The ir spectrum of **9d** showed a different absorption pattern from **9a** in the region corresponding to aromatic carbon–hydrogen bending vibrations; **9d** showed absorption at 1185 (s), 889 (m), and 772 (s) cm^{-1}, bands which were not shown by **9a**.

The dimeric product obtained from the D_2O reaction was identical to that obtained from the reaction of **9e** with carbon dioxide, and had spectra consonant with **10**. The mass spectrum showed a parent molecular ion corresponding to **10** (*m/e* 480); the intensity of the P + 2 and P + 4 peaks corresponded to a compound with two chlorine atoms. The nmr spectrum showed only two benzylic methyl peaks (τ 6.63 and 6.80, consistent with symmetric structure). These data, coupled with the fact that the ir spectrum of **10** showed no intense absorption near 810 cm^{-1}, which was observed for all benzo[*h*]quinolines (**7**, **3a**, **8a**) which contained two isolated aromatic hydrogen atoms, are rather convincing evidence that coupling was symmetric, as shown in structure **10**.

13-Bromo-20-chloronaphtho[2′,1′:12,13][10](2,4)pyridinophane (3b).—The Grignard reagent **3n** was treated with carbon dioxide and the acid **3l** was obtained in high yield (~100% crude, 79% after recrystallization). This product was identical to that obtained by hydrolysis of **3c**, which was obtained by reaction of **3b** with cuprous cyanide in dimethylformamide. The yield of pure acid from **3n** was 60 and 83%, respectively, in two subsequent reactions in which the entrainment agent (1,2-dibromoethane) was not employed. The acid **3l**, as other 2-substituted benzo[*h*]quinolines, did not form a hydrochloride salt when its solution (tetrahydrofuran cosolvent) in 5% hydrogen chloride was evaporated.[17]

The simplicity of the Grignard synthesis of **3l** from **3b** provided the model for an improved one-step conversion of **3b** into the ketone intermediate **3d**. This was achieved by inverse addition of **3n** to acetic anhydride in ether at Dry Ice–acetone temperature.[18] A liquid by-product in this synthesis was identified as 4-bromobutyl acetate, which was shown to form rapidly from hot tetrahydrofuran and magnesium bromide, with subsequent reaction with acetic anhydride.

Pyridylmethanols of type **3k** are important intermediates in the preparation of antimalarial drugs and are usually prepared[19] by reaction of the appropriate acid with excess 2-pyridyllithium followed by reduction (metal hydride) of the resulting ketone. Reaction of **3n** with pyridine-2-carboxaldehyde gave a mixture of the two diastereomeric racemates **3k** in quantitative yield, and these were separated into the two racemic pairs by fractional crystallization. This sequence is a superior route for the introduction of such functional groups into systems which form stable Grignard reagents.

While Grignard reagents are not generally considered useful intermediates for synthetic conversions in quinoline systems, these results establish that they are quite useful in the naphthopyridinophane series, and are useful to a lesser, but still practical, extent with 2-alkylbenzo[*h*]quinolines (**9b**). The stability and utility of these reagents is apparently not related to the decreased acidity[20] of α- or γ-alkyl hydrogen atoms in **3**, since no interchange of the type shown in Scheme II was noted for **9b**. Furthermore, studies of the reaction of **5** with magnesium, followed by carbonation, indicate that a rather complex mixture of products is formed.

Coupling can become the major reaction in the naphtho[*h*]quinoline series, as shown for **6**. While the mechanism of coupling is not known, the lack of coupling parallels steric hindrance of the azomethine linkage.

All of the benzo[*h*]quinolines studied showed an aromatic hydrogen absorption (nmr) at low field (τ 0.66 in **6**). This observation is consistent with R. H. Martin[21] and coworkers' assignment of this hydrogen as the one marked 10 in formula **6**.

Experimental Section

Analyses were performed by the M-H-W Laboratory, Garden City, Mich. Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrometer. Ultraviolet spectra were obtained on a Beckman Model DK-A. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model T-60 spectrometer. Melting point data were obtained with a Mel-Temp, and were uncorrected unless otherwise indicated. Petroleum ether is bp 60–70°, unless otherwise noted.

Benzo[*h*]quinolines.—Procedure A, using phenyl(trichloromethyl)mercury, was similar to that reported in ref 3; however, the hydrochloride salts of the resulting quinolines were not employed. Procedure B, using sodium trichloroacetate, was similar to those described in ref 6. Compounds were purified by chromatography [alumina, petroleum ether–benzene (5–50%) as eluent]. Most physical data are reported in Table I and only supporting data as to procedure are reported here.

13-Bromo-20-chloronaphtho[2′,1′:12,13][10](2,4)pyridinophane (3b). Procedure A. From Indole 2 (0.70 g, 1.82 mmol).—Product was purified by chromatography (Alcoa F-20 alumina) using petroleum ether–15% benzene as eluent, and was recrystallized from petroleum ether. **Procedure B.**—It was important to dissolve the sodium trichloroacetate by careful warming prior to adding indole to avoid tar formation. Yield was 91% (from petroleum ether) from 3.0 mmol of indole and 9.0 mmol of salt; yield was 60% when scale of reaction was increased tenfold.

9-Bromo-16-chloronaphtho[2′,1′:8,9][6](2,4)pyridinophane (4) was obtained from 5-bromo-7,8,9,10,11,12-hexahydro-13*H*-benzo[*g*]cyclooct[*b*]indole (0.352 g) by procedure A (as for **3b**): yield 0.308 g (77%), mp 187–189°; $uv_{max}^{cyclohexane}$ 218 mμ (log ϵ 4.40), 266 (4.62), 279 (4.56), 296 (sh, 4.15), 305 (sh, 4.02), 318 (3.94), 355 (3.39), 372 (3.42).

Anal. Calcd for $C_{19}H_{17}BrClN$: C, 60.90; H, 4.57; N, 3.74. Found: C, 60.97; H, 4.40; N, 3.54.

13-Bromo-18-chloro-12,13-benzo[10](2,4)pyridinophane (5) was obtained from 2-bromo-5,6,7,8,9,10,11,12,13,14,15-undecahydrocyclododec[*b*]indole (26.5 g, 0.079 mol) by procedure B; yield was 41% (mp 96–98°).

Anal. Calcd for $C_{19}H_{23}NBrCl$: C, 59.91; H, 6.09; N, 3.68. Found: C, 60.15; H, 6.22; N, 3.54.

20-Chloronaphtho[2′,1′:12,13][10](2,4)pyridinophane (3a) was obtained from 7,8,9,10,11,12,13,14,15,16-decahydro-17*H*-benzo-

(17) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946), reported that 2,8-disubstituted quinolines do not lead to stable hydrobromides, presumably for steric reasons.

(18) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

(19) D. W. Boykin, Jr., A. R. Patel, and R. E. Lutz, *J. Med. Chem.*, **11**, 273 (1968).

(20) It has been shown (ref 3) that substituents on the α-methylene carbon atom in the pyridinophane structure are resistant to S_N1 and S_N2 reactions, and it has been suggested that steric factors do not favor stabilization of a developing carbonium ion (sp^2 carbon) at this center. Similarly, one would not expect carbanions to be easily formed at this position. D. J. Cram and L. A. Singer, *J. Amer. Chem. Soc.*, **85**, 1084 (1963), have shown that, as the ring size in paracyclophanes is decreased, the acidity of benzylic methylene is decreased.

(21) R. H. Martin, N. Defay, F. Geerts-Evrard, and D. Bogaert-Verhoogen, *Tetrahedron, Suppl. 8*, Part I, 181 (1966).

[g]cyclododec[b]indole (1.00 g) by procedure A: yield 0.82 g (71%); mp 129–131°; $uv_{max}^{cyclohexane}$ 214 mμ (log ε 4.43) 221 (4.38), 242 (sh, 4.59), 247 (4.63), 253 (sh, 4.57), 273 (4.47), 285 (sh, 4.20), 304 (3.87), 322 (3.38), 337 (3.68), 353 (3.81).

Anal. Calcd for $C_{23}H_{26}ClN$: C, 78.50; H, 7.45; N, 3.98. Found: C, 78.61; H, 7.52; N, 3.92.

6-Bromobenzo[h]quinoline (6) was prepared from 4-bromo-α-naphthylamine using a general procedure for the Skraup synthesis reported by Manske, *et al.*[22] The pale green crystals (11.00 g, 43% yield, mp 112–113°) gave light yellow needles (mp 117–119°, lit.[23] 115–116.5°) when recrystallized from petroleum ether.

6-Bromo-3-chloro-2,4-dimethylbenzo[h]quinoline (**9b, Table II**) was obtained from 5-bromo-2,3-dimethylbenzo[g]indole (3.00 g, 0.11 mol) by procedure A. The precipitate contained phenylmercuric chloride and some **9b**. Combined precipitate and solid, obtained by removal of benzene, was chromatographed over 235 g of alumina using petroleum ether–benzene (to 25%) as eluent to give **9b** as white crystals: 2.69 g, 77% yield, mp 223–227°; yield 63%, mp 224–227° from petroleum ether; $uv_{max}^{cyclohexane}$ 212 mμ (log ε 4.32), 225 (sh, 4.33), 231 (4.36), 247 (sh, 4.59), 252 (4.69), 262 (sh, 4.43), 272 (4.50), 282 (sh, 4.22), 292 (4.05), 304 (4.10), 322 (3.48), 332 (sh, 3.30), 337 (3.81), 348 (sh, 3.30), 354 (3.91).

4-Bromo-α-naphthylhydrazine (1).—4-Bromo-α-naphthylamine (25.0 g) was converted to 1 by a modification of the procedure reported by Plant and Tomlinson.[24] The diazonium salt was reduced with stannous chloride as described in ref 24. The mixture was cooled; the solid was collected and crystallized from water–20% ethanol to give the hydrochloride of 1 as silver needles. This procedure is simpler than that previously reported. The free base is unstable to air and was stored as the hydrochloride. The hydrazine 1 was generated as needed by treating the salt with aqueous sodium acetate. The solid was crystallized from ethanol to give orange needles (66% overall yield, mp 134–136° dec, lit.[24] mp 138–139°).

Indoles.—Buu-Hoï, *et al.*,[25] reported the preparation of analogous indoles by treating the corresponding hydrazones with glacial acetic acid saturated with hydrogen chloride. When these conditions were employed, only black tars were isolated; much better results were obtained when only 1 equiv of hydrogen chloride was used.

5-Bromo-7,8,9,10,11,12-hexahydro-13*H*-benzo[g]cyclooct[b]indole (Precursor to 4).—The hydrazine 1 (0.85 g, 3.6 mmol) was added to a 125-ml flask along with 5 ml of ethanol and five drops of glacial acetic acid. Cyclooctanone (0.455 g, 3.6 mmol) was added and the mixture was heated for 45 min. The red oil obtained by removal of solvent was added to 15 ml of glacial acetic acid. One milliliter of glacial acetic acid saturated with hydrogen chloride was added and the mixture was heated at reflux for 2 hr. The product was poured into water and the mixture was extracted with benzene. The benzene was washed (aqueous Na_2CO_3), dried (Na_2SO_4), filtered from charcoal, and concentrated. The red oil was crystallized from petroleum ether and from ethanol–water to give the indole as light yellow needles [0.70 g, 59% yield, mp 112–114°; ν_{N-H} 3410 cm^{-1}].

Anal. Calcd for $C_{18}H_{18}BrN$: C, 65.85; H, 5.53; N, 4.27. Found: C, 65.79; H, 5.45; N, 4.18.

5-Bromo-7,8,9,10,11,12,13,14,15,16-decahydro-17*H*-benzo[g]cyclododec[b]indole (2) (Precursor to 3b).—The procedure was essentially identical to that described above but cyclododecanone was employed. An acetic acid solution of hydrazone and hydrogen chloride (1 equiv) was heated at the reflux temperature for 75 min; then the solution was quenched with ice water and the solid product was filtered and crystallized from ethanol–20% benzene to give white needles [10.15 g, 71%, yield, decomposition starts at 145°; ν_{N-H} 3420 (s) cm^{-1}].

Anal. Calcd for $C_{22}H_{26}BrN$: C, 68.75; H, 6.82; N, 3.65; Br, 20.78. Found: C, 68.73; H, 6.67; N, 3.53; Br, 21.09.

7,8,9,10,11,12,13,14,15,16-Decahydro-17*H*-benzo[g]cyclododec[b]indole (Precursor to 3a).—The procedure was that described above using α-naphthylhydrazine[26] and cyclododecanone. The crude product was chromatographed (alumina; eluent, petroleum ether–50% benzene) and the indole was obtained as a yellow oil which was crystallized from petroleum ether to give the indole as yellow clusters [2.17 g, 72% yield, mp 102–106°; ν_{N-H} 3460 (s) cm^{-1}]. Recrystallization from ethanol–water yielded white clusters (mp 105–106.5°).

Anal. Calcd for $C_{22}H_{27}N$: C, 86.50; H, 8.91; N, 4.59. Found: C, 86.33; H, 9.01; N, 4.44.

3-Bromo-5,6,7,8,9,10,11,12,13,14,15-undecahydrocyclododec[b]indole (Precursor of 5).—Prepared from 4-bromophenylhydrazine (22.3 g, 0.1 mol) and cyclododecanone (18.2 g, 0.1 mol) by general procedure of Buu-Hoï, *et al.*[25] Product was purified by recrystallization from petroleum ether (97% yield, mp 93–95°).

Anal. Calcd for $C_{18}H_{24}BrN$: C, 64.69; H, 7.18; N, 4.19; Br, 23.9. Found: C, 64.50; H, 7.36; N, 4.06; Br, 23.84.

5-Bromo-2,3-dimethylbenzo[g]indole (Precursor to 9b).—The procedure described above did not provide this indole; a modification of the procedure reported by Atkinson, *et al.*,[27] using boron trifluoride etherate in acetic acid was employed. The black oil gave the indole [5.65 g, 61% yield, mp 92° dec; ν_{N-H} 3405 (s) cm^{-1}] as tan needles subsequent to chromatography (alumina, petroleum ether–diethyl ether as eluent) and recrystallization.

Anal. Calcd for $C_{14}H_{12}BrN$: C, 61.32; H, 4.42; N, 5.11. Found: C, 61.54; H, 4.49; N, 5.03.

Solutions of the indole in CCl_4 or $CHCl_3$ rapidly turned to a purple dye when exposed to air.

20-Chloronaphtho[2′,1′:12,13][10](2,4)pyridinophane-13-nitrile (**3c**) was prepared from **3b** (2.15 g, 0.005 mol) and cuprous cyanide in dimethylformamide (6 hr at 155–160°) by the procedure described by Friedman and Schechter.[28] The yellowish-white crude nitrile [yield 1.78 g (100%), mp 229–230°] was recrystallized from benzene–petroleum ether to give colorless crystals (1.54 g, 86% yield, mp 231–232°; ν_{CN} 2208 cm^{-1}).

20-Chloronaphtho[2′,1′:12,13][10](2,4)pyridinophane-13-carboxylic Acid (3l). (1) **From 3c.**—The nitrile **3c** (1.25 g) was hydrolyzed with potassium hydroxide in glycerol (180°, 15 hr) by the procedure described by Campbell, *et al.*[4,5] The crude product was purified by chromatography (silica gel with chloroform and chloroform–methanol as eluent) to give **3c** (36% recovery) and **3l** (54% yield crude; 0.44 g, 33% from ethanol, mp 280–282°).

(2) **General Grignard Procedure.**—A mixture of quinoline **3b** (4.00 g, 9.29 mmol), magnesium turnings, (0.544 g, 0.0224 g-atom, 20% excess), and dry tetrahydrofuran (50 ml distilled from $LiAlH_4$) was heated in a glass apparatus (flame dried under nitrogen) at the reflux temperature under an atmosphere of nitrogen. 1,2-Dibromoethane (1.74 g, 9.2 mmol in 17 ml of tetrahydrofuran) was added dropwise over a 2-hr period while maintaining the reaction solution at the reflux temperature. The solution was then maintained at the temperature for an additional 30 min. After cooling the reaction solution to room temperature, dry carbon dioxide (Matheson) was bubbled through the solution for 2.5 hr and then 5% aqueous hydrochloric acid (15 ml) was added. The solvent was evaporated and the resulting crude solid was washed with 5% hydrochloric acid and water. After drying (vacuum desiccator), the product was crystallized from ethyl acetate to small white needles (2.92 g, 79% yield, mp 280–284°) which showed an undepressed mixture melting point when admixed with **3l** obtained from nitrile.

20-Chloronaphtho[2′,1′:12,13][10](2,4)pyridinophan-13-yl Methyl Ketone (**3d**). (1) **From 3c.**—The ketone was prepared by reaction of **3c** (0.753 g) with methylmagnesium iodide by the general procedure of Callen, *et al.*[29] The product was purified by chromatography [silica gel, benzene–petroleum ether (30%) as eluent] to give **3c** (0.24 g) and **3d** (57% yield, mp 207–208° from benzene–petroleum ether; $\nu_{C=O}$ 1690 cm^{-1}).

(2) **From 3n.**—The Grignard reagent prepared as described for **3l** was slowly added to a diethyl ether solution of acetic anhydride at ~−70° by the general procedure described by Newman and Smith,[18] and was purified by chromatography as described above; the methyl ketone (**3d**) from the column was washed with petroleum ether and dried (mp 210–211°, 70% yield). The petroleum ether washings were concentrated to the 4-bromobutyl acetate by-product.

(22) R. H. F. Manske, Leo Marion, and F. Leger, *Can. J. Res. Sect. B*, **20**, 133 (1942).

(23) W. P. Utermohlen, Jr., and C. S. Hamilton, *J. Amer. Chem. Soc.*, **63**, 156 (1941).

(24) S. G. P. Plant and M. L. Tomlinson, *J. Chem. Soc.*, 2192 (1932).

(25) Ng. Ph. Buu-Hoï, P. Jacquignon, and T. B. Loc, *ibid.*, 738 (1958).

(26) E. Fischer, *Justus Liebigs Ann. Chem.*, **232**, 236 (1886).

(27) C. M. Atkinson, J. C. E. Simpson, and A. Taylor, *J. Chem. Soc.*, 165 (1954).

(28) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).

(29) J. E. Callen, C. A. Dornfeld, and G. H. Colerman, *Org. Syn.*, Coll. Vol. **3**, 26 (1964).

(3) **From 3l.**—A solution of **3l** (0.70 g) in tetrahydrofuran was treated with methyllithium (4 equiv) at room temperature. The solution was stirred for 30 min and then quenched with water. The solvent was evaporated and the crude product was chromatographed (silica gel, eluent, petroleum ether–to 50% benzene) to give **3d** (32% yield, mp 212.5–214°) subsequent to crystallization from petroleum ether.

(4) **From 3e.**—Attempts to prepare the corresponding bromohydrin by reduction of **3e** by the general procedure of Winstein, *et al.*,[30] (Meerwein–Ponndorf reduction) gave primarily ketone **3d**.

20-Chloronaphtho[2′,1′:12,13][10](2,4)pyridinophan-13-yl Bromomethyl Ketone (3e).—A variety of conditions[4,5] were explored with yields of **3e** varying from 0[31] to 88%. Bromine (2.4 g, 0.015 mol) in acetic acid (30 ml) was added dropwise over a 1.5-hr period to a boiling solution of **3d** (5.90 g, 0.015 mol) in glacial acetic acid (210 ml). The solid, obtained by cooling the mixture and dilution with water, was extracted with chloroform and the extract was washed (aqueous sodium bicarbonate, water) and dried. The solid (7.83 g, mp 200–205°) obtained by evaporation of chloroform was purified by chromatography (silica gel, 400 g). The first product, eluted with benzene–petroleum ether, was dibromide **3o** (1.0 g, 12% yield, mp 161–162°; mp 164° from petroleum ether; $\nu_{C=O}$ 1692 cm^{-1}). The second fraction, eluted with benzene was **monobromide 3e** (6.19 g, 88% yield, mp 207–208° from chloroform–petroleum ether; $\nu_{C=O}$ 1700 cm^{-1}). The third fraction also eluted with benzene was recovered **3d** (3.4%).

Attempts to **reduce 3e to the epoxide** with sodium borohydride in methanol[32a] gave recovered **3e** (85%); reduction with sodium borohydride in diglyme[32b] gave a mixture of five products (tlc).

20-Chloro-α-(di-*n*-heptylaminomethyl)naphtho[2′,1′:12,13]-[10](2,4)pyridinophane-13-methanol (3g).—Di-*n*-heptylamine (0.266, 1.25 mmol) in dry benzene (20 ml) was added over a period of 1 hr to a solution of **3e** (0.236 g, 0.50 mmol) in dry benzene (30 ml) at 30° under nitrogen. The mixture was stirred for 24 hr and concentrated (rotatory evaporator); dry diethyl ether was added and di-*n*-heptylamine hybromide (135.5 mg, 94.4%) was filtered. The filtrate (which was kept at 30°), containing excess amine and **ketone 3f** ($\nu_{C=O}$ 1680 cm^{-1}), was added dropwise to a stirred suspension of $LiAlH_4$ (80 mg, 0.002 mol) in dry diethyl ether (20 ml) maintained at gentle reflux. The mixture was heated for an additional 40 min and was then cooled, filtered, and concentrated to an oil [di-*n*-heptylamine and **3g** (~100% yield)]. The mixture was chromatographed over silica gel. Elution with 2% methanol in benzene gave **one racemic isomer** (154 mg, 52% yield, mp 130–131° from petroleum ether). Further elution of the column with the same eluent gave the second diastereomer contaminated with some di-*n*-heptylamine. This product was rechromatographed (same conditions) to give the **second racemic isomer** as an oil with composition calculated for $C_{38}H_{59}ClN_2O$. Differences in R_f values and ir spectra suggested that the second isomer was free of the first.

20-Chloro-α-(di-*n*-butylaminomethyl)naphtho[2′,1′:12,13][10]-(2,4)pyridinophane-13-methanol (3i) was prepared from **3e** and di-*n*-butylamine as described for **3g**. The intermediate ketone **3h** ($\nu_{C=O}$ 1675 cm^{-1}) was unstable. The diastereomeric racemates (**3i**) were obtained as an oil (0.24 g, 82% yield) and no resolution was achieved by chromatography as described for **3g**.

20-Chloro-α-(2-pyridyl)naphtho[2′,1′:12,13][10](2,4)pyridinophane-13-methanol (3k).—The Grignard reagent **3n** (from 4.00 g, 9.27 mmol of **3b**) was prepared as described in the preparation of **3l**, and was treated with freshly distilled 2-pyridinecarboxyaldehyde (0.99 g, 9.27 mmol) at ice bath temperature; the mixture was allowed to warm to 30° before quenching with water. The dry oil obtained subsequent to neutralization (aqueous NH_4Cl) and extraction (diethyl ether) was chromatographed (silica gel; eluent, petroleum ether to diethyl ether), and 4.35 g (100% crude yield, mp 152–166°) of a mixture of the two diastereomeric racemates of **3k** was obtained. The mixture contained approximately 50% of each racemate (determined by nmr, the aromatic 12H proton absorbs at τ 2.00 for isomer A and at τ 2.14 for isomer B).

The mixture was crystallized from 95% ethanol and then 20% chloroform in petroleum ether to give isomer A as white crystals (mp 173–186°) in 40% yield (pure by nmr spectroscopy at τ 2.00). Several recrystallizations of a sample with the composition calculated for $C_{29}H_{31}ClN_2O$ did not sharpen the broad melting range.

The mother liquors from the above purification were concentrated and the resulting material was crystallized (20% $CHCl_3$ in petroleum ether) to give isomer B as white crystals (mp 174–176°) in 18% yield (pure by nmr spectroscopy at τ 2.14). The two diastereomers showed similar but not identical spectra and a mixture melting point of the two was depressed (mmp 157–179°).

When a 50% molar excess of 2-pyridinecarboxyaldehyde was used and the mixture was heated at the reflux temperature for 30 min, a **third component (3j)** was formed and isolated in 20% yield ($\nu_{C=O}$ 1672 cm^{-1}). The crude reaction mixture was separated by column chromatography (silica gel; eluent, petroleum ether to 80% diethyl ether) to give **3a** in 8%, **3j** in 20%, and **3k** in 61% yield.

Reaction of 6 with Magnesium.—6-Bromobenzo[*h*]quinoline (**6**) (2.40 g) was reacted with magnesium as described for the preparation of **3l** and carbon dioxide was introduced (2 hr) followed by the addition of 5% aqueous hydrochloric acid (15 ml). The solvent (THF) was removed and **dimer 8** was collected as a tan solid (74% yield, mp 325–330°). The dimer was most readily purified by sublimation (little loss) at 250° (0.005 mm): mp 342–345°; $\lambda_{max}^{95\%}$ 225 mμ (sh, log ε 4.75), 235 (4.86), 270 (4.70), 297 (sh, 4.19), 316 (371), 331 (3.76), 347 (3.78); nmr (12% in trifluoroacetic acid, areas relative to 16 protons) τ 0.48–0.89 (m, 5.5), 1.39–2.36 (m, 10.5); mass spectrum, base peak 356 (molecular ion), 178 (monomer), 29% of base peak.

Anal. Calcd for $C_{26}H_{16}N_2$: C, 87.61; H, 4.52; N, 7.86. Found: C, 87.53; H, 4.71; N, 7.70.

The acid filtrate from above was evaporated to dryness and extracted with chloroform (no carboxylic acid in extract). The residue, after removal of chloroform, was dissolved in water, made basic, and extracted with ether. The oil obtained from the ether extract was chromatographed [Alcoa F-20, petroleum ether–diethyl ether (to 25%)] to give benzo[*h*]quinoline (**7**) (13.3%, mp 49–52°, lit.[33] 52°; ir spectrum identical with that published).[34]

Reactions of 9b with Magnesium. (1) **Isolation of Acid 9c, Quinoline 9a, and Dimer 10.**—The reaction of **9b** (1.00 g, 3.12 mmol) with magnesium and carbon dioxide was effected as described for **6**. The reaction was quenched with 5% hydrochloric acid (6 ml), and after the mixture was stirred for 1 hr, the solvent was removed (rotatory evaporator) to a gray solid. A portion (0.329 g) of the gray solid thus obtained (0.817 g) was heated with benzene (25 ml, 4 hr). **Acid 9c** [$\nu_{C=O}$ 1684 (s) cm^{-1}] was insoluble in benzene; the extract contained **9a** (~6%) and dimer **10** (~6%), which were separated by preparative tlc (25 g of silica gel PF_{254} on 20 × 20 cm plate using petroleum ether–50% benzene). **The band with R_f 0.60 was 9a** (0.018 g, 6% yield, mp 113–115° from pentane): nmr (5% w/v $CDCl_3$) τ 0.56–0.75 (m, 1 ArH at 10 position), 2.04–2.40 (m, 5.0, ArH), 7.12 (s, 3.0, CH_3), 7.25 (s, 3.0, CH_3).

Anal. Calcd for $C_{15}H_{12}ClN$: C, 74.52; H, 5.00; N, 5.79. Found: C, 74.38; H, 5.14; N, 5.72.

The band with R_f 0.37 was dimer 10 (0.10 g, 6% yield, mp 330–334°): ir 3040 (w), 2900 (m), 2840 (w), 1580 (m), 1505 (m), 1438 (s), 1382 (s), 1010 (s), 865 (m), 768 (s), 750 (w), 740 (m), 730 (m) cm^{-1}; mass spectrum, molecular ion (*m/e* 480, base peak), intensity of P + 2 (66% of parent peak) and P + 4 (14% of parent peak) corresponding to 2 chlorines.

(2) **Isolation of 9d.**—The reagent **9e** was formed from **9b** (0.316 g) as described above and treated with deuterium oxide (2 ml); solvent was removed and the residue was extracted with chloroform. The solid obtained from the extract was purified by preparative tlc as described above. The derivative **9d** was obtained in 56% yield: mp and mmp (with **9a**) 114–115.5°; ir showed additional bands at 1185 (w), 889 (m), 772 (s) cm^{-1}; nmr (10% in $CDCl_3$) (areas relative to 11.4 protons) τ 0.60–0.88 (m, 1.0, ArH at 10 position), 2.05–2.44 (m, 4.4, ArH), 7.16 (s, 3.0, CH_3), 7.33 (s, 3.0, CH_3); mass spectrum showed molecular ion peak (*m/e* 242) as base peak and 60% deuterium incorporation. The **dimer 10** (0.015 g, 6% yield, mp 323–325°)

(30) (a) S. Winstein, T. L. Jacobs, R. B. Henderson, and W. H. Florsheim, *J. Org. Chem.*, **11**, 150 (1946); (b) S. Winstein, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1831 (1946).

(31) E. May and E. Mosettig, *J. Org. Chem.*, **11**, 10 (1946).

(32) (a) S. W. Chaikin and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 122 (1949); (b) E. T. McBee and T. M. Burton, *ibid.*, **74**, 3022 (1952).

(33) E. Bamberger and L. Stettenheimer, *Ber.*, **24**, 2473 (1891).

(34) "Sadtler Index of Infrared Spectra," Sadtler Research Laboratories, Philadelphia, Pa., 1967, No. 8691K.

was also isolated from the preparative tlc plate [ir spectrum identical to that obtained as described in (1), above].

Registry No.—**1**, 35158-78-2; **2**, 35158-79-3; **3a**, 35158-80-6; **3a** (precursor to), 13226-05-6; **3b**, 35158-82-8; **3c**, 35158-83-9; **3d**, 35158-84-0; **3e**, 35158-85-1; **3g** (one racemic isomer), 35158-86-2; **3g** (second racemic isomer), 35158-87-3; **3i** (one racemic isomer), 35158-88-4; **3i** (second racemic isomer), 35158-89-5; **3j**, 35158-90-8; **3k** (one racemic isomer), 35158-91-9; **3k** (second racemic isomer), 35158-92-0; **3l**, 35158-93-1; **3m**, 35158-94-2; **3o**, 35191-47-0; **4**, 35158-95-3; **4** (precursor to), 35158-96-4; **5**, 35158-97-5; **5** (precursor to), 35158-98-6; **8**, 35158-99-7; **9a**, 35159-00-3; **9b**, 35159-01-4; **9b** (precursor to), 35159-02-5; **9c**, 35159-03-6; **9d**, 35159-04-7; **10**, 35159-05-8.

Acknowledgment.—The authors wish to thank Mrs. T. T. Sun for the preparation of **5**.

Medium-Sized Cyclophanes. XIII. A Highly Selective Cycloisomerization Reaction of [2.2]Metacyclophanes to 1,2,3,3a,4,5-Hexahydropyrenes Induced by Iodine[1]

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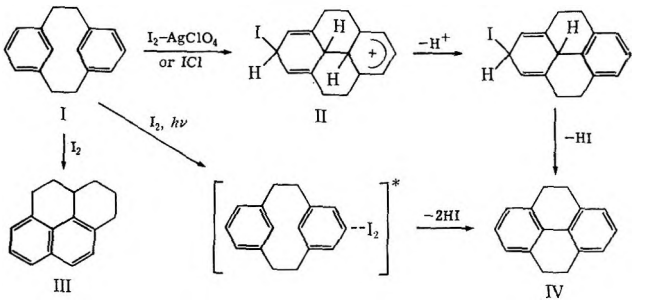
[2.2]Metacyclophane (I) underwent an iodine-induced cycloisomerization reaction to give 1,2,3,3a,4,5-hexahydropyrene (III) with remarkable ease and in high yield. The generality of the isomerization has been established using several alkyl derivatives (V–VII), which gave the corresponding hexahydropyrenes (VIII–XII), and efficacious reaction conditions have been broadly examined. Cross experiments using [2.2]metacyclophane-*8,16-d*$_2$ indicate the reaction might to involve intermolecular hydrogen transfer. Competitive experiments between I and alkyl derivatives suggest that a π-complex mechanism might apply.

Owing to electronic interactions between two benzene rings, the proximity of 8,16 positions, and the considerable strain energy, [2.2]metacyclophane (I) is prone to give transannular reaction products.[2] These are mostly explained by the initial formation of a dehydrogenation product, 4,5,9,10-tetrahydropyrene (IV) (Scheme I). It has been isolated under electrophilic,[3-6] radical,[7] and photolytic reaction conditions[4,8,9] together with other transformation products derived from IV.

Nitration with benzoyl nitrate[5] (reactive species, N_2O_5), which is preferred over nitric acid[3] for stoichiometric control and for homogeneous reaction conditions or bromination using iron catalyst[3,6] afforded substituted 4,5,9,10-tetrahydropyrene *via* IV. Attempted iodination of I using iodine and silver perchlorate[4,6] or iodine chloride[6] gave a high yield of IV. No further iodination occurred under the reaction conditions.

SCHEME I



A similar dehydrogenation–substitution scheme was postulated for a derivative of I.[3,10,11] Photolysis of I in the presence of iodine[4,8] or a suitable oxidant[9] afforded IV as the main product. Lack of conjugation between two aryl moieties in I demands a different mechanism from that postulated for *cis*-stilbene → phenanthrene.[12] It is likely to involve photoexcitation of the charge-transfer complex between I and iodine followed by dehydroiodination.[8] With iodine as a reactant the formation of IV is illustrated in Scheme I, where an addition–elimination mechanism is postulated for the attack of an electrophile.

We have found still another type of iodine-induced reaction of I which gives 1,2,3,3a,4,5-hexahydropyrene (III) with remarkable ease and with high selectivity.[1] When a benzene solution of I containing iodine was warmed at 60°, III[13] was produced in a quantitative yield. These reactions carried out in benzene and cyclohexane are summarized in Table I. No reaction

(1) Part XII: T. Sato, M. Wakabayashi, K. Hata, and M. Kainosho, *Tetrahedron*, **27**, 2737 (1971). For a preliminary account, see T. Sato, K. Nishiyama, and A. Murai, *Chem. Commun.*, 163 (1972).

(2) Reviews: R. W. Griffin, Jr., *Chem. Rev.*, **63**, 45 (1963); B. H. Smith, "Bridged Aromatic Compounds," Academic Press, New York, N. Y., 1964; T. Sato, *Kagaku no Ryoiki*, **23**, 672, 765 (1969); T. Sato, *Nippon Kagaku Zasshi*, **92**, 277 (1971).

(3) The formation of 2-nitro-4,5,9,10-tetrahydropyrene by the nitration with nitric acid was first explained by the oxidation of nitrated precursor and the possibility of an intermediacy of IV was eliminated [N. L. Allinger, M. A. DaRooge, and R. B. Hermann, *J. Amer. Chem. Soc.*, **83**, 1947 (1961)]. In the revised mechanism, which conforms with our results, IV is postulated as an intermediate [N. L. Allinger, B. J. Gordon, H.-E. Hu, and R. A. Ford, *J. Org. Chem.*, **32**, 2272 (1967)].

(4) T. Sato, E. Yamada, Y. Okamura, T. Amada, and K. Hata, *Bull. Chem. Soc. Jap.*, **38**, 1049 (1965).

(5) M. Fujimoto, T. Sato, and K. Hata, *ibid.*, **40**, 600 (1967).

(6) T. Sato, M. Wakabayashi, Y. Okamura, T. Amada, and K. Hata, *ibid.*, **40**, 2363 (1967).

(7) For example, the reaction of I with BPO or diisopropyl peroxydicarbonate gave IV along with substituted I (unpublished results).

(8) T. Sato, M. Wakabayashi, S. Hayashi, and K. Hata, *Bull. Chem. Soc. Jap.*, **42**, 773 (1969); H. Shizuka, K. Sorimachi, T. Morita, K. Nishiyama, and T. Sato, *ibid.*, **44**, 1983 (1971); S. Hayashi and T. Sato, *ibid.*, **45**, 2360 (1972).

(9) T. Sato, K. Nishiyama, S. Shimada, and K. Hata, *ibid.*, **44**, 2858 (1971).

(10) T. Sato, S. Akabori, S. Muto, and K. Hata, *Tetrahedron*, **24**, 5557 (1967).

(11) R. W. Griffin, Jr., and R. A. Coburn, *J. Org. Chem.*, **32**, 3956 (1967).

(12) F. R. Stermitz in "Organic Photochemistry," Vol. 1, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, p 249.

(13) J. W. Cook, C. L. Hewett, and I. Hieger, *J. Chem. Soc.*, 355, 396, 398 (1953).

TABLE I
THE FORMATION OF 1,2,3,3a,4,5-HEXAHYDROPYRENE (III) FROM [2.2]METACYCLOPHANE (I)[a]

Expt no.	MCP (M)	I_2 (equiv)	Solvent	Temp, °C	Hydropyrene Hexa-	Hydropyrene Tetra-
1	0.33	0.8	C_6H_6	80	95	1.9
2	0.32	0.14	C_6H_6	60	100	0
3	0.31	0.12	C_6H_6	80	63	4.9
4	0.24	0.11	C_6H_6	60	14	0
5	0.24	0.06	C_6H_6	60	0	0
6	0.16	0.82	C_6H_{12}	80	84	6.0
7	0.013	0.53	C_6H_{12}	60	0	0

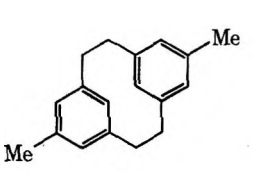
[a] Reaction time, 20 hr.

occurred in ethanol, acetic acid, carbon disulfide, or dimethylformamide.

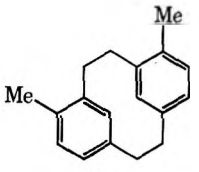
Concentration of both the substrate and iodine has a marked effect on the formation of III. Table I shows that the reaction rate is considerably lowered by using a lesser amount of iodine. Low concentration of I (<0.013 *M*) also retarded the reaction even when a sufficient amount of iodine was present. By contrast, a photocyclodehydrogenation reaction occurred in dilute benzene or cyclohexane solution (~4×10^{-3} *M*) containing only a catalytic amount of iodine. The formation of III was not noticed in the photolysis mixture except for those cases where rather concentrated solutions were exposed to sunlight in summer.

A small amount of iodinated material was formed when nearly equimolar iodine was employed. The only other by-product was IV which was formed in a small amount depending on the reaction conditions. When these by-products were formed, hydrogen iodide was noticed in the reaction mixture, which itself, however, was ineffective in the isomerization reaction. Iodine was found to be recoverable after the reaction as determined by titration of an aqueous extract.

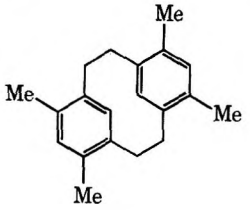
That the cycloisomerization reaction is general to this class of compounds has been confirmed by using 5,13-dimethyl- (V),[10] 4,14-dimethyl- (VI),[14] and 4,6,12,-14-tetramethyl[2.2]metacyclophanes (VII).[10] Under



V



VI



VII

similar reaction conditions used for I they gave high yields of the corresponding 1,2,3,3a,4,5-hexahydropyrenes (VIII–XII; only one enantiomer is shown in the formula). Physical properties of the products are collected in Table II. There was no indication of

(14) T. Sato, S. Akabori, M. Kainosho, and K. Hata, *Bull. Chem. Soc. Jap.*, **39**, 856 (1966); S. Akabori, T. Sato, and K. Hata, *J. Org. Chem.*, **33**, 3277 (1968).

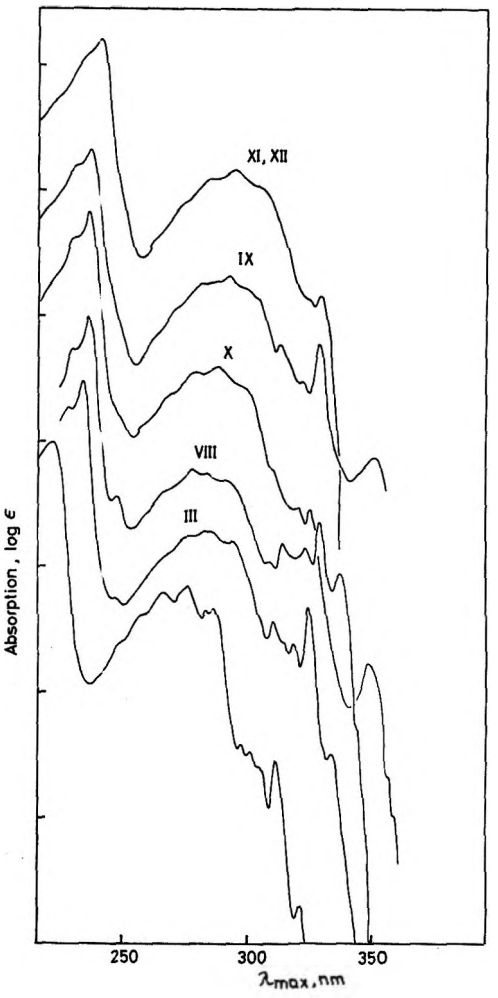


Figure 1.—Uv absorption spectra of naphthalene (bottom) and 1,2,3,3a,4,5-hexahydropyrenes in cyclohexane.

skeletal change nor alkyl migration. The only side reaction was the formation of the corresponding 4,5-9,10-tetrahydropyrenes.

From combustion analysis and parent ion peaks in the mass spectra, the products were inferred to be isomeric with the starting materials. The gross structures were indicated from the ir and uv spectra, which showed absorptions due to typical alkylated naphthalene chromophores (Figure 1, Table III). Fragmentation patterns in the mass spectrum were also in accord with the naphthalene structures. Detailed structural information including stereochemistry was gained from nmr measurements (Table IV; see later section).

2,7-Dimethyl-1,2,3,3a,4,5-hexahydropyrene (VIII) was obtained by the similar treatment of V with iodine. The structure was confirmed by dehydrogenation into 2,7-dimethylpyrene[15] over palladium/charcoal. By repeated chromatography on alumina, VIII was separated into two configurational isomers, VIIIa and VIIIb. In VIIIa the methyl group at C-2 is cis to the hydrogen at bridgehead (C-3a) and exists in a quasiaxial arrangement, while the methyl group in VIIIb is trans to the hydrogen and takes a quasiequatorial position. The ratio of VIIIa and VIIIb was 46:54 as determined from nmr spectra of the reaction mixture by integrating

(15) M. Orchin, L. Reggel, and R. A. Friedel, *J. Amer. Chem. Soc.*, **74**, 1094 (1952).

TABLE II

1,2,3,3a,4,5-HEXAHYDROPYRENES

Compd	Mp, °C	Yield,[a] %	Formula	Mol wt *m/e*	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found
III[b]	103–104	100[c]	$C_{16}H_{16}$	208	92.26	92.21	7.74	7.84
VIIIa	90–91	54	$C_{18}H_{20}$	236	91.47	91.14	8.53	8.31
VIIIb	163–164	46	$C_{18}H_{20}$	236				
IX	53–55	32	$C_{18}H_{20}$	236	91.47	91.02	8.53	8.74
X[d]	Liquid	68	$C_{18}H_{20}$	236				
XI	79–80	24	$C_{20}H_{24}$	264	90.85	91.04	9.15	9.48
XII[d]	136–141.5	52	$C_{20}H_{24}$	264				

[a] Determined by vpc and/or nmr. [b] See ref 14. [c] See Table I. [d] Mixtu re of diastereomers.

TABLE III

UV MAXIMA IN CYCLOHEXANE

Compd	λ_{max}, nm (log ϵ)
III	227.5 (4.78), 234 (4.96), 269 (3.61), 275 (3.73), 283.5 (3.80), 289 (3.79), 294.5 (3.70), 311 (3.08), 315.5 (2.89), 319.5 (2.89), 325 (3.18), 335 (2.02)
VIII	230 (4.74), 236 (4.98), 248 (3.55), 268 (3.62), 278 (3.78), 283 (3.75), 291 (3.70), 296 (3.65), 309 (3.04), 315 (3.20), 324 (3.15), 330 (3.38), 338 (2.96)
IX	230 (4.81), 236 (5.01), 248 (3.43), 257 (3.30), 268 (3.57), 279 (3.75), 289 (3.80), 299 (3.63), 310 (2.98), 321 (2.66), 325.5 (2.66)
X	230 (4.73), 237 (4.87), 271 (3.60), 281 (3.81), 292 (3.86), 305 (3.66), 313 (3.33), 322 (3.03), 328 (3.32)
XI, XII	234 (4.76), 240 (4.90), 275 (3.60), 284 (3.79), 295 (3.86), 307 (3.70), 323 (2.85), 329 (2.88)

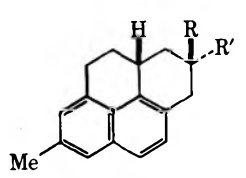
the methyl proton signals. The fact that VIIIb has a higher melting point and elutes from an alumina column slower than VIIIa provides additional evidence to support the assignment of the former to be the quasi-equatorial isomer.

An attempted equilibration experiment between VIIIa and VIIIb using sulfuric acid failed since the 1,2,3,3a,4,5-hexahydropyrene structure isomerized to 1,2,3,6,7,8-hexahydropyrene (XIV, *sym*-hexahydropyrene). Lewis acid or metal catalysts were not examined since fragmentation, rearrangement, and dehydrogenation[16] reactions were anticipated.

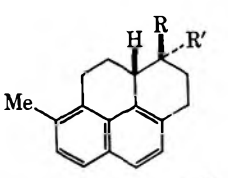
For compound VI a dual way of cyclization is possible. Indeed, we obtained two types of naphthalene compounds IX and X, which were formed in a 32:68 ratio as determined by gas chromatography. As a by-product 1,8-dimethyl-4,5,8,10-tetrahydropyrene was formed in a trace amount and characterized by mass spectroscopy. Compound IXb was assigned the quasi-axial methyl isomer structure based on the high field methyl proton signal occurring at δ 0.89 in the nmr spectrum. No diastereomeric compound IXa was isolated.

Compound X was obtained as an oily mixture of stereoisomers. A doublet signal at δ 1.29 and 1.36 indicates that each isomer has a methyl group at the benzylic position. The product ratio in the formation of IXa, IXb, and X was unchanged by increasing the reaction time up to 25 hr according to nmr. No epimerization appears to occur in the products on long contact with iodine.

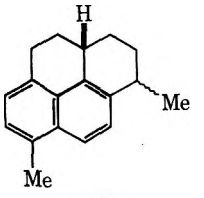
(16) E. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformation Analysis," Wiley-Interscience, New York, N. Y., 1965, p 141.



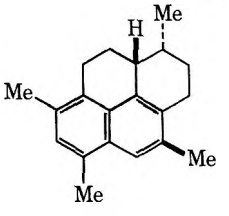
VIIIa, R = Me; R' = H
VIIIb, R = H; R' = Me



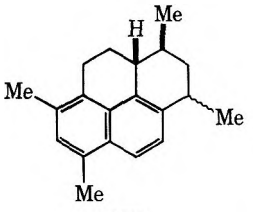
IXa, R = Me; R' = H
b, R = H; R' = Me



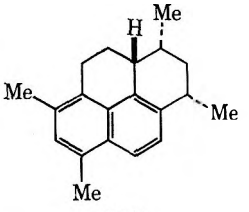
X



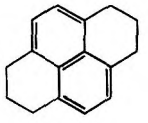
XI



XII



XIII



XIV

Compound VII gave three isomeric tetramethylhexahydropyrenes, XI and XII (mixture, 76%) and 1,3,6,8-tetramethyl-4,5,9,10-tetrahydropyrene (24%). The configurations of the methyl groups in XI and XII (mixture of diastereomers) was determined as shown in the formulae. The fourth isomer XIII, which would involve unfavorable 1,3-diaxial methyl interaction, was not detected.

Uv Spectra.—Uv data for hexahydropyrenes (III and VIII–XII) are summarized in Table III, and the absorption curves are shown in Figure 1. The number and location of alkyl substituents on a naphthalene ring has been correlated with band positions and absorption pattern.[17] Alkyl substitution at the α position, which extends conjugation in the transverse direction, causes both bathochromic and hyperchromic effects in the ^1L_a bands, whereas β substitution results in the red shift and intensifies the ^1L_b bands through

(17) W. L. Mosby, *J. Amer. Chem. Soc.*, **75**, 3348 (1953); H. H. Jaffè and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, p 303; R. W. Frank and E. G. Leser, *J. Org. Chem.*, **35**, 3932 (1970).

TABLE IV
NMR SPECTRAL DATA

Compd	Aromatic proton,[a] ppm (J = Hz) C-6	C-7	C-8	C-9	C-10	Methyl proton, ppm (J = Hz) Aliphatic	Aromatic[c]
III	7.17 (2.3, 7.7)	7.29 (7.4, 7.7)	7.58 (2.3, 7.4)	7.58 (8.5)	7.15 (8.5)		
VIIIa	7.05[b]		7.39[b]	7.50 (8.3)	7.12 (8.3)	1.11 (7.0)	2.43
VIIIb	7.03[c]		7.37[b]	7.45 (8.3)	7.15 (8.3)	1.13 (6.0)	2.43
IX		7.18 (8.3)	7.50 (8.3)	7.50 (8.3)	7.06 (8.3)	0.89 (7.0)	2.37
X	7.03 (7.6)	7.13 (7.6)		7.72 (8.8), 7.75 (8.8)	7.21 (8.8), 7.38 (8.8)	1.29 (7.5), 1.36 (7.0)	2.59
XI		7.08[c]		7.76 (9.0)	7.37 (9.0)	0.89 (7.0), 1.34 (7.0)	2.37, 2.60
XII		7.05[c]		7.70 (9.0), 7.73 (9.0)	7.16 (9.0), 7.34 (9.0)	1.15 (6.0), 1.22 (7.2), 1.35 (6.8)	2.35, 2.58

[a] Doublet or double doublet signals unless otherwise stated. [b] Broad singlet. [c] Singlet.

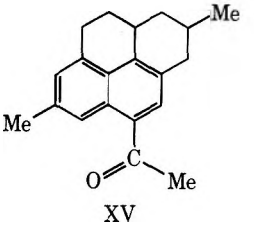
conjugation in the longitudinal direction. These have been studied in methyl-substituted naphthalenes.[17,18]

General trends are followed in the hexahydropyrenes. Compared with naphthalene, compound III which has two α and β substituents showed bathochromic shift of approximately 15 nm in all of three bands including ^1B_a. With additional β substituents VIII and IX showed a further red shift of 5 nm compared with III in the ^1L_b band. A similar red shift of a few nanometers in ^1L_a band was observed by going from III to X. For pentasubstituted naphthalenes XI and XII (determined as a mixture) further small bathochromic shifts and a loss of fine structure were observable. With highly overcrowded naphthalenes rather broad curves have been observed.[17,18]

Nmr Spectra.—Table IV summarizes spectral data for aryl and methyl protons determined in $CDCl_3$. Methylene and methine protons exhibited a complex pattern between about δ 1.2 and 3.3. Since an α proton in a naphthalene nucleus is known to be more deshielded than a β proton[19] and since there is virtually no coupling between protons in different rings,[19,20] aryl proton signals can be assigned by first-order analyses with the aid of benzyl decoupling.

Substitution of the C-7 hydrogen by a methyl group simplified the aromatic resonances and both VIIIa and VIIIb showed two broad singlets for each of the C-6 and C-8 protons. Methyl resonance signals for VIIIa and VIIIb appeared one as a singlet at δ 2.43 (C-8 methyl of both isomers), and the other as a doublet at δ 1.11 (J = 7.0 Hz) for VIIIa and at 1.13 (J = 6.0) for VIIIb. In methyl-substituted cyclohexanes and their heterocyclic analogs the vicinal coupling constants between methyl and methine protons are 5.6–6.3 Hz with equatorial and 6.3–7.2 Hz with axial isomers, and always smaller for equatorial isomers.[21] Accordingly VIIIb is assigned as possessing a quasiequatorial methyl group and VIIIa as a quasiaxial methyl group. On addition of C_6D_6 to a mixture of VIIIa and VIIIb in $CDCl_3$ the methyl signals shifted to a higher field, the magnitude of which was larger for VIIIb. This can be understood on the basis that the equatorial methyl is more exposed, and subject to an enhanced aromatic solvent induced shift.[22]

A varied amount of the shift reagent[23] was added to a $CDCl_3$ solution of 9-acetyl-2,7-dimethyl-1,2,3,3a,4,5-hexahydropyrene (XV, a mixture of configurational



XV

isomers), which was prepared by the Friedel–Crafts reaction[24] of VIII with acetyl chloride and aluminum chloride. In Figure 2 pseudocontact shifts of representative proton signals are shown as the function of the molar ratio of the reagent to XV. With $Eu(thd)_3$ the upfield shift was most prominent for the acetyl methyl and C-8 protons, while the C-10 proton showed a moderate shift. Remote protons such those at the C-6 and C-2 methyl did not show any significant change. It is noted that aryl methyl protons experience slight deshielding rather moving upfield. A similar phenomenon was noticed recently.[25] With $Pr(dpm)_3$ general downfield shifts were observed, especially the C-8 proton and acetyl methyl protons, which showed remarkable shifts as expected from the proximity of these to the metal.

Of the two isomeric hexahydropyrenes derived from VI, IX has the 1,2,7,8-tetrasubstituted naphthalene structure and exhibits two sets of an AB quartet of nearly equal chemical shifts and coupling constants. On the other hand X shows unequal sets of two AB

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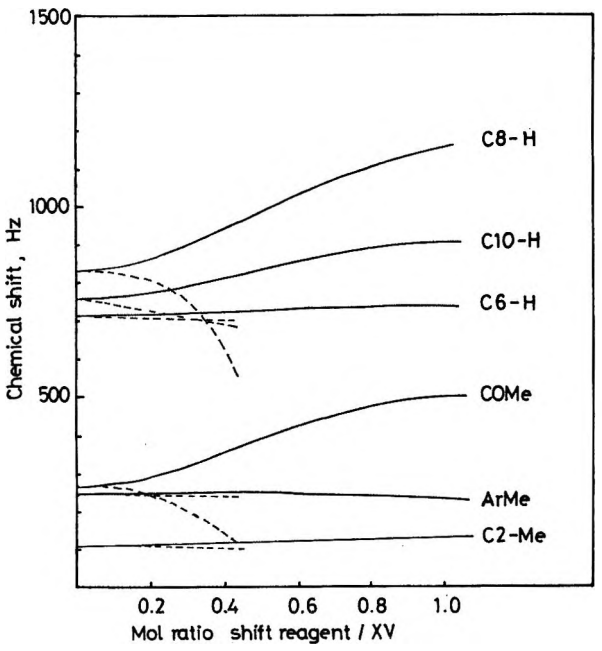
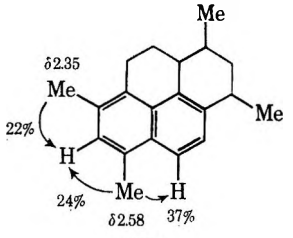


Figure 2.—Pseudo contact shifts in XV induced by $Eu(dpm)_3$ (———) and $Pr(dpm)_3$ (----) ($CDCl_3$).

quartets as expected from the structure. With IXb the methyl signal at C-3 absorbs at an unusually high field of δ 0.89, indicating the methyl group is axial and subject to a diamagnetic shift due to the naphthalene ring. The structures of X, XI, and XII were similarly determined. With XII the assignment of aryl methyl protons was achieved by NOE (see XVI).



XVI

Other Reagents.—Baker and coworkers[26] have noticed the formation of III by the treatment of I in carbon disulfide with aluminum chloride. By re-examination in our laboratory the reaction was found to give a complex mixture containing at least five materials besides III and XIV. The major product was pyrene. 4,5-Dihydropyrene (trace) and IV were also present. Those compounds preserving a cyclophane structure, such as [2.2]paracyclophane or [2.2]metaparacyclophane, were absent. The reaction of I with aluminum chloride involves fragmentation as well as disproportionation and is not so selective as the iodine-catalyzed reaction.

Cram and coworkers[27] reported the formation of III in small amount during the rearrangement of [2.2]-paracyclophane to [2.2]metaparacyclophane by means of $HAlCl_4$ in dichloromethane. The reaction involves protonated [2.2]paracyclophane as an intermediate which rearranges to the [2.2]metaparacyclophane system. In view of facile cycloisomerization of I with iodine and aluminium chloride, the origin of III could be I formed by the further rearrangement of [2.2]-paracyclophane. Although the cycloisomerization of I to III proceeds with aluminum chloride, whether there is a route *via* a protonated precursor is not known.

Other Lewis acids such as ferric chloride, cupric chloride (bromide), and nickel chloride were ineffective as catalysts for I → III.

Under electrophilic conditions bromination of I resulted in the formation of IV.[3,6] Boekelheide[28] reported that the irradiation of I with bromine gave pyrene. When I was treated with bromine in CCl_4 in the absence of catalyst, a 7% yield of III was obtained although the major product was IV. Bromine and particularly chlorine act as an electrophile to give IV *via* an addition–elimination mechanism. This may reflect the less electrophilic nature of iodine compared with other halogens and strongly suggests the participation of an iodine molecule rather than an iodonium ion. The reaction of I under ionic conditions (ICl or I_2–$AgClO_4$) gave IV in high yields, and not a trace of III was formed.[4,6] In view of a striking difference caused by the addition of silver perchlorate in the iodine reaction the effect of silver salts was examined. It is known that some silver salts promote strained σ bond rearrangement.[29] When I and silver perchlorate in benzene were warmed at 60° for 30 hr a trace of III resulted.

The treatment of I with concentrated sulfuric acid at room temperature produced IV, III, XIV, and pyrene together with sulfonated materials. Compound XIV was assumed to be formed from I *via* III since the latter was shown by a control experiment to be isomerized to XIV with sulfuric acid.[30]

Reaction Mechanism.—A marked difference in the rate of cycloisomerization among the methyl derivatives was noted. Accordingly, we carried out a series of competitive experiments between I and its methyl derivatives using an equimolar mixture of the substrates. The results are summarized in Table V. Figures indicate the rate of formation of the substituted hexahydropyrene relative to that of III. For comparison, the results for the ionic reaction using iodine–silver perchlorate are also shown. Cycloisomerization of V occured 4.2 times as fast as I, while under electrophilic conditions V underwent cyclodehydrogenation even more rapidly. For compound VI further enhancement in cycloisomerization was noticed but the cyclodehydrogenation rate was the same as that of V. It is noteworthy that VII undergoes very rapid cycloisomerization. Actually the rate is so rapid that VII was totally consumed after only 10 min at 60°, when only a few per cent of III was formed from I. These experiments provide three conclusions: (a) a methyl substituent enhances the rate of both cycloisomerization and cyclodehydrogenation; (b) the rate of enhancement is different between these two iodine-catalyzed reactions; (c) when methyl substituents are present at the position ortho to the bridging ethylene, cycloisomerization is anomalously accellerated. These

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(27) D. J. Cram, R. C. Helgeson, D. Lock, and L. A. Singer, *J. Amer. Chem. Soc.*, **88**, 1324 (1966); D. T. Hefelfinger and D. J. Cram, *ibid.*, **92**, 1073 (1970), **93**, 4754 (1971).

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(29) L. A. Paquette, *Accounts Chem. Res.*, **4**, 280 (1971).

(30) Under similar conditions [2.2]paracyclophane underwent only sulfonation.

TABLE V

COMPETITIVE REACTIONS[a] BETWEEN I AND METHYL DERIVATIVES AND STABILITIES FOR σ AND π COMPLEXES OF METHYLBENZENES[b]

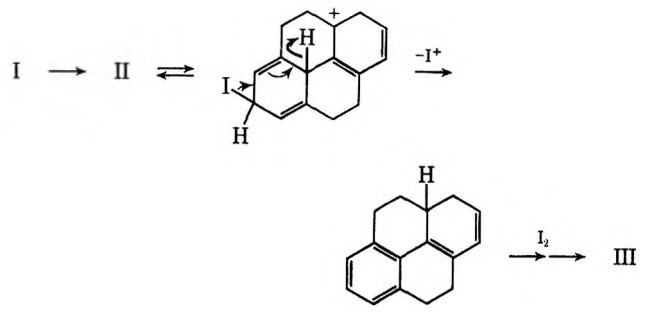
Compd	I_2 (heat)	I_2–$AgClO_4$	Compd	σ complex	π complex
I	1.0	1.0	*m*-Xylene	1.0	1.0
V	4.2	9.7	Mesitylene	630	1.3
VI	8.7	9.1	Pseudocummene	2.0	1.1
VII	Very fast		Durene	10	1.4

[a] Relative conversion to hexahydropyrenes taking I as 1 determined by treating an equimolar mixture of I and the methyl derivatives with iodine. [b] See ref 31.

data were compared with the reactivity of methylbenzenes corresponding to the half-part of the cyclophane molecules. Table V lists the stability of σ and π complexes for the model compounds.[31] The reactivities of I and V might be represented by those of *m*-xylene and mesitylene, respectively. Accordingly, one can expect strong enhancement in the reaction rate with V relative to I in a σ-complex mechanism. On the other hand moderate enhancement is to be expected with a π-complex mechanism. Strictly speaking, of course, one must consider transannular interaction and strain in the cyclophane compounds.

In electrophilic reactions, an iodonium ion attacks position 2 with concomittant bonding between C-8 and C-16 *via* σ complex II which then gives IV (Scheme I). The mechanism shown in Scheme II

SCHEME II



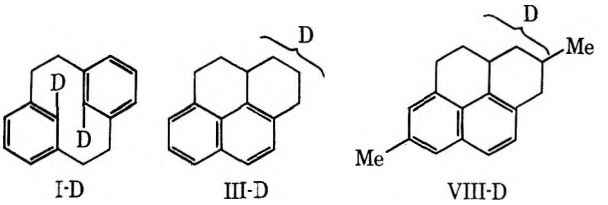
can be envisaged for the formation of III *via* a σ-complex mechanism. The scheme involves intramolecular hydride transfer in II followed by intermolecular hydride transfer and loss of iodonium ion.

The results of competitive experiments coupled with the fact that cycloisomerization does not occur in protic solvents, however, strongly suggest involvement of the iodine molecule, possibly *via* π complexation.

Indeed compound I and iodine in cyclohexane show a CT band at 334 nm. The band position is in agreement with the expected maximum, 336 nm, calculated from the ionization potential of I (8.41 eV).[32] The equilibrium constant was calculated to be 16.7 l./mol.[32]

For these cyclophanes having methyl groups ortho to the bridge ethylene one can not make reactivity comparisons with the methylbenzenes. Enhanced reactivity in VI and especially in VII can be taken as the indication of buttressing effects due to the *o*-methyl groups which raise the potential energy of the ground state by imposing additional strain.

Formally the cycloisomerization involves a transfer of four hydrogens at C-1,2,8,16, to C-4,5,6,7 positions with concomittant bonding between C-8 and C-16. Marked effects of substrate and iodine concentration on the rate of cycloisomerization suggest an intermolecular hydrogen transfer process. To test this by cross-breeding experiments, [2.2]metacyclophane-8,16-d_2 (I-D) (for deuterium contents, see Table VI)[33]



I-D III-D VIII-D

was prepared by the modified Wurtz dimerization of α,α'-dibromo-*m*-xylene-*2*-*d*. Compound I-D gave III-D by the treatment with iodine, whose deuterium content was determined by mass spectroscopy as shown in Table VI.

TABLE VI

DEUTERIUM DISTRIBUTION PER CENT

Compd	Source	d_0	d_1	d_2	d_3	d_4	d_5
I-D		1.7	21.3	77.0			
III-D	I-D	21.5	34.6	26.4	12.5	4.0	1.0
III-D	I-D + V	39.0	38.0	17.2	4.9	0.9	
VIII-D	I-D + V	52.3	34.7	10.7	2.1	0.2	

An equimolar mixture of I–D and V was similarly treated with iodine and the reaction mixture of III-D and VIII-D were separated. Their deuterium contents were determined by mass spectroscopy (Table VI). The results shows that a total of 48% of deuterium was transferred to VIII-D during the cross-breeding experiments suggesting an intermolecular mechanism. No deuterium transfer was observed in the control experiments in which a toluene-d_8–*m*-xylene–iodine system was similarly treated and analyzed. Owing to internal scrambling the position of labeling atoms in III-D and VIII-D could not be located from mass spectrometry.[34]

The formation of diastereomeric mixtures in approximately equal amounts in most cases during the cycloisomerization suggests that hydrogen transfer processes occur in a nonstereospecific manner. The fact that extended contact with iodine did not alter the product ratio shows that products formed are kinetically controlled. The driving force is ascribed to van der Waals and bond-bending strains in the ten-membered

(31) G. A. Olah, *Accounts Chem. Res.*, **4**, 240 (1971).

(32) S. Hayashi and T. Sato, *Nippon Kagaku Zasshi*, **91**, 950 (1970).

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(34) T. K. Bradshaw, J. H. Bowie, and P. W. White, *Chem. Commun.*, 537 (1970); R. G. Cooks, I. Howe, and S. W. Tam, *J. Amer. Chem. Soc.*, **90**, 4064 (1968); R. G. Cooks, I. Howe, and D. H. Williams, *Org. Mass Spectrom.*, **2**, 137 (1969).

ring, which amounts to be 13 kcal/mol[35] for I and should be larger for more strained molecules such as VII.

Experimental Section

Methods.—Pmr spectra were obtained on a Varian XL-100 spectrometer operated by deuterium lock mode. Chemical shifts are reported in parts per million downfield from TMS. Spectra were run in deuteriochloroform unless otherwise stated. Mass spectra were obtained on a Hitachi RMU-6E mass spectrometer with ionization current of either 10 eV (for deuterium content determination) or 70 eV. To determine deuterium content, contribution of ^{13}C was corrected through M + 1 to M + 4 using average values of three scans.[33] Uv and ir spectra were recorded on Hitachi EPS-3T and EPI-G2 spectrometers, respectively. Gas chromatographic analyses were performed on a Hitachi K-53 equipped with a flame-ionization detector using 3 mm by 1-m stainless steel columns packed with SE-30 or Apiezon grease L both on Daichrom A. All melting points were obtained in liquid bath and uncorrected.

Materials.—[2.2]Metacyclophane (I) was prepared as previously described[6] and was purified by sublimation followed by column chromatography and recrystallization from ethanol, mp 132–133°. Alkyl[2.2]metacyclophanes (V–VII) were prepared according to the reported procedures: 5,13-dimethyl- (V), mp 148–149°;[10] 4,14-dimethyl- (VI), mp 68–69°;[16] 4,6,12,14-tetramethyl- (VII), mp 205–206°.[10]

m-**Xylene-2-*d*.**—2-Bromo-*m*-xylene, prepared from 2,6-dimethylaniline by the diazo reaction, was converted to Grignard reagent in absolute THF, which was decomposed with excess deuterium oxide (99.8%). The resulting magnesium salt was treated with aqueous ammonium chloride solution. *m*-Xylene-2-*d* was distilled at 139–140°, and its deuterium content was determined by mass spectrometory to be 88.1%.

[2.2]**Metacyclophane-8,16-d_2 (I-D).**—α,α'-Dibromo-*m*-xylene-2-*d*, bp 160–180° (20 mm), crystals from *n*-hexane, prepared from *m*-xylene-2-*d* by the reaction with NBS, was subjected to high-dilution Wurtz dimerization reaction using a tetraphenylethylene–sodium adduct as a condensing reagent.[5] Addition of the bromide (10 g) took ~24 hr. After sublimation under reduced pressure the sublimate was purified by column chromatography on alumina followed by recrystallization from ethanol, mp 132–133°, ν_{C-D} 2230 cm^{-1}. (For deuterium content see Table VI.)

9-Acetyl-2,7-dimethyl-1,2,3,3a,4,5-hexahydropyrene (XV).—With stirring, a 2-ml CH_2Cl_2 solution containing 533 mg (6.9 mmol) of acetyl chloride and 933 mg (7.0 mmol) of aluminum chloride was added to 700 mg (3.0 mmol) of VIII dissolved in 10 ml of CH_2Cl_2 at room temperature. After 30 min of stirring followed by usual work-up, the mixture was passed through an alumina column which gave 400 mg (48% yield) of XV, mp 124–125°, as pale yellow plates, ν_{C-O}^{KBr} 1660 cm^{-1}.

The Reaction of [2.2]Metacyclophanes (I and V–VII) with Iodine. The Formation of 1,2,3,3a,4,5-Hexahydropyrenes (III and VIII–XII).—Physical properties of III and VIII–XII are shown in Table II. Table III and IV list the spectral data. A typical example is shown by the case of I.

In a sealed tube a solution of 99.4 mg (0.48 mmol) of I and 16.6 mg (0.07 mmol) of iodine in 1.5 ml of benzene was warmed at 60° for 20 hr. After washing with sodium thiosulfate solution the benzene solution was evaporated and the residue was treated with picric acid in ethanol. The picrate, mp 147.5–148°, was then subjected to column chromatography on alumina, eluted with benzene, to give colorless plates, mp 103–104°. The yield was quantitative.

The reaction was studied under several conditions as shown in Table I. No reaction occurred in ethanol, acetic acid, carbon disulfide, or dimethylformamide.

(35) C.-F. Shieh, D. McNally, and R. H. Boyd, *Tetrahedron*, **25**, 3653 (1969).

2,7-Dimethyl-1,2,3,3a,4,5-hexahydropyrenes (VIIIa and VIIIb).—These were prepared in the same way as above starting from 60.2 mg (0.26 mmol) of V, 43.5 mg (0.17 mmol) of iodine, and 1.5 ml of benzene (60°, 20 hr). The fraction which formed the picrate was subjected to column chromatography on alumina using *n*-hexane as eluent. Fast eluting fractions contained VIIIa as colorless needles, mp 90–91°, recrystallized from methanol. As a slow moving part VIIIb was isolated, mp 163–164°, recrystallized from ethanol. The combined yield of VIIIa and VIIIb was 45 mg (70%). The ratio of VIIIa and VIIIb was determined by nmr spectra to be 46:54.

3,6-Dimethyl-1,2,3,3a,4,5-hexahydropyrenes (IXa and IXb) and 1,8-Dimethyl-1,2,3,3a,4,5-hexahydropyrene (X).—These were obtained from 641.0 mg (2.71 mmol) of VI, 153.4 mg (0.60 mmol) of iodine, and 10 ml of benzene by the same reaction conditions as above (60°, 15 hr). Repeated chromatography on alumina with *n*-hexane as eluent afforded X as viscous oil and IX as colorless plates, mp 53–55°, crystallized from ethanol. Yields were obtained by gas chromatography and nmr analysis (Table II).

In one experiment the product mixture was further treated with iodine for 25 hr at 60° but the product ratio was found to be unchanged.

1,3,6,8-Tetramethyl-1,2,3,3a,4,5-hexahydropyrenes (XI and XII).—These were obtained from 103.0 mg (0.39 mmol) of VII, 58.0 mg (0.23 mmol) of iodine, and 1 ml of benzene (60°, 20 hr). By repeated chromatographic separation, XI, mp 79–80°, and XII, mp 136–141.5°, were obtained both as colorless plates. XII was found to be an equimolar mixture of diastereomers (XIIa and XIIb). Yields were obtained by gas chromatography and nmr analysis (Table II). The cycloisomerization of VII was later found to be very rapid and was nearly complete after 10 min at 60°.

Cross-Breeding Experiment between I-D and V.—A solution of 107.4 mg (0.51 mmol) of I-D, 99.5 mg (0.42 mmol) of V, and 149.0 mg (0.59 mmol) of iodine in 2 ml of benzene was subjected to the above reaction conditions. Decomposition of the picrate afforded 130 mg of mixture, from which III-D and VIII-D were isolated by column chromatography on alumina, eluted with *n*-hexane–benzene.

Their deuterium analysis data are shown in Table VI.

Competitive Experiments. A. Cycloisomerization.—A mixture of 48.1 mg (0.23 mmol) of I, 52.2 mg (0.22 mmol) of V, and 40.4 mg (0.16 mmol) of iodine in 2.5 ml of benzene was warmed at 60° for 30 min in a sealed tube. Data in Table V were obtained by gas chromatographic analyses. For a competitive experiment between I and VI the reaction mixture was warmed at 41° for 30 min.

B. Cyclodehydrogenation.—A mixture of 44.1 mg (0.21 mmol) of I, 52.9 mg (0.22 mmol) of V, 60.4 mg (0.24 mmol) of iodine, and ~50 mg (excess) of silver perchlorate in 4 ml of ether was stirred for 2 hr at room temperature.[4,6] The product analysis was performed by gas chromatography (see Table V).

Registry No.—I, 2319-97-3; I-D, 35191-48-1; III, 5385-37-5; III picrate, 35191-50-5; VIIIa, 35191-51-6; VIIIb, 35191-52-7; IXa, 35191-53-8; IXb, 35191-54-9; Xa, 35191-55-0; Xb, 35191-56-1; XI, 35191-57-2; XIIa, 35191-58-3; XIIb, 35141-01-6; XIV, 1732-13-4.

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Acidic Aromatic Hydrocarbons. Analogs of Fluoradene

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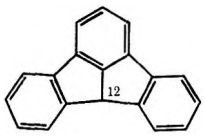
As part of a study of the debenzo analogs of fluoradene (1), which were predicted to be more acidic than the parent compound ($pK_a \cong 11$), 1*H*-cyclopent[*cd*]indene (11) was prepared. It could not be isomerized to 2a*H*-cyclopent[*cd*]indene (2) through protonation of the anion, and had a $pK_a \geqq 18$–20. 9b*H*-Cyclopenta[*jk*]fluorene (3) also was synthesized, but the absence of proton exchange in tritiated ethanol and the lack of anion formation in methanolic sodium methoxide indicated that, contrary to expectation, it was less acidic than fluoradene.

Fluoradene (1) was prepared as one of a series of aromatic hydrocarbons containing a benzene ring warped out of planarity by fused cyclopentano ring systems,[2] and it had the properties expected for such a strained compound with decreased aromatic stabilization.[3a] It also proved to be very strongly acidic, having a pK_a of about 11.[3a,b] This unusual acidity can be accounted for by the high resonance stabilization of the anion **1a** as compared to that of the parent hydro-



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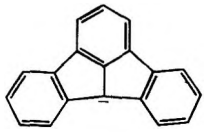
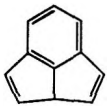


1a

carbon **1** and relief of strain in changing the hybridization at C-12 from tetrahedral to trigonal. The "$4n + 2$" or Huckel rule[4] for determining aromaticity obviously does not apply in the case of fluoradene anion, which has 20-π electrons. Molecular orbital calculations on 2a*H*-cyclopent[*cd*]indene (2)[5] indicate that the order of resonance stabilization should be anion > radical > cation. This prediction holds true for fluoradene, which is the dibenzo derivative of 2, since



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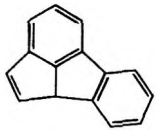


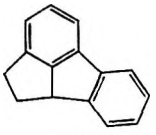
3

neither the radical nor the carbonium ion could be prepared.[3a]

It was postulated[3a] that acidity should increase in the order **1** < **3** < **2**, since there would be a greater difference in resonance stabilization between the hydrocarbon and anion as the resonance contributions of the fused benzene rings are removed (*cf.* fluorene,[6] indene,[7] and cyclopentadiene,[8] estimated pK_a's 25, 21, and 17, respectively). The same order would be postulated if relief of strain were considered a major factor in the acidity.

It has been proposed[9] that the acidity of a hydrocarbon can be correlated with ΔM, which is related to the difference in π-bond energy between the hydrocarbon, AH_i, and the corresponding anion, A_i^-. Comparisons by this calculation give the following values for ΔM: fluorene, 1.523; indene, 1.747; fluoradene (1), 2.115; 9b*H*-cyclopenta[*jk*]fluorene (3), 2.276; 2a*H*-cyclopent[*cd*]indene (2), 2.411. It should be noted that these calculations assume that strain energy is the same in the hydrocarbon and the anion; however, in the case of **1**, **2**, and **3**, less strain is anticipated in the anion.

These speculations and the availability of 2,2a,3,4-tetrahydro-1*H*-cyclopent[*cd*]idene (**5a**)[2a] and 2,9b-dihydro-1*H*-cyclopenta[*jk*]fluorene (**4**)[2c] prompted an

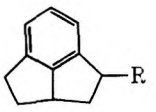


4

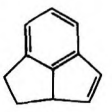
investigation of the synthesis and properties of 2 and 3.

2a*H*-Cyclopent[*cd*]indene (2).—The most direct route to 2 appeared to be didehydrohalogenation of the 1,4-dihalide of 2,2a,3,4-tetrahydro-1*H*-cyclopent[*cd*]indene (**5a**). Attempts at bromination of the 1-chloro[2b] or 1-bromo compounds (**5b** or **5c**) with *N*-bromosuccinimide followed, or accompanied, by didehydrobromination[10] were unsuccessful, but indicated spontaneous elimination of one hydrogen halide moiety to give an unstable olefin.

Accordingly, attention was directed toward a synthesis of 2,2a-dihydro-1*H*-cyclopent[*cd*]indene (6) and a study of its properties. The alcohol **5f** was recovered



5a, R = H
b, R = Cl
c, R = Br
d, R = $(CH_3)_2N$
e, R = $(CH_3)_2N\rightarrow O$
f, R = OH
g, R = $OCOCH_3$



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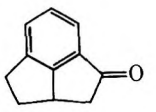

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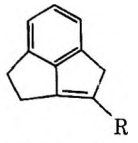


8, R = H
9, R = Br

quantitatively from an attempted dehydration *via* treatment of its tosylate in pyridine. Heating the bromide **5c** with potassium *tert*-butoxide in refluxing

(1) National Institutes of Health Predoctoral Fellow.

(2) (a) H. Rapoport and J. Z. Pasky, *J. Amer. Chem. Soc.*, **78**, 3788 (1956); (b) H. Rapoport and G. Smolinsky, *ibid.*, **82**, 1171 (1960); (c) B. L. McDowell, G. Smolinsky, and H. Rapoport, *ibid.*, **84**, 3531 (1962).

(3) (a) H. Rapoport and G. Smolinsky, *ibid.*, **82**, 934 (1960); (b) R. Kuhn and D. Rewicki, *Justus Liebigs Ann. Chem.*, **706**, 250 (1967).

(4) E. Huckel, *Z. Electrochem.*, **43**, 752 (1937).

(5) R. J. Windgassen, Jr., W. W. Saunders, Jr., and V. Boeklheide, *J. Amer. Chem. Soc.*, **81**, 1459 (1959).

(6) J. B. Conant and G. W. Wheland, *ibid.*, **54**, 1212 (1932).

(7) W. K. McEwan, *ibid.*, **58**, 1124 (1936).

(8) D. Peters, *J. Chem. Soc.*, 1274 (1960).

(9) A. Streitwieser, Jr., *Tetrahedron Lett.*, 23 (1960), and personal communication.

(10) R. A. Barnes, *J. Amer. Chem. Soc.*, **70**, 145 (1948).

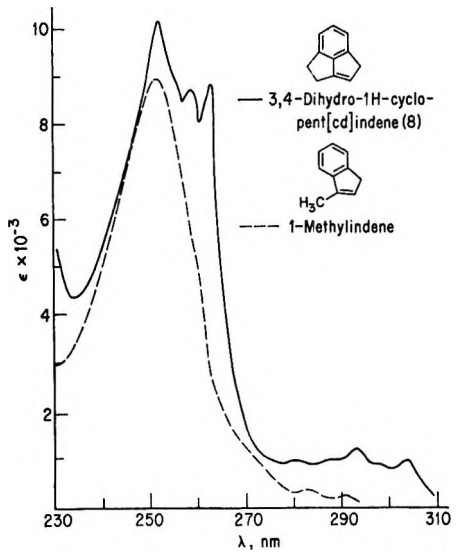


Figure 1.—Ultraviolet spectra in ethanol of 3,4-dihydro-1*H*-cyclopent[*cd*]indene (**8**) and 1-methylindene.

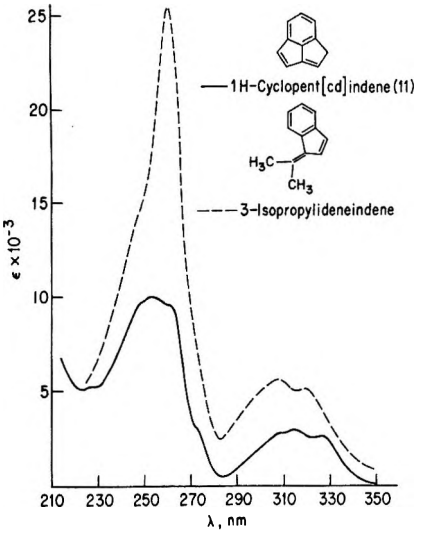


Figure 2.—Ultraviolet spectra in ethanol of 1*H*-cyclopent[*cd*]-indene (**11**) and 3-isopropylideneindene.

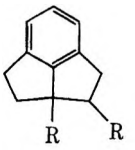
tert-butyl alcohol gave olefinic material as shown by the ultraviolet absorption of the product, but the isolated material had the composition $C_{11}H_{10}O$.

Elimination from the quaternary amine hydroxide was next investigated. The ketone **7** was converted in excellent yield by a Leuckart reaction[11] to the dimethylamine **5d**, which gave a crystalline methiodide. Pyrolysis of the corresponding quaternary hydroxide gave a 75% yield of a colorless, crystalline compound, $C_{11}H_{10}$, mp 40–44°, with the same ultraviolet absorption as observed in the dehydrobromination experiment. On several hours' exposure to air, this crystalline material turned to a slightly yellow oil identical with the monooxygenated compound obtained from the *tert*-butoxide reaction above.

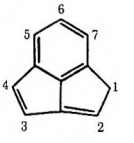
The $C_{11}H_{10}$ olefin was sensitive to acid, but could be stored indefinitely without change under nitrogen at −15°. Its nmr spectrum showed only one vinyl proton, establishing that the compound was not the expected olefin **6**, but the isomeric 3,4-dihydro-1*H*-cyclopent[*cd*]indene (**8**). The same olefin was obtained from pyrolysis of the *N*-oxide **5e** and pyrolysis of the acetate **5g**, even though both procedures[12,13] generally give little or no isomerization. The ultraviolet absorption of **8** is similar to that of 1-methylindene[14] (Figure 1) but does not show the expected decrease in extinction coefficient and smoothing out of fine structure, as does, for example, **5a**, when compared to an unstrained model compound.[2a] Evidently, effects other than simple strain are involved, probably involving interaction of the π electrons of the benzene ring and the double bond.

Dehydrobromination was again attempted as a method for introducing the second olefinic bond. A crystalline monobromo compound was obtained from the reaction of olefin **8** with *N*-bromosuccinimide, but it could not be dehydrobrominated. Nmr revealed that the compound was 2-bromo-3,4-dihydro-1*H*-cyclopent[*cd*]indene (**9**), the result of an unusual vinylic bromination. There was no vinyl proton absorption, and the rest of the spectrum was essentially the same as that of **8**.

A diolefin was finally obtained by the convenient acetate cracking procedure. Preparation of the diol **10a** by reaction of olefin **8** with osmium tetroxide and



10a, R = OH
b, R = $OCOCH_3$



11

its subsequent conversion to the diacetate **10b** went smoothly and in good yield. The diolefin, 1*H*-cyclopent[*cd*]indene (**11**), was isolated as an oil. Its ultraviolet spectrum corresponds well to that of 3-isopropylideneindene,[15] taking into account the expected bathochromic shift and decreased extinction coefficient[2] (Figure 2). Its nmr spectrum was in accord with the indicated structure (Figure 3). Diolefin **11** is sensitive to oxygen, but may be stored under nitrogen at −15° indefinitely.

When fluoradene is treated with sodium methoxide in methanol, an immediate change occurs[3a] in the ultraviolet absorption, indicating anion formation. Diolefin **11** was not expected to be as acidic as fluoradene and this was confirmed when no change occurred in its uv spectrum upon addition of methoxide (methanol) or isopropoxide (isopropyl alcohol). However, when 1*H*-cyclopent[*cd*]indene (**11**) was treated with potassium *tert*-butoxide in *tert*-butyl alcohol a gradual destruction of the spectrum occurred over 5 min, indicating that the pK_a is greater than 18–20.

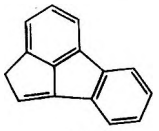
Several attempts were made to convert **11** to the desired isomeric diolefin **2**. The anion of **11** was prepared under argon with potassium *tert*-butoxide in dimethyl sulfoxide[16] and quenched with D_2O. Since the

(11) M. L. Moore in "Organic Reactions," Vol. V, Wiley, New York, N. Y., 1949, p 301.
(12) A. C. Cope, E. Czanek, and N. A. LeBel, *J. Amer. Chem. Soc.*, **81**, 2799 (1959).
(13) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, **21**, 543 (1956).
(14) P. Ramart and M. H. Hoch, *Bull. Soc. Chim. Fr.*, **5**, 848 (1938).
(15) A. Pullman, B. Pullman, E. D. Bergmann, G. Berthier, Y. Hirshberg, and Y. Sprinzak, *ibid.*, **18**, 702 (1951).
(16) D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *J. Amer. Chem. Soc.*, **83**, 3678 (1961).

charge density on C-2a is calculated to be greater than on C-1,[5,9] rate-controlled protonation should give 2-*2a-d*. Instead, only 11-*1-d*, as determined by nmr (Figure 3), was recovered, even when the anion was quenched with D_2O containing a slight excess of *p*-toluenesulfonic acid. It was not possible to distinguish whether only 11-*1-d* was formed initially, or whether deuteration took place to give 2-*2a-d* followed by isomerization to 11-*1-d*. If the latter were the case, then 2 would be strongly acidic, as predicted. It is also possible that deuteration occurred on the central carbon, C-7b, followed by isomerization. Calculations[9] indicate that the compound so formed (ΔM 2.314) would not be as acidic as 2 (ΔM 2.411), but more acidic than 11 (ΔM 1.924).

It is evident that 2, if capable of existence, would have to be synthesized by a totally different route designed to prevent the ready isomerization of the double bonds.[17]

9b*H*-Cyclopenta[*jk*]fluorene (3).—The monodebenzo analog of fluoradene was prepared by the reaction of 2,9b-dihydro-1*H*-cyclopenta[*jk*]fluorene (4) and *N*-bromosuccinimide followed by spontaneous elimination of hydrogen bromide. The crude reaction mixture also contained 2*H*-cyclopenta[*jk*]fluorene (12), nmr



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easily distinguishing between the two isomers and integration indicating that the mixture was 70–80% 3. The nmr spectrum of the mixture remained the same whether the carbon tetrachloride solution was washed with H_2O, D_2O, aqueous bicarbonate, or aqueous hydrochloric acid, or if hydrogen bromide or deuterium bromide were bubbled through the refluxing carbon tetrachloride solution. These experiments show that there is no equilibration between the isomers under either the reaction or work-up conditions, and therefore, the mixture must result from bromination occurring at the different positions (probably 2a and 9b) at similar rates.

The ultraviolet absorption of the mixture was not useful, since it did not resemble either the spectrum of 1,10b-dihydrofluoranthene or 2,3-dihydrofluoranthene.[15] The mixture of 3 and 12 is extremely sensitive to oxygen, changing to an insoluble orange solid after a few seconds' exposure to air, even in carbon tetrachloride solution. Analysis of the material obtained on short-path distillation showed substantial oxygen incorporation, and the uv absorption of the distillate was quite different from that before distillation. The reaction mixture was also unstable to chromatography.

No change was observed in the uv spectrum of the mixture containing 3 when methanolic sodium methoxide was added; however, potassium *tert*-butoxide in *tert*-butyl alcohol caused immediate destruction of the spectrum, indicating that the pK_a lies between 16 and 20. Since the C-12 hydrogen of fluoradene is exchanged for deuterium in refluxing deuterium ethoxide, a similar attempt was made to exchange the 9b hydrogen of 3, but total decomposition occurred. Some exchange took place in tritiated ethanol at room temperature, but the exchanged material was at least 400 times less active than fluoradene treated in the same manner.

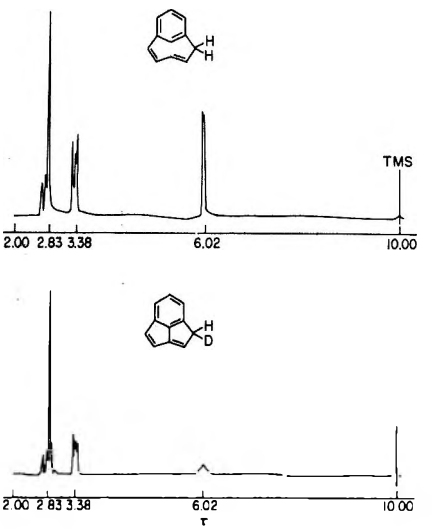

Figure 3.—Nuclear magnetic resonance spectra of 1*H*-cyclopent[*cd*]indene (11) and 1*H*-cyclopent[*cd*]indene-*1-d*.

These findings are clearly contrary to expectation. Probably the best explanation is that strain is not relieved to as great an extent as anticipated, so that the difference in resonance stabilization between the hydrocarbon and the anion is not as large in 3 as in fluoradene. There might be other factors that come into play in this unusual system, such as spatial interaction of the π system and steric inhibition of resonance, that are difficult to predict and whose magnitude would be difficult to estimate. It must also be borne in mind that MO calculations on nonalternant hydrocarbons give only rough estimates of their properties, and, therefore, the lack of agreement in the present case may not be too surprising.

It is interesting to note that structure 3 was postulated by Goldschmidt in 1880 as the structure of fluoranthene, whose relationship to fluorene was quickly established by oxidation experiments. The original analyses for fluoranthene were low in carbon, leading to a $C_{15}H_{10}$ formulation.[18] The situation was resolved by von Braun, who thought structure 3 was untenable on theoretical grounds, and synthesized the correct structure for fluoranthene.[19]

Experimental Section[20]

1-Bromo-2,2a,3,4-tetrahydro-1*H*-cyclopent[*cd*]indene (5c).—The bromide 5c was prepared (88% yield) in the same manner as the chloride 5b,[2b] substituting HBr for HCl.

Anal. Calcd for $C_{11}H_{11}Br$: C, 59.2; H, 4.9; Br, 35.8. Found: C, 58.9; H, 4.8; Br, 35.8.

(17) A recent publication [P. Eilbracht and K. Hafner, *Angew. Chem., Int. Ed. Engl.*, **10**, 751 (1971)] reports similar weak acidity for 1*H*-cyclopent[*cd*]indene (11) and similar properties for this compound prepared by a different method.

(18) G. Goldschmidt, *Monatsh. Chem.*, **1**, 221 (1880), and references cited therein.

(19) J. von Braun and G. Manz, *Ber.*, **63**, 2608 (1930).

(20) Melting points were taken on a Kofler hot stage; microanalyses were by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley. Ultraviolet spectra were taken in ethanol or methanol with a Cary Model 14 recording spectrophotometer and are reported in nanometers, and nuclear magnetic resonance spectra are reported as τ values and were taken in carbon tetrachloride with tetramethylsilane as internal standard using a Varian A-60 spectrometer, unless otherwise noted.

Attempted Dehydrobromination of 5c.—A solution prepared from 80 mg (2 mg-atoms) of potassium and 5 ml of *tert*-butyl alcohol was heated at reflux for 1 hr after addition of 446 mg (2 mmol) of **5c**. The *tert*-butyl alcohol was evaporated, the residue was extracted into ether, and the ether was washed with 1 *N* HCl and 10% $NaHCO_3$. Short-path distillation (90°, 2 μ) gave 30 mg (10%) of a yellow oil, uv max 248 and 295 nm.

Anal. Calcd for $C_{11}H_{10}O$: C, 83.5; H, 6.4. Found: C, 83.1; H, 6.2.

1-Dimethylamino-2,2a,3,4-tetrahydro-1*H*-cyclopent[*cd*]indene (5d).—A mixture of 2.00 g (13 mmol) of ketone **7**,[2a] 3.67 g (50 mol) of dimethmylformamide, and 1 ml of 85% formic acid was heated at 175° in a flask fitted with a short air condenser. After 2 hr, an additional 2 ml of 85% formic acid was added and heating was continued overnight. The dark reaction mixture was diluted with three times its volume of 0.5 *N* HCl, washed with benzene, made alkaline with concentrated NaOH, and extracted four times with benzene. Evaporation of the combined benzene extracts and short-path distillation at 65° (5 mm) of the residue gave 1.81 g (76%) of the amine **5d** as a colorless oil.

Anal. Calcd for $C_{13}H_{17}N$: C, 83.4; H, 9.1; N, 7.5. Found: C, 83.2; H, 9.3; N, 7.2.

The methiodide of **5d** was prepared with methyl iodide in methanol and was recrystallized from absolute ethanol, mp 205°.

Anal. Calcd for $C_{14}H_{20}NI$: C, 51.1; H, 6.1. Found: C, 51.4; H, 6.2.

3,4-Dihydro-1*H*-cyclopent[*cd*]indene (8).—Silver oxide, freshly prepared from 0.89 g (22 mmol) of sodium hydroxide and 1.90 g (11 mmol) of silver nitrate, was added to a warm solution of 1.00 g of **5d** methiodide in 25 ml of CO_2-free water. The grey suspension was shaken for several hours and filtered, and most of the water was evaporated. Distillation was continued in an oil bath at 200° under a stream of nitrogen until decomposition was complete. Water was added in three separate portions to complete steam distillation of the product, which was dissolved in ether. The ether solution was washed with pH 4.5 phosphate buffer and bicarbonate, and evaporated under a stream of nitrogen. Sublimation at 50° (10 mm) gave 0.32 g (75%) of colorless crystals of olefin **8**: mp 40–44°; uv max 252 nm (ε 10,100), 259 (8700), 263 (8700), 281 (960), 293 (1200), 304 (970); nmr τ 3.10 (3, ArH), 4.44 (t, 1, =CH), 6.47 (m, 4, $ArCH_2$), 7.13 (t, 2, $ArCH_2CH_2C$=).

Anal. Calcd for $C_{11}H_{10}$: C, 92.9; H, 7.1. Found: C, 92.6; H, 7.0.

The olefin **8** also was prepared by pyrolysis of *N*-oxide **5e**. To an ice-cooled solution of 270 mg (1.45 mmol) of amine **5d** in 7 ml of ether was added 18 ml of a 0.4 *M* ethereal solution of monoperphthalic acid (7.2 mmol). A gum precipitated immediately which dissolved slowly when the solution was warmed to room temperature and 10 ml of saturated $NaHCO_3$ was added. The ether was washed with saturated $NaHCO_3$ and the combined bicarbonate washes were extracted exhaustively with chloroform to give 270 mg of yellow oil on evaporation. This oil was sublimed at 70–90° (25–35 mm), giving 110 mg (53%) of olefin **8**.

The same olefin **8** was obtained by pyrolysis of 1-acetoxy-2,2a-3,4-tetrahydro-1*H*-cyclopent[*cd*]indene (**5g**). The alcohol **5f**[2a] (540 mg, 3.4 mmol) was heated with 1 ml of acetic anhydride in 10 ml of pyridine at reflux for 4 hr. Evaporation of the reaction mixture left an oil, which was dissolved in benzene and passed through a tube, packed with glass helices, at 480° in a slow stream of nitrogen. The eluent was collected in a Dry Ice–acetone cooled trap. The contents of the trap were washed into benzene, the benzene solution was washed with water, dried, and evaporated, and the residue was sublimed at 50° (10 mm) to give 360 mg (75%) of crystalline olefin **8**.

2-Bromo-3,4-dihydro-1*H*-cyclopent[*cd*]indene (9).—A mixture of 260 mg (1.5 mmol) of *N*-bromosuccinimide and 210 mg (1.5 mmol) of olefin **8** in 5 ml of carbon tetrachloride was heated at reflux overnight under nitrogen. Ether was added, the solution was washed with water and 5% $NaHCO_3$, the ether was evaporated, and the residue was sublimed at 70° (10 mm) to give 220 mg (67%) of yellow crystals of vinyl bromide **9** melting around room temperature: uv max 261, 270, 297, 308 nm; nmr τ 3.1 (3, ArH), 6.3 (2, $ArCH_2C$=), 6.6 (2, $ArCH_2$-), 7.2 (2, $ArCH_2CH_2$-C=).

Anal. Calcd for $C_{11}H_9Br$: C, 59.7; H, 4.5; Br, 35.8. Found: C, 59.4; H, 4.8; Br, 35.9.

2,2a-Dihydroxy-2,2a,3,4-tetrahydro-1*H*-cyclopent[*cd*]indene (10a).—A mixture of 690 mg (2.3 mmol) of osmium tetroxide and 320 mg (2.2 mmol) of olefin **8** in 6 ml of ether and 5 drops of pyridine was kept at room temperature for 18 hr, and then poured into a solution of 10.5 g of sodium sulfite and 8.7 g of sodium bicarbonate in 120 ml of water layered with 50 ml of benzene and 60 ml of methanol. The whole was shaken for several hours, and the brick-red precipitate was removed using Celite, the precipitate was washed with a small amount of methanol–benzene, and the benzene phase was removed. The aqueous layer was stripped of methanol and extracted with chloroform. The oily residue from evaporation of the combined benzene and chloroform layers was treated with a small amount of benzene and the resulting crystals were sublimed at 100° (1 mm) and recrystallized from benzene to give 330 mg (85%) of diol **10a**, mp 139–140°.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8 Found: C, 75.0; H, 7.0.

2,2a-Diacetoxy-2,2a,3,4-tetrahydro-1*H*-cyclopent[*cd*]indene (10b).—A solution of 90 mg (0.5 mmol) of diol **10a** in 0.2 ml of acetic anhydride and 2 ml of pyridine was heated at reflux under nitrogen for 4 hr. Ether and water were added, and the ether layer was washed with 1 *N* HCl and 5% $NaHCO_3$, dried, and evaporated. Short-path distillation at 80° (1 mm) of the residue gave 110 mg (85%) of the diacetate **10b** as a slightly yellow oil, nmr τ 8.02, 8.04 (2 s, 6, CH_3CO-), 4.78 (q, 1, >CHOCO-).

Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.2; H, 6.2. Found: C, 69.6; H, 6.3.

1*H*-Cyclopent[*cd*]indene (11).—Crude diacetate **10b**, prepared from 60 mg (0.34 mmol) of diol **10a**, was dissolved in a small amount of benzene and passed through a 20-cm tube, packed with glass helices, at 480° in a slow steam of nitrogen. The pyrolysate was collected in a Dry Ice–acetone cooled trap and taken up in ether, and the ether was washed with water, dried, and evaporated. The residue was distilled (45°, 2.5 mm) onto a cold finger to give 25 mg (52% based on diol **10a**) of diolefin **11** as a slightly yellow oil: uv max 252 nm (ε 10,000), 315 (3400), 327 (2800); nmr τ 6.02 (d, 2, J = 1.6 Hz, $-CH_2$-), 3.35 (t, 2, -CH=CH-), 2.6–3.0 (4, HC=, ArH).[17]

Anal. Calcd for $C_{11}H_8$: C, 94.3; H, 5.7. Found: C, 94.1; H, 5.9.

Attempted Preparation of 2a*H*-Cyclopent[*cd*]indene (2).—Diolefin **11** was dissolved in 0.5 ml of dimethyl sulfoxide (dried over molecular sieves) and added through a serum cap to excess sublimed potassium *tert*-butoxide in 0.5 ml of DMSO under argon in a closed flask. The resulting dark red solution was immediately syringed out and added to 7 ml of D_2O. Carbon tetrachloride was added and argon was bubbled through the mixture. The carbon tetrachloride solution was withdrawn into a syringe, filtered through $MgSO_4$, and evaporated in a stream of helium to a small volume in an nmr tube. The process was repeated in a second experiment with D_2O containing a slight excess of deuterium-exchanged *p*-toluenesulfonic acid, with the same results: uv max same as diolefin **11**; nmr τ 6.00 (broad, -CHD-), 3.35 (t, 2, -CH=CH-), 2.6–3.0 (4, HC=, ArH).

9b*H*-Cyclopenta[*jk*]fluorene (3).—2,9b-Dihydro-1*H*-cyclopenta[*jk*]fluorene (**4**), 38.3 mg (0.2 mmol), was dissolved in 1 ml of carbon tetrachloride, and 35.6 mg (0.2 mmol) of *N*-bromosuccinimide was added. The mixture was heated on a steam bath for 20 min under nitrogen as hydrogen bromide was evolved. The cooled mixture was filtered, the filtrate was evaporated to *ca.* 0.3 ml, and the nmr spectrum was taken Alternatively, H_2O or D_2O was added as nitrogen was bubbled through, the carbon tetrachloride layer was withdrawn with a syringe, filtered through $MgSO_4$ and evaporated, or the solution was washed with 10% $NaHCO_3$ or with 0.5 *N* HCl or refluxed with additional *N*-bromosuccinimide, HBr, or DBr. From all procedures, short-path distillation at 70° (3 mm) gave the same yellow oil, which was about a 3:1 mixture of 9b*H*-cyclopenta[*jk*]fluorene (**3**) and 2*H*-cyclopenta[*jk*]fluorene (**12**): nmr of **3**, τ 4.84 (d, 1, J = 4 Hz, ArCH=C), 5.68 (q, 1, J = 16, 4 Hz, ArC=CH), 6.83 (d, 1, J = 16 Hz, ArCH); nmr of **12**, τ 3.42 (t, 1, CH_2CH=), 6.08 (d, 2, $ArCH_2$).

Tritium Exchange Studies with Fluoradene (1) and 9b*H*-Cyclopenta[*jk*]fluorene (3).—Fluoradene (**1**) (12 mg) was dissolved in 5 ml of tritiated ethanol (200 μCi/ml) and the solution was allowed to sit at room temperature for 48 hr. The solvent then was removed under high vacuum and the residue was sublimed, giving recovered fluoradene (**1**) with an average count of 6.6×10^6 dpm/mmol.

The same procedure applied to the 9b*H*-cyclopenta[*jk*]fluorene (**3**) prepared above gave recovered material with an average count of 1.6×10^4 dpm/mmol.

1,10b-Dihydrofluoranthene.—3-Oxo-1,2,3,10b-tetrahydrofluoranthene[2c] (60 mg, 0.33 mmol) in 2 ml of methanol was re-

duced with 1 g of sodium borohydride in 2 ml of 50% aqueous methanol. Addition of water precipitated 3-oxy-1,2,3,10b-tetrahydrofluoranthene, which after sublimation (100°, 0.5 mm) had mp 112° (lit.[21] mp 130–134° for the alcohol obtained by reduction of the ketone with sodium amalgam).

Anal. Calcd for $C_{16}H_{14}O$: C, 86.5; H, 6.3. Found: C, 86.2; H, 6.2.

The alcohol was heated under reflux with 2 ml of pyridine and 0.5 ml of acetic anhydride for 15 hr, after which water and ether were added. After the ether phase was washed with 1 *N* HCl and 5% $NaHCO_3$, it was dried and evaporated to yield crude acetate, which was dissolved in toluene and passed through a packed tube at 470°. The pyrolysate was washed from the Dry Ice–acetone cooled trap with toluene, the toluene was evaporated, and the residue was crystallized from ethanol and then sublimed at 60° (1 mm) to give 1,10b-dihydrofluoranthene: mp 78–79°; uv max 235 nm (ε 18,900), 267 (21,000), 275 (20,700), 286 (18,500 311 (3000), 323 (3400), 341 (2300), 357 (2300); nmr τ 6.13 (q, 1, Ar_2CH), 3.93 (m, 1, ArC=CH), 3.45 (d, 1, ArCH=C).

Anal. Calcd for $C_{16}H_{12}$: C, 94.1; H, 5.9. Found: C, 93.8; H, 6.1.

(21) J. von Braun and G. Manz, *Justus Liebigs Ann. Chem.*, **488**, 111 (1931).

Registry No.—**1**, 205-94-7; **3**, 35324-19-7; **5c**, 35324-20-0; **5d**, 35324-21-1; **5d** MeI, 35324-22-2; **8**, 14310-97-5; **9**, 35324-24-4; **10a**, 35324-25-5; **10b**, 35324-26-6; **11**, 209-69-8; **12**, 208-69-5; 3-oxy-1,2,3,-10b-tetrahydrofluoranthene, 35324-28-8; 1,10b-dihydrofluoranthene, 35324-29-9.

β-Carbonylamides in Peptide Chemistry. β-Aminoenones and β-Aminoenediones from *N*-Acetoacetyl Derivatives of Secondary Amino Acids

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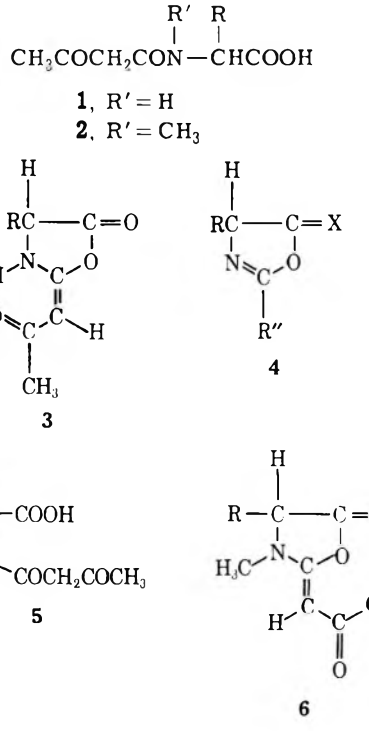
A comparative study on the behavior of some *N*-acetoacetyl (AcA) derivatives of secondary amino acids with dicyclohexylcarbodiimide was made. *N*-Methyl-AcA-amino acids yield 2-acetonylideneoxazolidin-5-ones (**6**), whose stereochemistry and condensation with nucleophiles are reported. *N*-AcA-Proline, in turn, forms a bicyclic azlactone (**7**) and a tetramic derivative (**8**); the latter reacts with nucleophiles yielding diastereomeric β-aminoenediones (**10**, **10′**) stabilized through hydrogen bonding.

During previous research[1] on the reactions of *N*-acetoacetylamino acids (AcA-aa, **1**) with dicyclohexylcarbodiimide (DCCI) we obtained 2-acetonylideneoxazolidin-5-ones **3**, which behave as possible intermediates in the condensation with nucleophiles; in some cases, we observed a condensation–racemization ratio more favorable than known for 2-oxazolin-5-ones (**4**, X = O), which racemize through enolates or mesoionic species.[2]

A 2-acetonyloxazoline structure (**4**, R″ = CH_2C-OCH_3, X = R_2 or RH), tautomerically related to **3**, was recently proposed, in turn, for the transformation products of pertinent acetoacetamides.[3]

In this paper we report on the behavior of AcA derivatives of *N*-methylamino acids and proline in the presence of the same activator of the carboxyl groups, namely DCCI. Furthermore, we studied how the eventual formation of oxazole derivatives would affect the retention of configuration in the condensation reaction.

N-Methyl-AcA-aa (**2**) condenses with amino acid esters in the presence of DCCI to give racemized *N*-methyl-AcA dipeptides. On the other hand, when **2** is treated with DCCI in the absence of nucleophiles, the very reactive 2-acetonylidene-3-methyloxazolidin-5-ones (**6**) are obtained in almost quantitative yields. Structure **6** is supported by strong carbonyl absorption at 1840 cm^{-1}, β-aminoenone maximum near 275 nm (ε >20,000),[4] and the presence of singlets for the vinyl proton and the CH_3CO group at δ 4.8 and 2.3, respectively. The hypsochromic–hyperchromic shift of the uv maximum and the strong shift of the vinyl proton with respect to the chelated structures **3** [uv max 285 nm (ε *ca.* 12,000); =CH at δ 5.2],[1] confirm that the present compounds have the thermodynamically favored trans configuration **6**. In no reaction could the alternative diastereomer be detected. This contrasts with the related β-aminoalkenoates and β-aminoenones, which are obtained under proper conditions as cis–



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(2) *Cf.* M. Goodman and C. Glaser in "Peptides, Chemistry and Biochemistry," B. Weinstein and S. Lande, Ed., Marcel Dekker, New York, N. Y., 1970.

(3) T. Kato and M. Sato, *Chem. Pharm. Bull.*, **17**, 2405 (1969); T. Kato, Y. Yamamoto, and M. Sato, *Yakugaku Zasshi*, **91**, 384 (1971).

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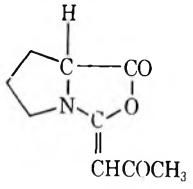
trans mixtures.[5] Further studies on the stereochemistry of the compounds described in this paper will be reported;[6a] circular dichroism data on **3** and **6** have been published.[6b]

When an azlactone (**6**) was treated with an amino acid ester or amine, the corresponding peptide or amide was obtained, as in the straightforward condensation of an *N*-methyl-AcA-aa with the nucleophile in the presence of DCCI. We investigated the retention of optical activity both in the stepwise and in the direct condensation. In spite of the fact that some *N*-acyl-*N*-alkylamino acids have a smaller tendency to racemize than *N*-acylamino acids,[2] we obtained under both sets of conditions partially racemized *N*-methyl-AcA-L-valine benzylamide, in contrast with the related AcA-L-leucine benzylamide and analogous valine derivatives.[1] The loss of optical purity may be due in part to the positive charge at the tertiary nitrogen of the trans aminoenone chromophore.[4,5]

When *N*-AcA-L-proline (**5**) was treated with an amino acid ester in the presence of DCCI, each *N*-AcA-L-prolyl dipeptide was obtained in rather low yield, and was contaminated by a second condensation product which displayed β-aminoenedione properties. This was somehow unexpected, although complications accompany the synthesis of prolyl peptides due, in part, to the rigidity at the C_α–N bond.[7]

The outcome of parallel reactions of **5** with DCCI in the absence of a nucleophile led to the elucidation of the nature of the unexpected β-aminoenediones. The reaction mixtures obtained in various solvents absorbed at 1845 cm^{-1} and contained an acylating species, which we believe to be the azlactone **7** and not



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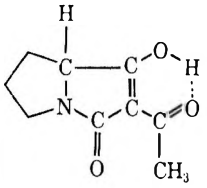

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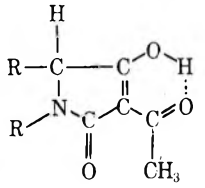

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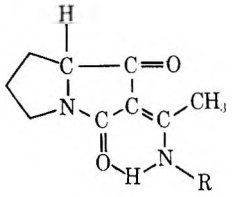
an anhydride;[8] **7** could not be isolated in sufficiently pure state to allow stereochemical conclusions. Instead, we isolated an isomer of **7**, namely the pyrrolizine derivative **8**. Uv, ir, and nmr spectra of **8**, as well as of the β-aminoenediones, fit the properties of related "tetramic acids" **9**;[9e,10] furthermore, **8** reacts promptly with nucleophiles, yielding the β-aminoenediones. In agreement with the preferred orientation in the reactions of nucleophiles onto tetramic acids[9a,f] and other tricarbonylic substrates,[10a] we believe that the aminoenediones bear the amino ester residue linked to the chain. We assume that such orientation will yield two diastereomers almost equally stabilized through hydrogen bonding (**10**, **10′**); actually, the nmr spectrum at 90 Mc of each reaction product displays two lines for the ethylidene methyl group near δ 2.5 and two distinct signals for the amino group near δ 11, in agreement with the proposed structure.



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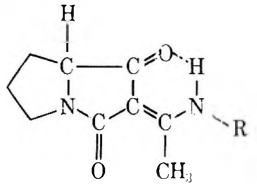
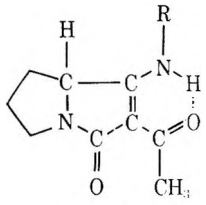


10′



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The available data indicate that an irreversible intramolecular C → C attack competes with the straightforward condensation and/or an intramolecular O → C attack leading to the acylating intermediate (**7**). Alternative hypotheses, such as the existence of slowly interconverting prolinamide rotamers[11] or fast equilibrating diastereomers (**10**, **10′**) admixed with an isomer (**11**) formed by attack on the ring, are ruled out.

AcA-prolyl dipeptide esters undergo deacetoacetylation with hydroxylamine[1] to the pertinent prolyl dipeptide esters; the β-aminoenedione (**10**, **10′**) undergoes, under the same conditions, displacement of the amino acid ester, in analogy with amine replacements reported for related aminoenones and aminoenediones.[10b] In a series of reactions of many AcA-aa with DCCI, particularly in DMF solution,[12] no tetramic derivatives could be detected, although the reaction mixtures were examined carefully by chromatography. This stresses the special effect of proline on the reaction outcome.

In conclusion, as regards the behavior of AcA-aa (**1**),[1] *N*-methyl-AcA-aa (**2**), and AcA-proline (**5**) toward carboxyl group activation *via* DCCI, **1** and **2** yield 2-acetonylideneoxazolidin-5-ones (**3**, **6**), which have the opposite stereochemistry at the olefin side chain. **5**, on the other hand, undergoes a major side reaction and yields the unexpected pyrrolizine derivatives **8** and **10**.

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(11) *Cf.* H. L. Maia, K. G. Orrell, and H. N. Rydon, *Chem. Commun.*, 1209 (1971), and references cited therein.

(12) Details of these reactions are omitted for sake of brevity.

Experimental Section[13]

N-Acetoacetyl-*N*-methylamino acids (2) and *N*-acetoacetyl-L-proline (5) were obtained by stirring a solution of *N*-methylamino acid[14] or L-proline in the equivalent amount of 2 *N* sodium hydroxide, with 1 mol of diketene at 0° until the latter was completely dissolved (1–2 hr). The solution was washed with ether, acidified to pH 1, and extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and concentrated to give AcA-L-proline,[1,9b] $[\alpha]$ −58° (*c* 2.0), and the following new *N*-methyl AcA-aa.

N-Acetoacetyl-*N*-methyl-L-alanine (2a) was an oil (80%), uv max 256 nm (ε 3800), $[\alpha]$ −33.4° (*c* 2.0). It was analyzed as the dicyclohexylammonium salt, mp 146–147°. *Anal.* Calcd for $C_8H_{13}NO_4 \cdot C_{12}H_{23}N$: C, 65.18; H, 9.85; N, 7.60. Found: C, 65.55; H, 9.74; N, 7.59.

N-Acetoacetyl-*N*-methyl-L-valine (2b) was an oil (82%), uv max 257 nm (ε 5370), $[\alpha]$ −94.0° (*c* 2.0). *Anal.* Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.20; H, 7.69; N, 6.47.

N-Acetoacetyl-*N*-methyl-L-leucine (2c) was colorless prisms: mp 85–86° (68%), $[\alpha]$ −31.9° (*c* 2.0); uv max 254 nm (ε 5630). *Anal.* Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.44; H, 7.90; N, 6.12.

2-Acetonylidene-3,4-dimethyloxazolidin-5-one (6a).—The solution of AcA-*N*-methyl-L-alanine (2a) (167 mg, 0.89 mmol) in 3 ml of dioxane was added to DCCI (190 mg, 0.89 mmol); after 2 hr standing, the DCU (182 mg, 92%) was filtered off and the solution was lyophilized. An oil was obtained: $[\alpha]$ −3° (*c* 1.5); uv max 278 nm (ε 24,000); nmr δ 1.5 (d, C_4CH_3), 2.25 (s, $CO-CH_3$), 2.9 (NCH_3), 4.15 (q, C_4H), 4.7 (s, =CH). *Anal.* Calcd for $C_8H_{11}NO_3$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.70; H, 6.45; N, 8.23.

Compounds 6b,c were obtained in an identical way from AcA-*N*-methyl-L-valine and AcA-*N*-methyl-L-leucine, respectively, and had the following properties.

2-Acetonylidene-3-methyl-4-isopropyloxazolidin-5-one (6b) was colorless prisms: mp 89–90°; $[\alpha]$ −4.3° (*c* 1.85); uv max 276 nm (ε 20,900). *Anal.* Calcd for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.31; H, 7.72; N, 7.28.

2-Acetonylidene-3-methyl-4-isobutyloxazolidin-5-one (6c) had mp 59–60°; $[\alpha]$ −0.7°; uv max 275 nm (ε 26,900). *Anal.* Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.62; H, 8.76; N, 6.74.

N-Acetoacetyl-*N*-methylvaline Benzylamide.—A sample of *N*-methyl-AcA-L-valine (2b) (215 mg, 1 mmol), dissolved in 5 ml of dioxane, was treated with DCCI (206 mg, 1 mmol) and allowed to stand for 2 hr. The DCU was filtered and the solution was treated with benzylamine (107 mg, 1 mmol) and left overnight. Concentration yielded an oil (A) that was redissolved in ethyl acetate and washed with aqueous sodium bicarbonate and then with water. The solution, taken to dryness, gave an oil (220 mg, 70%), $[\alpha]$ −7.2° (*c* 4.2). *Anal.* Calcd for $C_{17}H_{24}N_2O_3$: C, 67.08; H, 7.95; N, 9.20. Found: C, 67.14; H, 7.92; N, 9.14.

N-Benzyloxycarbonyl-*N*-methylvaline Benzylamide.—A sample of the above crude oil (A) obtained in an identical run was dissolved in 2 ml of ethanol–acetic acid–water (4:1:1) and added with 70 mg (1 mmol) of hydroxylamine hydrochloride. The mixture was heated at 40° for 30 min and the resulting solution was taken to dryness. After working up,[1] the aqueous extract, containing *N*-methylvaline benzylamide hydrochloride, was treated with benzyloxycarbonyl chloride in the presence of sodium hydroxide at 0°. An oil separated and was extracted with chloroform. After washing with water, 1.0 *N* HCl, and water, the solution was taken to dryness. A thick oil (90%) was obtained, $[\alpha]$ −22.9° (*c* 1.8, ethanol). *Anal.* Calcd for $C_{21}H_{26}N_2O_3$: C, 71.16; H, 7.39; N, 7.30. Found: C, 71.0; H, 7.20; N, 7.22.

The same product was obtained by treating (*Z*)-L-valine with benzylamine in the presence of DCCI, *via* symmetric anhydride,[15] yield 93%, $[\alpha]$ −80.1° (*c* 2.02, ethanol), indicative that in the preparation *via* the *N*-methyl-AcA-aa (2b) (see above) there had been 37.5% racemization. Finally, a third sample of *N*-methyl-(*Z*)-valine benzylamide was obtained by N-deacetoacetylation followed by N-benzyloxycarbonylation of a sample of the oil (A) prepared in turn by treating 2b with benzylamine and then with DCCI; this sample had $[\alpha]$ −17.6°, indicative that extensive racemization had occurred also in this case.

N-Acetoacetyl-*N*-methylvalylglycine Ethyl Ester.—A sample of compound 2b (645 mg, 3 mmol) in 5 ml of acetonitrile was added with DCCI (618 mg, 3 mmol), allowed to stand for 2 hr, and treated with a solution of glycine ethyl ester hydrochloride (460 mg, 3.3 mmol) and triethylamine (313 mg, 3.1 mmol) in 5 ml of acetonitrile. The mixture was let stand overnight, the DCU was filtered off, and the solution was taken to dryness. The oil was redissolved in ethyl acetate and washed with water, 0.1 *N* HCl, water, aqueous sodium bicarbonate, and again water; the solution was dried and concentrated *in vacuo*. An oil was obtained (800 mg, 87%), $[\alpha]$ −2° (*c* 3.6), uv max 253 nm (methanol). *Anal.* Calcd for $C_{14}H_{24}N_2O_5$: C, 55.98; H, 8.05; N, 9.32. Found: C, 55.61; H, 8.30; N, 9.29.

N-Acetoacetyl-*N*-methylvalyl-L-valine Methyl Ester.—This compound was prepared from 2b and L-valine methyl ester, as an oil (85%); it consisted probably of a diastereomeric mixture, but no resolution was apparent on tlc. *Anal.* Calcd for $C_{16}H_{28}N_2O_5$: C, 58.51; H, 8.59; N, 8.53. Found: C, 58.08; H, 8.42; N, 8.25.

1-Hydroxy-2-acetyl-3-oxo-3,5,6,7,7a-pentahydropyrrolizine (8). A.—AcA-L-proline[1,9b] was converted into its methyl ester and then into the corresponding tetramic derivative (8,[9b] sodium salt) (10.0 g, 98%).[9b] A sample was dissolved in 0.1 *N* hydrochloric acid. Extraction with ethyl acetate gave a solution that was washed with a little water and taken to dryness as an oil, $[\alpha]$ −95.2° (*c* 2.1), uv max 277 nm (ε 12,600). *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.74; H, 6.35; N, 7.58.

B.—AcA-L-proline was treated with DCCI in dioxane or acetonitrile, following the procedure used to obtain 6a. DCU was filtered after 10–15 hr from the solution, which absorbed at 1845 cm^{-1}; the solution was concentrated to dryness and taken up with ethyl acetate–aqueous sodium bicarbonate. Concentration of the organic layer and purification on a column of SiO_2 gave *N*-acetoacetylprolylurea as an oil, $[\alpha]$ 78.3° (*c* 2.67). *Anal.* Calcd for $C_{22}H_{35}N_3O_4$: C, 65.16; H, 8.70; N, 10.36. Found: C, 65.20; H, 8.65; N, 10.41. The aqueous layer was extracted with ethyl acetate at various pH's; the presence of 8 and unchanged *N*-acetoacetylproline was demonstrated on tlc, by comparison with authentic samples.

2-(α-Ethoxycarbonylmethylamino)ethylidene-1,3-dioxopyrrolizidine (10, 10′, R = $CH_2COOC_2H_5$) and *N*-Acetoacetyl-L-prolylglycine Ethyl Ester.—Samples of *N*-acetoacetylproline (4.18 g, 0.021 mol) and glycine ethyl ester hydrochloride (2.9 g, 0.018 mol) were dissolved in a mixture of DMF (20 ml) and acetonitrile (100 ml); triethylamine (2.8 ml, 0.02 mol) was added under stirring and cooling at −10°. The mixture was treated with DCCI (4.66 g, 0.023 mol) and kept for 1 hr at −10° and then for 16 hr at 20° under stirring. From the resulting suspension, the DCU was filtered off (100%) and the solution was evaporated to dryness. The residue was extracted with ethyl acetate that left undissolved the triethylammonium hydrochloride formed (100%); the extract was washed with water and 1 *N* HCl until neutral, dried, and concentrated to a solid. This work-up caused the disappearance of absorption at 1845 cm^{-1}, possibly due to reconversion of the azlactone 7 into AcA-proline 5 (*ca.* 10%). The solid was extracted with ether and recrystallized from ethyl acetate–petroleum ether (bp 40–60°) as colorless prisms (0.8 g, 20%): mp 135–136°; $[\alpha]$ −28° (*c* 2.0, methanol); uv max 305 nm (ε 20,000); ir 3450, 1750, 1710, 1675, 1630, 1600 cm^{-1}; nmr δ 1.3 (t, CH_2CH_3), 1.8–2.3 (m, CH_2CH_2), 2.5, 2.53 (CH_3C=), 2.9–3.3 (m, $C_{7a}H$), 3.55–4.0 (m, CH_2N), 4–4.4 (m, CH_2O, NCH_2CO), 10.95 (t, NH), 11.3 (t, NH). The twin signals at δ 2.5 and 2.53 did not collapse to a single peak upon irradiation of the spectrum; on deuteration, the amino proton peak disappears in about 16 min and uncoupling of the CH_2N was observed. *Anal.* Calcd for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N,

(13) Elemental analyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, at the care of Professor Eloisa Celon Mazzucato. Uv and ir spectra and optical activities (line D, at 25°, concentration in parentheses) were measured in dioxane, unless otherwise stated. Nmr spectra were measured in $CDCl_3$, using a Bruker Spectrospin, 90 Mc, and are given in (δ) parts per million, using $(CH_3)_4Si$ as internal standard. The molecular weight of the β-aminoenedione (10, 10′) was measured with a vapor pressure osmometer Hewlett-Packard 301A in benzene and with a mass spectrometer Hitachi Perkin-Elmer RMV6, with recorder H.P.E. 196. For tlc, precoated layers of silica gel Merck and ethyl acetate–benzene (2:1) as eluent were used; acetoacetyl derivatives gave blue-violet spots using an iron chloride spray.

(14) H. N. Rydon and P. W. G. Smith, *J. Chem. Soc.*, 3646 (1956).

(15) L. Kisfaludy and M. Löw, "Peptides 1962," G. T. Young, Ed., Pergamon Press, Oxford, 1963, p 93.

10.52; mol wt, 266.3. Found: C, 59.23; H, 6.79; N, 10.64; mol wt, 261 (C_6H_6), *m/e* 266. The same product was obtained by treating the pyrrolizinone **8** with glycine ethyl ester, in the condition described below for **10**, **10'a**.

The above ether extract was evaporated to dryness, yielding an oil whose physical properties and elemental analysis indicated that it was crude AcA-pro-gly-OEt (4.0 g, 60%). Upon treatment with hydroxylamine hydrochloride[1] it yielded L-prolylglycine ethyl ester hydrochloride, identical with an authentic specimen.[16]

A sample of **10**, **10'** was treated with hydroxylamine, under the same conditions;[1] chromatography showed the release of glycine ethyl ester hydrochloride and of a derivative, giving a strong blue spot with iron chloride, identical with the one obtained by mixing equimolecular quantities of **8** and hydroxylamine hydrochloride.[9f,10b]

Several other reactions of AcA-proline with glycine ethyl ester and DCCI were run using different solvents (acetonitrile alone, dioxane, $CDCl_3$); work-up always gave mixtures of **10**, **10'** and AcA-prolylglycine ethyl ester.

2-(α-1-Ethoxycarbonyl-1-ethylamino)ethylidene-1,3-dioxopyrrolizidine (**10**, **10'a**, **R** = $CHCH_3COOC_2H_5$).—A sample of **8** as the sodium salt (812 mg, 0.004 mol), suspended in ethanol (20 ml), was treated with L-alanine ethyl ester hydrochloride (615 mg, 0.004 mol), refluxed for 1 hr, and filtered. The solution was taken to dryness and the residue was redissolved in ethyl acetate. The solution was washed with water, 1 *N* hydrochloric acid, and water, dried on sodium sulfate, and concentrated to dryness as an oil (0.54 g, 49%): uv max 306 nm (ε 20,000); [α] +30.5 (*c* 2.2); nmr δ 1.3 (t, CH_2CH_3), 1.6 (d, CH_3), 1.7–2.3 (m, CH_2CH_2), 2.50, 2.52 (=CCH_3), 2.9–3.4 (m, C_{7a} H), 3.4–3.9 (m, CH_2N), 4.0–4.6 (m, OCH_2, C_α H), 10.8 (d), 11.1 (d, NH). *Anal.* Calcd for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 59.81; H, 6.95; N, 9.61.

(16) S. Guttman, J. Pless, and R. A. Boissonas, *Helv. Chim. Acta*, **45**, 170 (1962).

Registry No.—**2a**, 35211-90-6; **2b**, 35191-59-4; **2c**, 35141-03-8; **6a**, 35141-04-9; **6b**, 35141-05-0; **6c**, 35141-06-1; **8**, 2113-85-1; **10** (R = $CH_2CO_2C_2H_5$), 35191-60-7; **10'** (R = $CH_2CO_2C_2H_5$), 35141-08-3; **10** (R = $CHCH_3CO_2C_2H_5$), 35141-09-4; **10'** (R = $CHCH_3CO_2C_2H_5$), 35191-61-8; *N*-acetoacetyl-*N*-methylvaline benzylamide, 35191-62-9; *N*-benzyloxycarbonyl-*N*-methylvaline benzylamide, 35191-63-0; *N*-acetoacetyl-*N*-methylvalylglycine ethyl ester, 35191-64-1; *N*-acetoacetyl-*N*-methylvalyl-L-valine methyl ester, 35141-10-7; *N*-acetoacetylprolylurea, 35191-67-4.

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Photolysis of Dibenzylamine. Formation of Benzylamino and Dibenzylamino Radicals

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Direct irradiation of *N,N*-dibenzylamine in solution at 254 nm leads to efficient homolysis of the benzyl–nitrogen bond. Product studies show that the subsequent dark reactions observed are primarily those of the *N*-benzylamino radical with dibenzylamine to afford benzylamine and the dibenzylamino radical by abstraction from the N–H bond. There is no evidence for the intermediacy of the isomeric carbon-centered radical. Combination and disproportionation reactions of the benzylamino and the dibenzylamino radicals are discussed.

Early photochemical studies of nitrogen-containing systems primarily involved decomposition of ammonia[1] and simple alkylamines[2] in the gas phase. Primary and secondary alkylamines were shown to decompose by a homogeneous cleavage of the N–H bond when subjected to light from a mercury arc lamp.[3,4] Only with tertiary amines, in which no N–H bond was available, did alkyl–nitrogen homolysis become important. The photolysis of a series of primary and secondary methylamines at 77°K afforded esr spectra, which were attributed to nitrogen-centered radicals.[5]

Studies with both *n*-amylamine and *n*-butylamine showed that no decomposition corresponding to a Norrish type II reaction was associated with the photolysis of simple alkylamines.[6a] Extensive polymer formation and product arising from other than simple radical processes have obscured the elucidation of the mechanistic details of the gas-phase reactions. The solution photochemistry of amines subsequently showed that the products initially formed, when both primary and secondary amines were photolyzed in hydrocarbon media, were similar to those formed in the gas phase.[6b,7] Ammonia, always present as a secondary reaction product in photolyses carried out in the vapor phase, however, was shown to be absent in solution.[8,9]

Kinetic studies[10] involving the attack of alkyl radicals

(1) (a) E. Warburg, *Sitzungsber. Preuss. Akad. Wiss.*, 746 (1911); *Chem. Abstr.*, **6**, 20 (1912). (b) E. Warburg, *Sitzungsber. Preuss. Akad. Wiss.*, 216 (1912); *Chem. Abstr.*, **6**, 3356 (1912). (c) W. Kuhn, *C. R. Acad. Sci.*, **177**, 956 (1923); *Chem. Abstr.*, **18**, 789 (1924). (d) W. Kuhn, *C. R. Acad. Sci.*, **178**, 708 (1924); *Chem. Abstr.*, **8**, 1787 (1924). (e) W. Kuhn, *J. Chim. Phys.*, **23**, 521 (1926); *Chem. Abstr.*, **20**, 3646 (1926). (f) J. R. Bates and H. S. Taylor, *J. Amer. Chem. Soc.*, **49**, 2438 (1927). (g) W. E. Groth, U. Schurath, and R. N. Schindler, *J. Phys. Chem.*, **72**, 3914 (1968).

(2) (a) H. J. Emeleus and H. S. Taylor, *J. Amer. Chem. Soc.*, **53**, 3370 (1931); (b) H. J. Emeleus and L. J. Jolley, *J. Chem. Soc.*, 1612 (1935).

(3) C. H. Bamford, *J. Chem. Soc.*, 17 (1939).

(4) J. V. Michael and W. A. Noyes, Jr., *J. Amer. Chem. Soc.*, **85**, 1228 (1963).

(5) S. G. Hadley and D. H. Volman, *ibid.*, **89**, 1053 (1967). See also T. Richerzhagen and D. H. Volman, *ibid.*, **93**, 2062 (1971).

(6) (a) C. H. Bamford and R. G. W. Norrish, *J. Chem. Soc.*, 1504 (1935); (b) G. H. Booth and R. G. W. Norrish, *ibid.*, 188 (1952).

(7) For other photochemical reactions of amines see (a) J. A. Barltrop and R. J. Owers, *Chem. Commun.*, 1462 (1970); (b) D. R. G. Brimage and R. S. Davidson, *ibid.*, 1385 (1971); (c) C. H. Niu and V. I. Stenberg, *ibid.*, 1430 (1971); (d) D. Bryce-Smith, M. T. Clarke, A. Gilbert, G. Klunkin, and G. Manning, *ibid.*, 916 (1971); (e) N. Paillous and A. Lattes, *Tetrahedron Lett.*, 4945 (1971).

(8) The photolysis of both di- and triethylamine has been carried out on the neat liquids with a medium-pressure mercury lamp.[9] Due to the long periods of irradiation (90 hr) and the consequent complexity of the resulting products, mechanistic arguments should be considered tenuous.[9a]

(9) (a) L. T. Allan and G. A. Swan, *J. Chem. Soc.*, 4822 (1965); (b) C. H. Niu and V. I. Stenberg, *Chem. Commun.*, 1430 (1971).

(10) (a) P. J. Kozak and H. Gesser, *J. Chem. Soc.*, 448 (1960); (b) R. K. Brinton, *Can. J. Chem.*, **38**, 1339 (1960); (c) P. Gray and J. C. J. Thynne, *Trans. Faraday Soc.*, **59**, 2275 (1963); (d) P. Gray and A. Jones, *ibid.*, **62**, 112 (1966); (e) P. Gray, A. Jones, and J. C. J. Thynne, *ibid.*, **61**, 474 (1965); (f) D. A. Edwards, J. A. Kerr, A. C. Lloyd, and A. F. Trotman-Dickerson, *J. Chem. Soc. A*, 1500 (1966).

on various alkylamines, and the determination of bond dissociation energies of amines,[11] have contributed to an understanding of the chemistry of nitrogen-centered radicals. The heats of formation of amino radicals generally decrease with alkyl substitution in the order $\dot{N}H_2 > CH_3\dot{N}H > (CH_3)_2\dot{N}$ [that is, ΔH_f = 47.2, 45.2, and 38.2 kcal mol^{-1}, respectively].[12] Thus, the stability of radicals centered on nitrogen exhibits the same trend as those of the carbon analogs.

Most of our knowledge of the reactions of the nitrogen-centered radicals has come from the dimethylamino radical generated thermally or photochemically from tetramethyltetrazene.[13,14] This radical is reported to abstract the α hydrogen atom from cumene (as evidenced by the formation of dimethylamine and bicumyl)[15] and add to α-methylstyrene.[16] The photolysis of *N*-(*tert*-butyl)-*N*-chloroacetamide in benzene afforded the amido radical, which failed to add to any of a series of olefins.[17] It was concluded that neutral amino, alkylamino, or acylamino radicals abstract hydrogen from olefins in preference to addition to the double bond. The possible exceptions to this generalization are protonated amino radicals. The previously observed addition to α-methylstyrene[16] may be an abstraction reaction followed by radical combination. Support for this view was provided by the fact that no addition products were formed when the dimethylamino radical was produced in the presence of stilbene.[18] However, the addition of the dimethylamino radical to ethylene in a vapor phase process has been reported.[19] Mackay and Waters[20] generated the dimethylamino radical photochemically from the tetrazene in the presence of hydrogen donors and concluded that hydrogen abstraction by a nitrogen-centered radical is a very selective process and occurs only when a relatively stable radical results.

In light of the divergent data surrounding amino radicals, we have investigated the photochemical decomposition of *N*,*N*-dibenzylamine as a system for the production of amino radicals.

Results and Discussion

Dibenzylamine decomposed to a mixture of products when irradiated with 253-nm light. Hydrogen, found to be a major product in the photolysis of primary and secondary aliphatic amines[3] in the gas phase, was not detected in solution.[21] We find that the major products included toluene, benzylamine, and *N*-benzylbenzaldimine. Tribenzylamine and bibenzyl are formed in lesser quantities but of equal importance for mechanistic considerations. Table I lists the compounds identified from the photolysis carried out in several solvents. These product studies are based on reactions allowed to proceed to only ~10% completion, thus avoiding complications due to secondary photolysis of the initially formed products. The presence of bibenzyl, toluene, and benzylamine suggests an initial C–N bond homolysis (eq 1) from which both toluene and benzylamine could result by subsequent hydrogen abstraction.

TABLE I
PRODUCTS FROM THE PHOTOLYSIS OF DIBENZYLAMINE AT 253 nm[a]

	Product, mmol				
Concn, *M*	$PhCH_3$	$PhCH_2NH_2$	$PhCH{=}NCH_2Ph$	$(PhCH_2)_3N$	$(PhCH_2)_2$
0.02[b]	0.04	0.05	0.03	0.002	0.01
0.15[c]	0.06	0.06	0.09	0.02	0.02
0.20[c]	0.10	0.07	0.10	0.02	0.02
0.25[c]	0.11	0.09	0.11	0.03	0.02
0.50[c]	0.14	0.13	0.12	0.05	0.02
0.75[c]	0.16	0.16	0.15	0.07	0.02
1.00[c]	0.165	0.19	0.16	0.08	0.02
1.50[c]	0.19	0.23	0.17	0.10	0.02
0.25[d]	0.09	0.07	0.09	0.04	0.027
0.50[d]	0.11	0.11	0.11	0.06	0.030
0.75[d]	0.12	0.12	0.12	0.07	0.035
1.00[d]	0.13	0.14	0.14	0.10	0.035
1.50[d]	0.14	0.16	0.15	0.12	0.33
0.5[e]	0.06	0.04	0.07	0.02	0.01
1.0[e]	0.07	0.05	0.09	0.03	0.01

[a] Photolysis for 60 min. [b] Pentane. [c] Cyclohexane. [d] Acetonitrile. [e] Methanol.

$$(PhCH_2)_2NH \xrightarrow{h\nu} PhCH_2\cdot + PhCH_2\dot{N}H \qquad (1)$$

Both cyclohexene and bicyclohexyl are products from the bimolecular reaction of two cyclohexyl radicals. The absence of detectable amounts of these compounds indicates that attack on this solvent is minor and that the products arise predominantly by reaction with substrate. The benzyl radical is not expected to attack cyclohexane to any significant extent at room temperature and our observation that the benzylamino radical does not dehydrogenate cyclohexane is in general agreement with the MacKay and Waters[20] studies with the dimethylamino radical. Similarly, the absence of succinonitrile precludes appreciable attack at the α hydrogens of acetonitrile.

If attack on the substrate is considered to be the primary process, four reactions involving the abstraction of hydrogen from dibenzylamine are possible

$$(PhCH_2)_2NH + PhCH_2\cdot \begin{cases} \rightarrow PhCH_3 + (PhCH_2)_2N\cdot & (2a) \\ \rightarrow PhCH_3 + PhC\dot{H}NHCH_2Ph & (2b) \end{cases}$$

$$(PhCH_2)_2NH + PhCH_2\dot{N}H \begin{cases} \rightarrow PhCH_2NH_2 + (PhCH_2)_2N\cdot & (2c) \\ \rightarrow PhCH_2NH_2 + PhC\dot{H}NHCH_2Ph & (2d) \end{cases}$$

(11) (a) M. Szwarc, *Proc. Roy. Soc., Ser. A*, **198**, 285 (1949); (b) M. Szwarc, *ibid.*, **197**, 267 (1949); (c) J. A. Kerr, R. C. Serhar, and A. F. Trotman-Dickerson, *J. Chem. Soc.*, 3217 (1963); (d) B. G. Gowenlock, P. P. Jones, and J. R. Majer, *Trans. Faraday Soc.*, **57**, 23 (1961); (e) N. J. Friswell and B. G. Gowenlock, *Advan. Free Radical Chem.*, **2**, 7 (1967).

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(20) D. Mackay and W. A. Waters, *J. Chem. Soc. C*, 813 (1966).

(21) It has recently been suggested,[14a] however, that dimethylamino radicals generated photochemically from tetramethylurea or dimethylacetamide afford hydrogen by disproportionation.

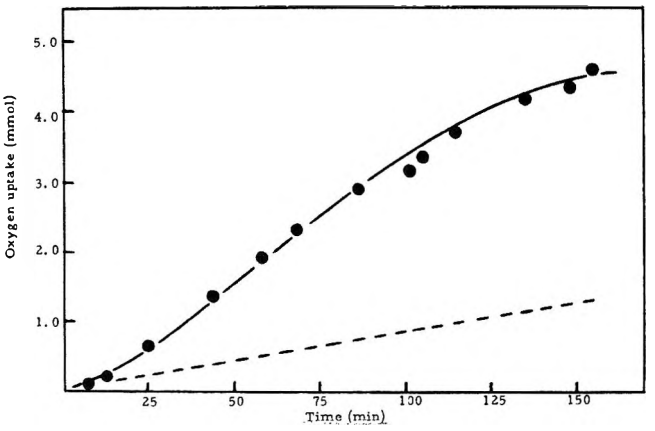

Figure 1.—Oxygen uptake in thermal decomposition of dicumyl peroxide in dibenzylamine: (●) experimental; (——) theoretical uptake assuming no chain reaction (125°).

(eq 2). Several results indicate that attack is mainly at the N–H bond. Since there are no authenticated examples of 1,2-hydrogen shifts[22] (eq 3), the formation

$$\underset{\mathbf{2}}{\mathrm{PhCHNCH_2Ph}} \xrightarrow{\text{O}} \underset{\mathbf{1}}{\mathrm{PhCH_2NCH_2Ph}} \qquad (3)$$

of tribenzylamine is best explained as a dimerization process involving a benzyl radical and a dibenzylamino radical formed in either step 2a or 2c.

Tribenzylamine was identified (after separation by preparative vpc) by its pmr spectrum and it mass spectral fragmentation pattern when compared with authentic tribenzylamine. The mass spectrum of tribenzylamine shows a molecular ion at *m/e* 287, an M − 1 peak at *m/e* 286, and major peaks at *m/e* 196 [$(PhCH_2)_2N^+$], 210 [$(PhCH_2)_2NCH_2^+$], and 91 [$PhCH_2^+$]. The isomer $PhCH_2CH(Ph)NHCH_2Ph$ (**3**), which would be expected from the dimerization of the carbon-centered radical **2** and a benzyl radical, has a completely different fragmentation pattern. Neither a molecular ion nor an M − 1 peak is observed in **3**, and the most prominent ion is at *m/e* 106 ($PhCH_2NH^+$).

The chemistry of the carbon-centered radical **2** was further studied by examining the reaction of dibenzylamine with alkoxy radicals, which were generated thermally from both di-*tert*-butyl and dicumyl peroxide (eq 4 and 5). The carbon–carbon dimer **4** and

$$\mathrm{RO\cdot} + (\mathrm{PhCH_2})_2\mathrm{NH} \longrightarrow \mathrm{ROH} + \underset{\mathbf{2}}{\mathrm{PhCHNCH_2Ph}} \qquad (4)$$

$$2\,\underset{\mathbf{2}}{\mathrm{PhCHNCH_2Ph}} \begin{cases} \longrightarrow \mathrm{PhCH{=}NCH_2Ph} + (\mathrm{PhCH_2})_2\mathrm{NH} \\ \longrightarrow \underset{\mathbf{4}}{\mathrm{PhCHNHCH_2Ph}} \\ \qquad\quad \mathrm{PhCHNHCH_2Ph} \end{cases} \qquad (5)$$

N-benzylbenzaldimine are the predominant products, as shown in Table II. It is apparent that alkoxy attack occurred predominantly at carbon[23] to produce radical **2**, since the results differ from those observed with the *N,N*-dibenzylamino radical derived from the decomposition of tetrabenzyltetrazene (*vide infra*). The

(22) O. L. Chapman, "Organic Photochemistry," Vol. I, Marcel Dekker, New York, N. Y., 1967.

(23) E. S. Huyser, C. J. Bredeweg, and R. M. Van Scoy, *J. Amer. Chem. Soc.*, **86**, 4148 (1964).

TABLE II

REACTION OF DIALKYL PEROXIDES AND DIBENZYLAMINE[a]

Peroxide R	Peroxide mmol	Product, mmol: Alcohol[e]	Ketone[f]	PhCH= NCH$_2$Ph	Dimer **4**	PhCHO
tert-Butyl[b]	1.4	2.12		0.51	0.59	
Cumyl[c]	1.04	2.0		0.60	0.35	0.59[d]
Cumyl	1.12	2.20	0.2	0.65	0.24	
Cumyl	3.5	6.5	0.5	2.2	1.0	

[a] Run in 15 ml of neat amine at 130° for 6 hr (degassed with N_2). [b] Di-*tert*-butyl peroxide. [c] Dicumyl peroxide. [d] Only after acid hydrolysis. [e] Either *tert*-butyl alcohol or cumyl alcohol. [f] Either acetone or acetophenone.

absence of toluene and bibenzyl indicates that β scission (eq 6) is not important for the radical **2**. The oxy-

$$\mathrm{PhCHNCH_2Ph} \longrightarrow \mathrm{PhCH{=}NH} + \mathrm{PhCH_2\cdot} \qquad (6)$$

gen analog of **2**, however, generated in dibenzyl ether is known to cleave directly to benzaldehyde and a benzyl radical.[24]

When oxygen was introduced into the system, the yield of dimer dropped below detectable limits, and the imine yield increased well beyond the stoichiometric limit imposed by the peroxide (Table III).

TABLE III

EFFECT OF OXYGEN ON PEROXIDE REACTIONS WITH DIBENZYLAMINE[a]

Dicumyl peroxide	O_2	Product, mmol: Ph-C(CH$_3$)$_2$-OH	PhCCH$_3$ (O)	PhCH= NCH$_2$Ph	PhCHO: *d*	PhCHO: *e*
1.10	*b,f*	2.1	0.1	3.95		
1.10	7.0[c,g]	1.91	0.23	5.73	2.3	8.0
1.10	5.5[c,h]	1.80	0.4	4.6	1.9	6.6

[a] Same conditions as previously described, except that oxygen was present. [b] Run under 20 psi oxygen. [c] Oxygen uptake followed manometrically. [d] Yield before hydrolysis. [e] Yield after hydrolysis. [f] Run 360 min. [g] Run 250 min. [h] Run 150 min.

Autoxidation of the amine was not evident in the absence of peroxide. The difference in the yield of benzaldehyde before and after hydrolysis was identical with the amount of imine present and indicates that no other aldehyde precursor was formed (*e.g.*, PhCH= NH). The effect of oxygen can be interpreted as trapping the radical **2** to produce an intermediate peroxy radical **5**, which is known to undergo a wide

$$\underset{\mathbf{2}}{\mathrm{PhCHNCH_2Ph}} + \mathrm{O_2} \longrightarrow \underset{\mathbf{5}}{\mathrm{PhCHNCH_2Ph}} \qquad (7)$$

variety of reactions.[25] Further mechanistic details of the reaction were not investigated, although, as Figure 1 indicates, some radical chain process occurs in which the peroxy radical **5** could be a possible intermediate. Alternatively, the intermediacy of a nitroxide moiety in a mechanism similar to that suggested by DeLaMare[26] to explain the oxidation of dibenzyl-

(24) R. L. Huang, H. H. Lee, and S. H. Ong, *J. Chem. Soc.*, 3336 (1962); R. L. Huang, H. H. Lee, and M. S. Malhotra, *ibid.*, Suppl. 2, 5947 (1964).

(25) G. A. Russell, "Peroxide Reaction Mechanisms," J. Edwards, Ed., Interscience, New York, N. Y., 1962.

(26) (a) H. E. DeLaMare, *J. Org. Chem.*, **25**, 2114 (1960); (b) G. M. Coppinger and J. D. Swalen, *J. Amer. Chem. Soc.*, **83**, 4900 (1961).

amine to the imine by *tert*-butyl hydroperoxide is possible.

The presence of the dimer **4** in the peroxide reaction (eq 4, 5) indicates that both combination and disproportionation reactions between two carbon-centered radicals **2** does occur. The absence of such dimers in the photochemical reaction further rules out the involvement of radical **2** to any significant degree in that reaction.

An independent source for the dibenzylamino radical **1** was sought, and *N*,*N*,*N*′,*N*′-tetrabenzylhydrazine (**6**) was first used, since this compound was expected to decompose photochemically to a pair of dibenzylamino radicals. Table IV lists the yields of the products

TABLE IV

PHOTOLYSIS OF TETRABENZYLHYDRAZINE AT 253 nm[a]

Hydrazine[b]		Product, mmol				
Start	End	$PhCH_3$	$(PhCH_2)_2$	PhCHO[c]	$(PhCH_2)_2$-NH	PhCH= NCH_2Ph
0.38	t	0.30	0.14	~0.1	t	t

[a] Photolysis time, 320 min. [b] In cyclohexane (mmol). [c] Only after acid hydrolysis. t = trace (<0.01 mmol).

identified from the photolysis of **6**. The high yield of toluene and the absence of dibenzylamine, however, indicates that C–N bond cleavage occurs rather than a process to produce the desired radical **1**. This reaction was not studied further, since radical **1** could be generated from tetrabenzyltetrazene **7**. The photolysis was carried out at 310 nm, which represents the tail of the tetrazene band having a maximum at 290 nm (ϵ 1.15 × 10^4). At this wavelength all of the products are optically transparent and nitrogen is liberated quantitatively. The yield of dibenzylamine was approximately 30% greater than the yield of the imine, as shown in Table V. The results are consistent with

TABLE V

PHOTOLYSIS OF TETRABENZYLTETRAZENE AT 310 nm[a]

Tetrazene,[b] mmol	Product, mmol			ΣN compd
	N_2	$(PhCH_2)_2NH$	PhCH= NCH_2Ph	$2N_2$
0.24	0.236	0.29	0.21	1.07
0.24	0.27	0.27	0.18	0.84
0.48	0.465	0.58	0.38	1.03

[a] Pyrex filter. [b] In 10 ml of cyclohexane.

the general scheme shown below, although some attack on the solvent is indicated.[27]

$$(PhCH_2)_2NN{=}NN(CH_2Ph)_2 \xrightarrow{h\nu} N_2 + 2(PhCH_2)_2N\cdot \quad (8)$$
7

$$2(PhCH_2)_2N\cdot \longrightarrow (PhCH_2)_2NH + PhCH{=}NCH_2Ph \quad (9)$$
1

$$1 \not\longrightarrow (PhCH_2)_2NN(CH_2Ph)_2$$
6

The reaction between the two dibenzylamino radicals represented in eq 9 is interesting, since the absence of the hydrazine dimer **6** implies that the radical **1** only undergoes disproportionation to the exclusion of dimerization.[28] A 1,2-hydrogen shift from carbon to nitrogen is also ruled out,[22] since it would produce radical **2** and subsequently the dimer **4**. It thus appears that any reaction leading to the nitrogen-centered radical **1** will result in disproportionation to the exclusion of dimerization, whereas carbon-centered radicals afford dimers as well as disproportionation products.[30]

Since the involvement of the carbon-centered radical **2** can be ruled out, two alternative reactions, 2a and 2c, remain. To evaluate the importance of reaction 2a, *N*-deuteriodibenzylamine was photolyzed and the toluene was isolated by preparative gas chromatography (see Experimental Section). The pmr spectrum of the toluene obtained in this manner showed a relative intensity of the aromatic to methyl protons in a ratio of 5.0 to 3.0. The absence of labeled toluene thus eliminates reaction 2a and leaves 2c as the most likely process occurring in the dark, subsequent to homolysis.[31]

$$(PhCH_2)_2ND + PhCH_2\cdot \not\longrightarrow PhCH_2D + (PhCH_2)_2N\cdot$$

Although bibenzyl was formed in the photolysis of dibenzylamine and almost certainly results from a radical combination reaction, the corresponding dimer *N*,*N*-dibenzylhydrazine **8** from the benzylamino radical was not detected. This observation further strengthens the argument favoring reaction 2c as the major dark reaction, since such an abstraction process would remove the benzylamino radical and thereby prevent its dimerization. *sym*-Dibenzylhydrazine **8** is the expected product if hydrogen abstraction leading to benzylamine were not efficient. The stability of **8** under the reaction conditions was established (see Experimental Section).

The formation of both the imine and tribenzylamine could arise by the following series of reactions (eq 10).

$$PhCH_2\cdot + (PhCH_2)_2N\cdot \longrightarrow (PhCH_2)_3N \quad (10a)$$

$$(PhCH_2)_2N\cdot \longrightarrow PhCH_3 + PhCH{=}NCH_2Ph \quad (10b)$$

$$2\,(PhCH_2)_2N\cdot \longrightarrow (PhCH_2)_2NH + PhCH{=}NCH_2Ph \quad (10c)$$

The stoichiometric relationship between the imine, toluene, and benzylamine is shown in Table VI. If only reactions 2c and 10b were involved in the formation

(27) Attack on solvent by the dibenzylamino radical under these conditions is not necessarily inconsistent with our previous conclusion regarding the absence of solvent attack during the photolysis of dibenzylamine. In the former case the dibenzylamino radical can attack solvent or undergo (cage) combination–disproportionation reactions. The relative concentrations of the solvent and radicals would permit attack on solvent even if it were energetically unfavorable. In the second case, the initially formed benzylamino radical can react with more substrate (dibenzylamine) rather than react with the solvent. To preclude attack on solvent the relative rate constants for attack on substrate should be more than ten times faster than attack on solvent.

(28) Moreover, the oxidation of dibenzylamine with nickel peroxide also led to no dimeric products.[29]

(29) K. S. Balachandran, I. Bhatnagar, and M. V. George, *J. Org. Chem.*, **33**, 3891 (1968).

(30) However, disproportionation of dimethylamino radicals to imine and hydrogen has been proposed.[14a]

(31) Benzyl radicals have been postulated to attack the N–H bond in at least one example [J. Hutton and W. A. Waters, *J. Chem. Soc.*, 4253 (1965)]. It was suggested that di-*tert*-butyl peroxide in refluxing toluene produced benzyl radicals, which attack indole by a free-radical abstraction process and ultimately afford *N*-benzylindole. In this case, however, there appears to have been no attempt to eliminate the possibility of a radical addition mechanism.

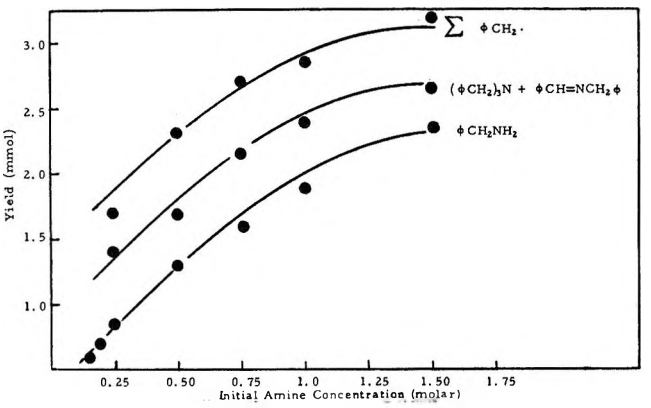

Figure 2. Stoichiometric relationship of the products formed in the photolysis of dibenzylamine: $\Sigma\phi CH_2 = \phi CH_3 + (\phi CH_2)_2 + (\phi CH_2)_3N$.

of these compounds, the ratio shown in the last column of Table VI should be 2.

TABLE VI
STOICHIOMETRY OF IMINE FORMATION

	Product, mmol				$\frac{PhCH_3 + PhCH_2NH_2}{PhCH=NCH_2Ph}$
$(PhCH_2)_2NH$[a]	$PhCH_3$	$PhCH_2NH_2$	$PhCH=NCH_2Ph$	$PhCHO$[b]	
0.26	0.28	0.22	0.35	0.36	1.45
0.52	0.41	0.29	0.43	0.47	1.60
1.55	0.64	0.55	0.63	0.68	1.89
2.6	0.66	0.79	0.72	0.84	2.02
3.9	0.86	0.94	0.88	0.94	2.05
5.2 (neat)	0.92	1.14	1.05	1.08	1.95

[a] Molar concentration in CH_3CN (10 ml). [b] After acid hydrolysis.

A ratio of 2 was indeed observed at higher amine conentrations. The greater yield of imine compared to toluene obtained in some cases, however, indicates that the disproportionation of two amino radicals (eq 10c) remains as a possible minor pathway. The overall stoichiometric relationship among the products of the reaction is shown in Figure 2. Although the yield of benzylamine remains below the yield of products derived from the benzyl radical, the difference is constant throughout the range of concentrations studied.[32]

The disappearance of dibenzylamine in Figure 3 is initially rapid, but is apparently inhibited by the product (imine), which has a much larger absorbance (ϵ 18,000) than that of the reactant (ϵ 357). The filtering of the light can be shown by the retardation of the rate due to the deliberate addition of imine (Figure 3) which can be recovered quantitatively. At higher conversions, the percentage increase in the concentration of the imine is no longer significant and the reaction appears to be linear. We found the imine to be completely stable under our photolytic conditions, although other workers have shown that compounds of this type under-

(32) The absence of a complete material balance (especially at low concentrations of amine) may be due to loss of nitrogenous fragments, particularly the benzylamino radical. The cage disproportionation of benzyl and benzylamino radicals is one such possibility, but the absence of excess toluene makes it unlikely. The formation of benzaldimine was not tested directly due to its instability (*cf.* P. A. Smith, "Open Chain Nitrogen Compounds," Vol. I, W. A. Benjamin, New York, N. Y., 1965, p 301).

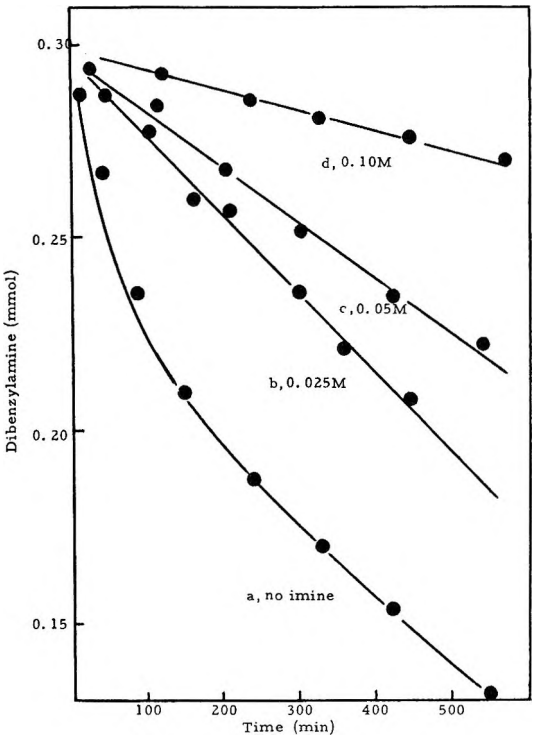

Figure 3—The effect of added *N*-benzylbenzaldimine on the rate of photolysis of dibenzylamine: $(\phi CH_2)_2NH$, 0.1 *M*; imine concentration shown.

go photochemical dimerizations, particularly in alcoholic media.[33-35]

A mechanism generally consistent with the foregoing discussion is summarized below.

$$(PhCH_2)_2NH \overset{h\nu}{\rightleftharpoons} PhCH_2\cdot + PhCH_2\dot{N}H$$

$$PhCH_2\dot{N}H + (PhCH_2)_2NH \longrightarrow PhCH_2NH_2 + (PhCH_2)_2N\cdot$$

$$PhCH_2\cdot +$$

$$(PhCH_2)_2N\cdot \longrightarrow PhCH_3 + PhCH{=}NCH_2Ph$$

$$(PhCH_2)_2N\cdot \longrightarrow (PhCH_2)_3N$$

$$2PhCH_2\cdot \longrightarrow PhCH_2CH_2Ph$$

$$2(PhCH_2)_2N\cdot \longrightarrow (PhCH_2)_2NH + PhCH{=}NCH_2Ph$$

A study of the effects of changes in the viscosity of the medium on the quantum yield for the formation of benzylamine is presented in the following study.[36] A mechanism is formulated in terms of the reactions of the geminate radical pair formed in the initial step of the photodissociation.

Experimental Section

Dibenzylamine.—Commercial dibenzylamine was found to contain significant amounts of *N*-benzylbenzaldimine and lesser quantities of benzylamine. Two methods of purification were found satisfactory.

Into a 2-l. flask was place 400 ml of the amine and 400 ml of dimethoxyethane. Ten grams of sodium borohydride was added and the mixture was refluxed for 12 hr. To the slightly cooled solution was added 1 l. of a saturated solution of sodium bicar-

(33) A. Padwa, W. Bergmark, and D. Pashayan, *J. Amer. Chem. Soc.*, **91**, 2653 (1969).

(34) B. Fraser-Reid, A. McLean, and E. Usherwood, *Can. J. Chem.*, **47**, 4511 (1969).

(35) P. Beak and C. R. Payet, *J. Org. Chem.*, **35**, 3281 (1970).

(36) M. A. Ratcliff, Jr., and J. K. Kochi, *J. Org. Chem.*, **37**, 3275 (1972).

bonate. The mixture was then heated to 60° and stirred for 1 hr to hydrolyze the borate formed during reduction. The amine was extracted with two 500-ml portions of ether. The ether was removed by rotary evaporation and the amine was distilled at 140° (3 mm). Alternatively, the amine was dissolved in an equal volume of 95% ethanol and 1 g of 5% palladium on charcoal was added. The resulting mixture was shaken at room temperature under a hydrogen atmosphere of 50 psi for 6 hr. The palladium was removed by filtration and the alcohol was removed by rotary evaporation. The amine was distilled as before.

Both methods completely removed the imine and left only trace amounts of benzylamine as analyzed by gas chromatography.

Solvents.—Solvents used in the photolyses were, when available, commercial spectrograde solvents. These were used without further purification. Other hydrocarbon solvents were purified for photolysis by passing them through a column packed with acid-washed alumina impregnated by 10% silver nitrate.[37] All solvents used in these experiments had an absorbance of less than 0.05 in a 1-cm cell.

***N*-Deuteriodibenzylamine** [$(PhCH_2)_2ND$].—Dibenzylamine (25 g) and 100 ml of deuterium oxide were placed in a 250-ml round-bottom flask. Three drops of concentrated sulfuric acid was added and the mixture was shaken for 3 days. The amine was extracted with ether, which was removed by rotary evaporation. This process was repeated three additional times. After the final exchange, the ether extract was thoroughly dried over sodium sulfate and filtered, and the ether was removed as before. The amine was distilled under vacuum. Proton magnetic resonance (pmr) analysis indicated the deuterium enrichment to be greater than 98%.

Benzalazine ($PhCH{=}NN{=}CHPh$).—Benzaldehyde (100 g) was dissolved in 200 ml of benzene and placed in a round-bottom flask equipped with a Dean–Stark trap. The solution was warmed and 25 g of hydrazine hydrate was added from a dropping funnel. The water formed was removed as a benzene azeotrope. After the theoretical amount of water had been obtained the benzene was removed by rotary evaporation, leaving a yellow solid which was recrystallized from ethanol.

***sym*-Dibenzylhydrazine** ($PhCH_2NHNHCH_2Ph$).—Benzalazine (5 g) and 1 g of platinum on calcium carbonate (5%) were placed in an hydrogenation flask and 100 ml of ethyl acetate was added. The mixture was shaken on a Parr apparatus at room temperature under 50 psi hydrogen for 8 hr. The ethyl acetate was removed by rotary evaporation and the residual oil was added to an aqueous hydrochloric acid solution. The hydrochloride was washed with methanol and ether, mp 212° dec (lit.[38] mp 215–217° dec).

Acetylhydrazide ($CH_3CONHNH_2$).—Over a period of 1 hr, 46 g of ethyl acetate was added to a refluxing solution of 25 g of hydrazine hydrate and 15 ml of ethanol. After the addition of the ethyl acetate was completed, the mixture was refluxed for an additional 4 hr, after which time the heat was removed and the mixture was allowed to stand overnight. The ethanol and remaining ethyl acetate were removed by rotary evaporation, leaving an oil containing unreacted hydrazine hydrate and an oil which was distilled under vacuum. Water heated to 75° was pumped through the condenser to prevent solidification, and the receiver was also placed in a hot water bath for the same purpose. The fraction boiling at 134–136° (21 mm) was retained, mp 59–60° (lit.[39] mp 60°).

Tetrabenzylhydrazine [$(PhCH_2)_2NN(CH_2Ph)_2$].—Benzyl bromide (55 g, 0.6 *M*) was added dropwise to a solution of 200 ml of water, 60 g of sodium carbonate monohydrate, and 15 g of acetylhydrazide heated to 60°. After the addition was completed, the mixture was refluxed for 1 hr, during which time an oily layer separated. The mixture was cooled and extracted with three 100-ml portions of ether. Removal of the ether by rotary evaporation left a white solid. The solid was taken up in a minimum amount of hot 95% ethanol and allowed to crystallize. The flat white needles which formed were collected by filtration and air dried: mp 139–139.5° (lit.[40] mp 139–140°); pmr[41] δ 3.77 (2.0) ($-CH_2-$) s, 7.10 (5.0) (aromatic) s.

***unsym*-Dibenzylhydrazine** [$(PhCH_2)_2NNH_2$].—Hydrazine hydrate (200 g) was placed in a three-necked, round-bottom flask equipped with a magnetic stirrer. The flask was immersed in a Dry Ice–isopropyl alcohol bath, and benzyl bromide (100 g) was added from a dropping funnel at a rate such that the temperature remained below 10°. After the addition was complete, the solution was heated to 75° for 2 hr and upon cooling, extracted with benzene. The benzene was removed by rotary evaporation and the residual oil (which solidified upon cooling) was distilled under vacuum. Water heated to 75° was pumped through the condenser to prevent solidification. The collected fraction had bp 169–171° (5 mm), solidified upon cooling, and was recrystallized from a mixture of ethanol and petroleum ether (bp 30–60°): mp 64–66° (lit. mp 63–64°,[42] 65°,[43] 81–83°,[44] 54–56°[45]); pmr[41] δ 2.82 (1.0) ($-NH_2$) s, 3.80 (1.95) ($-CH_2-$) s, 7.32 (5.05) (aromatic) s.

Tetrabenzyltetrazene [$(PhCH_2)_2NN{=}NN(CH_2Ph)_2$].—*unsym*-Dibenzylhydrazine (11 g) was placed in a 500-ml, three-necked round-bottom flask. Ethanol (200 ml) was added and the solution was degassed with a nitrogen stream. Freshly prepared mercuric oxide (21 g) was added to the solution. The mixture was then heated in an oil bath for 3 hr at a temperature which allowed the ethanol to reflux gently. After cooling, the mixture was filtered and the filtrate was heated to boiling and refiltered. Upon cooling to room temperature, long white needles formed, mp 96.5–98°. After a second recrystallization the melting point was 96.5–97° (lit. mp 99–100°,[46] 95–96°[47]): pmr[41] δ 4.36 (2.0) ($-CH_2-$) s, 7.23 (5.0) (aromatic) s (broad); uv λ_{max} 290 nm (ε 11,500), 215 (45,000); ir 6.7 (m), 6.9 (m), 9.4 (m), 10.5 μ (s).

Anal. Calcd for $C_{28}H_{28}N_4$: C, 80.00; H, 6.66; N, 13.33. Found: C, 79.99; H, 6.55; N, 13.56.

Product Analysis.—All quantitative analyses were performed by vapor phase chromatography (vpc) on a Varian Aerograph Model 1200 gas chromatograph equipped with a flame ionization detector. Products were identified by comparing their retention times with those of authentic samples on at least two columns whose separation characteristics differed. Quantitative analysis was performed by the internal standard method with a marker chosen, where possible, which had similar functional group characteristics and a retention time close to that of the compound being determined. Basic materials were analyzed by adding a known amount of marker to a measured portion of the reaction solution. This solution was analyzed directly by vpc.

Neutral materials and hydrolysis products (*i.e.*, benzaldehyde from the imine) were determined after acidic hydrolysis. A partition technique was used. Into a 2-dram vial was measured 1 ml of the reaction mixture, 1 ml of a standard marker solution, and 1 ml of an 8 *N* sulfuric acid solution. Three milliliters of ether or hexane was then added to the solution and the vial was capped. Samples were taken from the organic layer for vpc analysis. Calibrations were performed under conditions identical with those of the analysis.

Infrared spectra were obtained on a Perkin-Elmer Model 137b or Beckman IR-8 spectrometer. Pmr spectra were taken, unless otherwise specified, in deuteriochloroform on a Varian A-60A spectrometer. Chemical shifts are reported in δ units relative to tetramethylsilane as an internal standard. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Mass spectra were recorded on a Varian CH-7 mass spectrometer. Ultraviolet spectra were obtained with a Beckman DB-G spectrophotometer.

Analysis of *sym*-Dibenzylhydrazine.—The hydrazine, stored as the hydrochloride, was released with dilute base. For vpc

(37) E. C. Murray and R. N. Keller, *J. Org. Chem.*, **34**, 2234 (1969).

(38) A. F. Bickel and W. A. Waters, *Recl. Trav. Chim. Pays-Bas*, **69**, 312 (1950).

(39) A. N. Kost and R. S. Sagitullin, *Zh. Obshch. Khim.*, **27**, 3338 (1957); *Chem. Abstr.*, **52**, 9071c (1958).

(40) R. T. Merrow and R. van Dolah, *J. Amer. Chem. Soc.*, **76**, 4522 (1954).

(41) Proton abundance by integration are shown in parentheses and assignments are given. Abbreviations are s, singlet; d, doublet; q, quartet; and m, multiplet.

(42) A. N. Kost and R'S. Sagitullin, *Fiz. Khim.*, **14**, 225 (1959); *Chem. Abstr.*, **53**, 21894a (1959).

(43) G. Fedor, *Chem. Phys.*, **2**, 167 (1949); *Chem. Abstr.*, **44**, 6414a (1950).

(44) L. A. Carpino, *J. Amer. Chem. Soc.*, **82**, 3133 (1960).

(45) H. Fox, J. T. Gibas, and A. Motchane, *J. Org. Chem.*, **21**, 349 (1956).

(46) C. G. Overberger and B. S. Marks, *J. Amer. Chem. Soc.*, **77**, 4104 (1955).

(47) R. L. Hinman and K. L. Hamm, *ibid.*, **81**, 3294 (1959).

analysis, the hydrochloride was weighed into a 2-dram vial to which 2 ml of 3 *N* potassium hydroxide was added together with a known amount of marker (in acetonitrile) and 3 ml of ether. The organic layer was analyzed directly. It was found that in the presence of air the hydrazine decomposed over a period of 4 hr to unidentified products. Under nitrogen, however, it appeared to be stable indefinitely.

To test the stability of the hydrazine under reaction conditions, a weighed quantity of the hydrochloride was dissolved in base and the hydrazine was extracted with the dibenzylamine solution to be photolyzed (0.5 *M* in cyclohexane). The organic layer was dried over sodium sulfate, placed in a photolysis tube, capped, and deaerated. One milliliter was removed with a surgical syringe and analyzed immediately as described above. After photolysis the analytical procedure was repeated and no loss of the hydrazine was apparent.

Photolysis. Product Studies.—Samples were weighed into 10-ml volumetric flasks and diluted to volume with the appropriate solvent. The solution was then transferred to a round quartz tube (15 × 1.5 cm) and deaerated by passing a slow stream of nitrogen through the solution for 10 min. The tube was sealed with a gas-tight rubber septum. The photolyses were carried out in a Rayonet RPR-100 photochemical reactor (The Southern New England Ultraviolet Co.) using 16 253-nm region lamps. The samples were rotated using a Rayonet MGR-100 merry-go-round. Photolysis times varying from 2 to 6 hr showed similar product distributions as did photolyses using 4 rather than 16 lamps.

Photolysis of *N*-Deuteriodibenzylamine [$(PhCH_2)_2ND$].—Equal amounts of the amine (12 g) were placed in two photolysis tubes and deaerated with nitrogen. The tubes were sealed with rubber septa and photolyzed as a neat liquid for 420 min. At the completion of the photolysis the amine mixture was diluted with water and acidified with 8 *N* sulfuric acid. The aqueous mixture was extracted with three 50-ml portions of ether, and the volume was reduced to one-half the original by distillation. The ether extract was washed with three 10-ml portions of saturated aqueous sodium bisulfite to remove benzaldehyde and with three 20-ml portions of water. The ether layer was then dried over magnesium sulfate and filtered twice through activated charcoal to remove the light yellow coloration which developed during the photolysis. The ether was distilled until the volume was reduced to approximately 0.5 ml. Vpc showed that benzaldehyde was present in amounts corresponding to 1% of the toluene. Preparative vpc on a 4 ft XF 1150 column (100°) was employed to obtain a sample of approximately 15–20 μl of toluene. Pmr analysis in deuteriochloroform showed an intensity ratio of 5.0 to 3.01 for the aromatic to methyl protons, which indicated within experimental error that no deuterium incorporation occurred in the toluene.

Photolysis of Tetrabenzyltetrazene [$(PhCH_2)_2NN{=}NN(CH_2Ph)_2$].—The tetrazene was weighed into a 10-ml volumetric flask and dissolved in spectrograde cyclohexane. The solution was transferred to a Pyrex tube, deaerated with nitrogen, and photolyzed with 310 nm light, to which all products are optically transparent. The nitrogen formed was analyzed by vpc on a 6 ft molecular sieve column using oxygen as an internal marker. Care was taken to prevent air entering either the reaction tube or the syringe used in the analysis. Careful calibrations showed this technique to be quantitative and reproducible.

Thermal Decomposition of Peroxides in the Presence of $(PhCH_2)_2NH$.—Approximately 1.0 mmol of either di-*tert*-butyl peroxide or dicumyl peroxide was weighed directly into a 25-ml round-bottom flask equipped with a side arm for degassing. To this flask was added 15 ml of the neat amine by means of a volumetric pipette. A small reflux condenser was placed on the flask and both the side arm and the top of the condenser were sealed with tight-fitting rubber septa. The contents of the flask was deaerated *via* the side arm by slowly passing nitrogen from a surgical needle through the solution for 35 min.

The decomposition of the peroxide was effected in an oil bath thermostated at 130 ± 2°. The reaction flask was kept in the oil bath for a period of time which varied from 3 to 6 hr. At the completion of the reaction, the contents of the flask was poured into a graduated cylinder. The flask and condenser were washed with two 2-ml portions of acetonitrile, which were combined with the reaction mixture. Acetonitrile was then added to the graduated cylinder to bring the combined volume to 20 ml. Samples were taken from this solution for analysis.

Thermal Decomposition of Dicumyl Peroxide in Dibenzylamine and the Isolation of 4.—Dicumyl peroxide (6.81 g) was weighed into a 250-ml round-bottom flask, and 100 ml of dibenzylamine was added. The flask was fitted with a 3-in. glass adaptor which was capped with a rubber septum. The solution was stirred magnetically and deaerated with a stream of nitrogen for 45 min. The flask was heated with stirring in a silicone oil bath thermostated at 130 ± 2°. On completion, the reaction mixture was distilled under vacuum to remove the liquid fractions which boiled at temperatures corresponding to those of cumyl alcohol and dibenzylamine. The residual liquid, when cooled, yielded a white solid which was recrystallized three times from 95% ethanol. The product was a white amorphous powder: mp 149–150° (lit.[48] mp 151°); pmr[41] δ 1.68 (1.0) (NH) s, 3.4 (2.07) (NCH_2Ph) q, $J \cong 1$–2 Hz, 3.75 (1.00) (PhCH) s, 7.23 (9.8) (aromatic) m; mass spectrum (70 eV) *m/e* molecular ion, 392; $PhCHNHCH_2Ph^+$, 196; $PhCH_2NHCHCHPh^+$, 286; $PhCH_2NH^+$, 106; $PhCH_2^+$, 91.

Anal. Calcd for $C_{28}H_{28}N_2$: C, 85.67; H, 7.19; N, 7.14. Found: C, 85.66; H, 7.21; N, 6.92.

Thermal Decomposition of Dicumyl Peroxide in Dibenzylamine in the Presence of O_2.—The procedure for reactions carried out in the presence of oxygen differed little from that where nitrogen was used for degassing. The peroxide and amine were added in a similar manner and the procedure for work-up was the same. In the present case, however, a rubber septum was placed over the side arm and the condenser was connected to a mercury buret of 250-ml capacity. The main body of the buret was filled and emptied twice with oxygen and finally filled with 200 ml of oxygen at atmospheric pressure. After the system was flushed with oxygen, it was placed in the thermostated oil bath and the reaction was allowed to proceed. The oxygen within the flask and buret was maintained at atmospheric pressure and the uptake was monitored continuously until oxygen was no longer absorbed. The contents of the flask were then transferred for analysis as previously described.

The Effect of Acid.—The addition of acid to the photochemical reaction in acetonitrile is shown in Table VII. The only effect observed was a decrease in the free amine present, since the amine was found to undergo its usual photochemical reactions. The inertness of dibenzylammonium trifluoroacetate was at first disturbing, since we felt that it was the aromatic chromophore which was involved in the absorption process leading to reaction. Another study, however, indicated that, while quaternary and tertiary ammonium salts do undergo photodecomposition, secondary and primary salts represented here are inert.[35]

TABLE VII

EFFECT OF ACID ON THE PHOTOLYSIS OF DIBENZYLAMINE[a]

			Product, mmol		
Amine[b]	Acid[b,c]	Free amine[b]	$PhCH_3$	$PhCH_2NH$	$PhCH{=}NCH_2Ph$
5.25	1.3	3.95	0.31	0.23	0.31
5.25	2.6	2.65	0.27	0.23	0.29
2.58	0	2.58	0.26	0.20	0.29

[a] Photolysis time, 200 min. [b] Number of millimoles in 10 ml of CH_3CN solution. [c] Trifluoroacetic acid.

Registry No.—**4**, 24431-19-4; dibenzylamine, 103-49-1; tetrabenzylhydrazine, 5416-62-6; tetrabenzyltetrazene, 23456-88-4.

Acknowledgment.—We wish to thank the National Science Foundation, the Petroleum Research Fund of the American Chemical Society, and the U. S. Army Edgewood Arsenal for financial support of this research.

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Cage Effects and the Viscosity Dependence of the Photolysis of Dibenzylamine and Tribenzylamine

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The fates of the radical pairs formed in the photolytic decomposition of *N,N*-dibenzylamine and *N,N,N*-tribenzylamine in solution are examined. Viscosity of the medium is used to probe a model for the "cage effect," in which radicals suffer competition among recombination, diffusion, and reaction with the solvent or amine.

The photolytic decomposition of amines serves as a model for the reaction of alkylamino radicals in solution. The product study of the photolysis of *N,N*-dibenzylamine presented in the foregoing paper[1] is accommodated by an initial homolysis of the benzyl–nitrogen bond. The benzylamino and dibenzylamino

$$\overset{H}{PhCH_2NCH_2Ph} \xrightarrow{h\nu} PhC\dot{H}_2 + H\dot{N}CH_2Ph$$

radicals are involved in subsequent dark reactions following the photodissociation of *N,N*-dibenzylamine. In this study we examine the viscosity dependence of the quantum yield for reaction, in an attempt to obtain a more quantitative understanding of the initial reactions. The results are compared with the photolysis of *N,N,N*-tribenzylamine and interpreted in terms of a model for the "cage effect," in which the fate of the radical pair depends on the competition among recombination, diffusion, and scavenging.[2-19] Although the photochemistry of this system is also of interest, we are concerned here primarily with the thermal reactions subsequent to homolysis.

Results and Discussion

The quantum yields were determined for reactions allowed to reach no more than 0.1% completion (see Experimental Section). In two cases, 0.1 and 1.0 *M* dibenzylamine in cyclohexane, the value was taken from the slope of a line obtained by plotting the yield of benzylamine as a function of time. Problems associated with filtering due to the formation of imine were avoided by this method. The quantum yields obtained in this manner are listed in Table I and plotted as a function of dibenzylamine concentration in Figure 1. All quantum yields were obtained at one lamp intensity. The possible dependence of the quantum yield on the intensity of irradiation was not investigated.

TABLE I

QUANTUM YIELD FOR BENZYLAMINE FORMATION AT 253 nm

$(PhCH_2)_2NH$[a] concn	$\Phi(PhCH_2NH_2)$
0.02	0.025 ± 0.002
0.05	0.036 ± 0.002
0.10	0.061 ± 0.004
0.30	0.093 ± 0.002
0.50	0.112 ± 0.009
0.70	0.123 ± 0.003
0.90	0.129 ± 0.001
1.00	0.137 ± 0.011
1.50	0.141 ± 0.001
2.00	0.141 ± 0.003
2.50	0.139 ± 0.006
3.00	0.140 ± 0.001

[a] Molar concentration in cyclohexane. [b] Error limits are average deviations based on from four to eight separate determinations.

The C–N bond strength in dibenzylamine is approximately 55 kcal mol^{-1} based on the trend observed with other amines[20] and the value of 59.8 kcal mol^{-1} for benzylamine.[21] During photolysis at 254 nm, the energy in excess of that required to break the bond (~60 kcal mol^{-1}) is partly partitioned as translational energy to separate the two fragments.[22-24] If the particles recombine before they have diffused more than one molecular diameter from each other, the process becomes kinetically equivalent to thermal deactivation of an excited state.[25] This result has been termed "primary recombination."[18] Prior to recombination, there may or may not be a residual interaction between the radical fragments, *i.e.*, the motion of one may influence the motion of the other. If, however, the fragments escape the primary recombination, they can diffuse independently of one another and at distances from one to two molecular diameters apart.[18] If recombination then occurs between these original partners the process is known as "secondary recombination,"[18] which may be more generally expressed to include all recombinations of original (geminate) partners which have not had time to reach a statistical distribution in solution as a result of random diffusion. If, at the same time, a scavenger(s) is present which is capable of reacting with one of the radicals formed in the

(1) M. A. Ratcliff, Jr., and J. K. Kochi, *J. Org. Chem.*, **37**, 3268 (1972).
(2) J. Franck and E. Rabinowitch, *Trans. Faraday Soc.*, **30**, 120 (1934).
(3) S. Kodama, *Bull. Chem. Soc. Jap.*, **35**, 652, 658, 824, 827 (1962).
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(9) H. Kiefer and T. Traylor, *ibid.*, **89**, 6667 (1967).
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(17) H. A. Gillis, R. R. Williams, Jr., and W. H. Hamill, *ibid.*, **83**, 17 (1961).
(18) (a) R. M. Noyes, *ibid.*, **77**, 2042 (1955). (b) For a recent discussion see also D. L. Bunker and B. S. Jacobson, *ibid.*, **94**, 1843 (1972).
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(20) J. A. Kerr, R. C. Serhar, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 3217 (1963).
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(24) J. Franck and E. Rabinowitsch, *Trans. Faraday Soc.*, **30**, 120 (1934).
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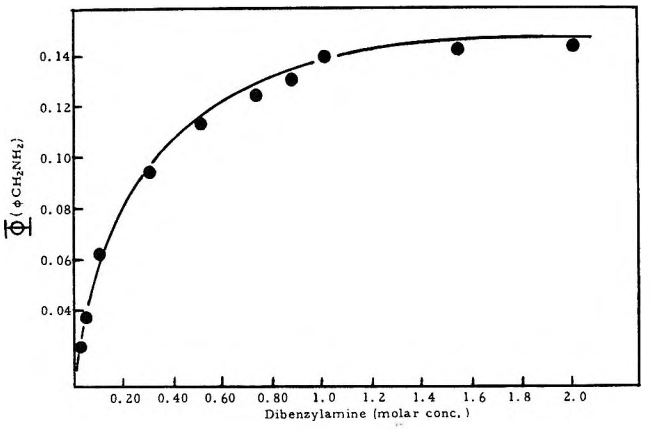

Figure 1.—Quantum yield of benzylamine formation *vs.* the concentration of dibenzylamine.

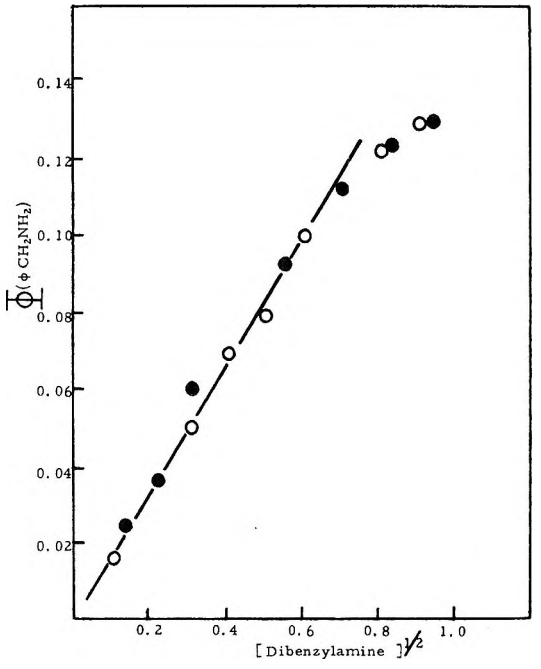

Figure 2.—Quantum yield of benzylamine formation *vs.* the square root of the concentration of dibenzylamine: (●) experimental; (○) taken from curve in Figure 1.

dissociation, it may compete with the secondary recombination step. Such a competition can be seen as a partitioning between two processes represented by k_r,

$$\text{R–R} \xleftarrow[k_r]{} [\text{R}\cdot, \text{R}\cdot] \xrightarrow[k_s]{S} \text{P}$$

the rate constant for secondary recombination, and k_s, the rate constant for scavenging of the geminate radical pair.

Noyes has treated the kinetics of this scavenging process in a series of papers.[18,26] The lifetime of the cage reaction (secondary recombination) is best viewed as the time interval during which there is a finite probability for the pair to recombine.[27] At times greater than this, the probability for the reencounter of original partners becomes negligible. Noyes obtained an ex-

(26) (a) R. M. Noyes, *J. Amer. Chem. Soc.*, **78**, 5486 (1956); (b) H. Rosman and R. M. Noyes, *ibid.*, **80**, 2410 (1958); (c) R. M. Noyes, *Z. Elektrochem.*, **64**, 153 (1960); (d) R. M. Noyes, *J. Phys. Chem.*, **65**, 763 (1961).

(27) W. Braun, L. Rajenbach, and F. R. Eirich, *J. Phys. Chem.*, **66**, 1591 (1962).

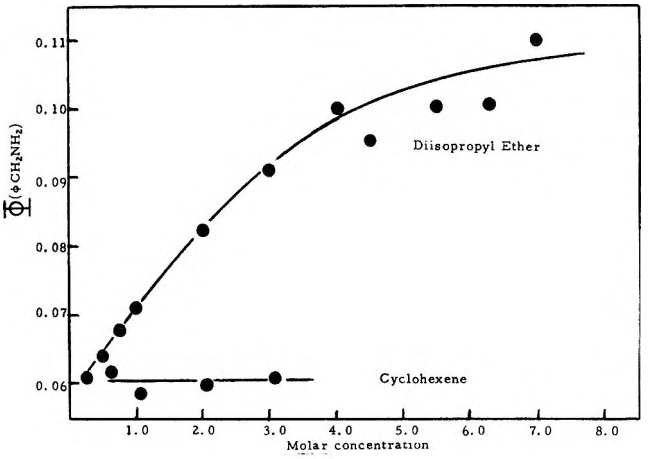

Figure 3.—Quantum yield of benzylamine formation *vs.* the concentration of potential scavengers.

pression (eq 1) relating the quantum yield to the square root of scavenger concentration,[28] where Φ is the ob-

$$\Phi = \Phi_r + C(S)^{1/2} \quad (1)$$

served quantum yield, S is the scavenger concentration, and C is a term containing molecular parameters to be discussed later. The term Φ_r was described by Jortner[25] as the "residual yield," and defined as the quantum yield in the presence of scavenger at concentrations sufficient to prevent recombination from bulk solution, but too low to compete with secondary recombination.

For the photolysis of dibenzylamine this effect can be described as a competition between k_r and k_s (eq 2),

$$(\text{PhCH}_2)_2\text{NH} \underset{k_r}{\overset{h\nu}{\rightleftharpoons}} [\text{PhC}\dot{\text{H}}_2, \text{H}\dot{\text{N}}\text{CH}_2\text{Ph}] \quad (2a)$$

$$[\text{PhC}\dot{\text{H}}_2, \text{H}\dot{\text{N}}\text{CH}_2\text{Ph}] \xrightarrow[(\text{PhCH}_2)_2\text{NH}]{k_s} \text{PhC}\dot{\text{H}}_2 + \dot{\text{N}}(\text{CH}_2\text{Ph})_2 + \text{PhCH}_2\text{NH}_2 \quad (2b)$$

in which k_r represents return to starting material and k_s that leading to products. A plot of $\Phi(\text{PhCH}_2\text{NH}_2)$ *vs.* $[(\text{PhCH}_2)_2\text{NH}]^{1/2}$ is shown in Figure 2. Above concentrations of approximately 0.5 M in amine, however, the plot deviates greatly from linearity. At the higher concentrations, dibenzylamine may exist as hydrogen-bonded aggregates which could affect the measured quantum yields (*vide infra*).[29] The results are further complicated by the fact that the scavenger is also the photoreactive species.

Both cyclohexene and diisopropyl ether were examined as possible hydrogen donors, and each was expected to compete effectively with the dibenzylamine for the amino radicals. For two potential scavengers, eq 1 can be expanded to eq 3, where S' refers to either cyclohexene or diisopropyl ether. The results (Table II) for both cases are shown in Figure 3.

$$\Phi = \Phi_r + C(S)^{1/2} + C'(S')^{1/2} \quad (3)$$

That no effect was observed with cyclohexene was unexpected, but the dependence on diisopropyl ether concentration agrees with the relative reactivities of

(28) For a review see R. M. Noyes, *Progr. React. Kinet.*, **1**, 129 (1961).

(29) (a) Furthermore, approximations made during the derivation (*i.e.*, approximating an integral by a series expansion with the subsequent deletion of all but the first term) could cause deviations at higher scavenger concentrations.[28] (b) We wish to thank the referee for this suggestion.

TABLE II

THE EFFECT OF THE ADDITION OF CYCLOHEXENE AND DIISOPROPYL ETHER ON $\Phi(PhCH_2NH_2)$[a]

Cyclohexene			Diisopropyl Ether		
Concn[b]	$S^{1/2}$	$\Phi(PhCH_2NH_2)$	Concn[b]	$S^{1/2}$	$\Phi(PhCH_2NH_2)$
0.51	0.71	0.062	0.25	0.50	0.061
1.02	1.00	0.059	0.50	0.71	0.064
2.04	1.43	0.060	0.75	0.86	0.068
3.06	1.75	0.061	1.0	1.0	0.071
4.08	2.02	0.072	2.0	1.41	0.082
			3.0	1.73	0.091
			4.0	2.0	0.100
			4.5	2.12	0.095
			5.5	2.34	0.102
			6.26	2.50	0.104
			6.97	2.64	0.110

[a] Solutions of 0.1 M in $(PhCH_2)_2NH$ irradiated at 25° with 253-nm radiation. [b] Molar concentration in cyclohexane.

the two reagents. For example, diisopropyl ether has been found to be approximately ten times as reactive as cyclohexene toward n-hexyl radicals,[30] but the relative reactivities toward benzylamino radical are unknown. A plot of the data according to eq 3 is shown in Figure 4.

In the derivation of eq 1, the constant, C, is given by $C = 2a\varphi\sqrt{\pi k_s}$, where a is a constant, k_s is the rate constant for scavenging, and φ is a term defined to be "the quantum yield of radical pairs escaping primary recombination,"[29] From Fick's law, one can obtain an expression for the rate constant, k_s, applicable to steady-state diffusion (eq 4). This expression was suggested

$$k_s = 4\pi r_{AB} D_{AB} \quad (4)$$

by Noyes[26a] and is similar to that obtained by Smoluchowski[31] in his early treatments of diffusion-controlled reactions. In this expression, r_{AB} is the encounter distance between the potentially reacting species, and D_{AB} is the diffusion coefficient for their relative motion. In order for eq 4 to be strictly valid, however, the diffusion process must be the rate-limiting step.[32] That the reaction under consideration meets these requirements is not obvious, although the reaction of the benzylamino radical with dibenzylamine should be exothermic. Furthermore, the photolysis yielded no material resulting from the dimerization of the benzylamino radical under conditions in which bibenzyl was readily detected.[1]

The expression for k_s is introduced into eq 1 for purposes of testing the effect of viscosity changes on the quantum yield, by substituting the right-hand side of eq 4 and using a Stokes–Einstein relationship (eq 6),

$$\Phi = \Phi_r + 4\pi a\varphi\sqrt{[S] r_{AB} D_{AB}} \quad (5)$$

where k is Boltzman's constant and T the absolute temperature.[32] If all terms but the viscosity and the

$$D_{AB} = \frac{2kT}{3\pi\eta r_{AB}} \quad (6)$$

scavenger concentration are constant, eq 7 predicts that the quantum yield will vary inversely with the square root of fluidity $(1/\eta)$ at constant scavenger (*i.e.*, dibenzylamine) concentration.

$$\Phi = \Phi_r + C\sqrt{(S)/\eta} \quad (7)$$

(30) D. R. DeTar and D. V. Wells, *J. Amer. Chem. Soc.*, **82**, 5839 (1960).
(31) M. V. Smoluchowski, *Z. Phys. Chem.*, **92**, 129 (1917).
(32) A. M. North, *Quart. Rev., Chem. Soc.*, **20**, 421 (1966).

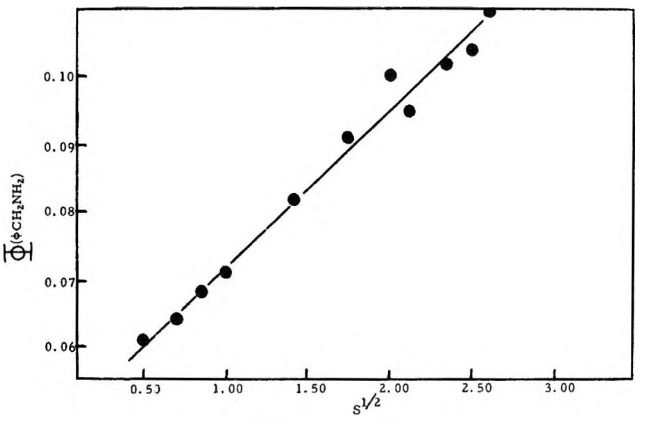

Figure 4.—Quantum yield of benzylamine formation *vs.* the square root of isopropyl ether concentration(s).

The quantum yield for the formation of benzylamine was measured in a series of hydrocarbon solvents of varying viscosity. The results (Table III) when

TABLE III

EFFECT OF VISCOSITY ON THE QUANTUM YIELDS OF DIBENZYLAMINE PHOTOLYSIS

Solvent	D, g/ml	ν, cSt	η, cP	$\Phi(PhCH_2NH_2)$
Pentane	0.614	0.340	0.208	0.130
Hexane	0.648	0.441	0.285	0.111
Heptane	0.673	0.537	0.362	0.103
Isooctane	0.682	0.644	0.439	0.092
Nonane	0.708	0.856	0.606	0.078
Cyclohexane	0.767	1.028	0.788	0.061
Nujol (40%)[a]	0.757	2.214	1.676	0.044
Nujol (60%)[a]	0.793	5.164	4.095	0.027
Nujol (80%)[a]	0.828	15.84	13.11	0.018
Nujol (90%)[a]	0.852	32.27	27.49	0.006
DIPE (1.0)[b]	0.760	0.850	0.646	0.071
DIPE (2.0)[b]	0.757	0.730	0.553	0.082
DIPE (3.0)[b]	0.745	0.631	0.471	0.091
DIPE (5.0)[b]	0.731	0.501	0.367	0.103
DIPE (6.0)[b]	0.726	0.457	0.332	0.106

[a] By volume, remainder is isooctane. [b] Concentration (M) of diisopropyl ether in cyclohexane.

plotted according to eq 7 give the predicted relationship (Figure 5). It can be seen that the quantum yield does approach zero as the viscosity increases.

The effect of diisopropyl ether was reinvestigated in light of this result, and the results are listed in Table III. The relationship between the quantum yield and the concentration of ether (Figures 3, 4) indeed appears to have been fortuitous, and the correlation is more adequately explained as a viscosity effect. The latter implies that neither cyclohexene nor diisopropyl ether reacted with the benzylamino radical as previously suggested. This conclusion may not be unwarranted due to the generally unreactive nature of alkylamino radicals[33–35] and their apparent highly polar character.[36–38]

The product distribution for the photolysis of dibenzylamine was determined in several of the solvents

(33) B. R. Cowley and W. A. Waters, *J. Chem. Soc.*, 1228 (1961).
(34) D. Mackay and W. A. Waters, *J. Chem. Soc. C*, 813 (1966).
(35) K. M. Johnston, G. H. Williams, and H. J. Williams, *J. Chem. Soc. B*, 1114 (1966).
(36) E. L. O'Brian, F. M. Beringer, and R. B. Mesrobian, *J. Amer. Chem. Soc.*, **81**, 1506 (1959).
(37) R. S. Neale and E. Gross, *ibid.*, **89**, 6579 (1967).
(38) S. F. Nelson and D. H Heath, *ibid.*, **91**, 6452 (1969).

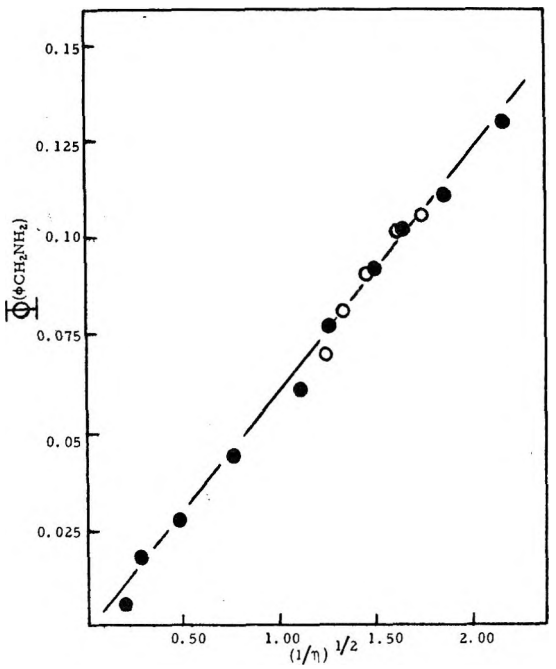

Figure 5.—Quantum yield of benzylamine formation vs. viscosity function: (●) hydrocarbon solvents; (○) isopropyl ether.

used for quantum yield studies in order to assure that the formation of benzylamine was not abnormally depressed relative to the other products by the nature of the solvent. As Table IV shows, the distribution

TABLE IV
PRODUCT DISTRIBUTION AS A FUNCTION OF VISCOSITY AT 253 nm

		Product, mmol				
Solvent	η, cP	PhCH3	PhCH2-NH2	PhCH=NCH2Ph	(Ph-CH2)3N	(PhCH2)2
Pentane[a]	0.208	0.15	0.21	0.16	0.072	0.04
Hexane[a]	0.285	0.13	0.19	0.16	0.070	0.03
Heptane[a]	0.362	0.133	0.18	0.14	0.063	0.027
Isooctane[a]	0.439	0.138	0.17	0.14	0.060	0.024
Nonane[a]	0.606	0.13	0.14	0.12	0.050	0.02
Methanol[a]	0.498	0.06	0.04	0.07	0.02	0.01
Cyclohexene[b]		0.167	0.39	0.45	0.11	
Cyclohexane[b]	0.778	0.182	0.36	0.45	0.13	

[a] Photolysis time, 60 min; $(PhCH_2)_2NH$ 0.5 *M*. [b] Photolysis time, 300 min; $(PhCH_2)_2NH$ 0.7 *M*.

of products remains more or less constant, the principal variation being in the absolute amounts produced. With the effect of viscosity clarified, the results obtained from varying the concentration of dibenzylamine in cyclohexane were investigated. Equation 7 can be rewritten as eq 8, and the quantum yield data

$$\Phi\eta^{1/2} = \Phi_r\eta^{1/2} + C(S)^{1/2} \quad (8)$$

(including the viscosities of the solutions of dibenzylamine in cyclohexane) are listed in Table V. A plot of the left-hand portion of eq 8 against the square root of the dibenzylamine concentration is shown in Figure 6. The term $\Phi_r\eta^{1/2}$ is zero by extrapolation of the amine concentration in Figure 2. The inability of eq 8 to predict the results may not be surprising considering the assumptions made. Nevertheless, some interesting observations can be made regarding the two apparently linear portions of the curve in Figure 6. Increasing the concentration of the amine has the effect of enhancing the quantum yield, whereas the accompanying increase in the viscosity with concentration tends to reduce it. The lower part of the curve, between 0.02 and 0.7 *M*, is influenced largely by changes in the concentration. In this region the concentration changes by a factor of 35 while the viscosity increases by only 12%. Above approximately 0.9 *M*, the influence due to the viscosity change becomes important. Thus, from 1.0 to 3.0 *M*, the concentration of the amine changes by only a factor of 3 while the viscosity increases by over 100%. It is also important to recognize that, at the higher concentrations, the solvent cage surrounding the radical pair probably contains substrate molecules, especially if dibenzylamine is aggregated as hydrogen-bonded species. When the solvent cage has a high probability of containing one scavenger molecule, further increases in scavenger concentration should have little significance in terms of the foregoing expressions. Furthermore, the quantum yield should not show the same concentration dependence.[39]

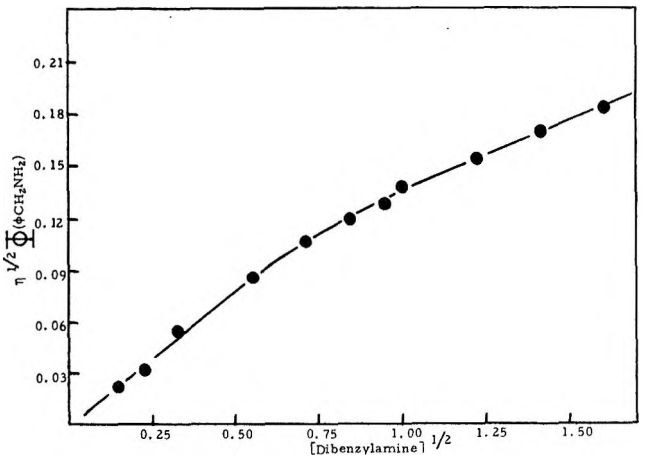

Figure 6.—Quantum yield dependence on both viscosity and molar concentration of dibenzylamine.

TABLE V
EFFECT ON QUANTUM YIELDS DUE TO VISCOSITY CHANGES IN SOLUTIONS OF DIBENZYLAMINE IN CYCLOHEXANE

$(PhCH_2)_2NH$, *M*	$(S)^{1/2}$	η	$\Phi(PhCH_2NH_2)$	$\Phi\eta^{1/2}$
0.02	0.14	0.790	0.025	0.022
0.05	0.22	0.795	0.036	0.032
0.10	0.32	0.803	0.061	0.055
0.30	0.55	0.837	0.093	0.085
0.50	0.71	0.882	0.112	0.105
0.70	0.84	0.926	0.123	0.118
0.90	0.95	0.980	0.129	0.128
1.00	1.00	1.019	0.137	0.138
1.50	1.22	1.169	0.141	0.152
2.00	1.41	1.416	0.141	0.168
2.50	1.60	1.657	0.139	0.181
3.00	1.73	2.015	0.140	0.199

The effect due to viscosity, when considering the dual effect exerted on the quantum yield by increases in the concentration of dibenzylamine, can be discussed from an alternative point of view. Koenig has derived an equation which relates the rate constant for diffusive separation of a radical pair to the square root of fluidity.[40] This would correspond to k_d (eq 9) under

(39) A further test for eq 8 should involve studying the effect of changes in concentration at constant viscosity. This would eliminate problems associated with the probable viscosity dependence of the term C in eq 8.

(40) T. Koenig, *J. Amer. Chem. Soc.*, **91**, 2558 (1969).

$$(PhCH_2)_2NH \underset{k_r}{\overset{h\nu}{\rightleftharpoons}} [PhCH_2\cdot, \dot{N}HCH_2Ph] \xrightarrow{k_d} PhCH_2\cdot + HNCH_2Ph \quad (9)$$

conditions in which a scavenger is not present. The radicals resulting from this diffusion process would have reached the point mentioned above in which the probability of geminate recombination has become negligible. A semiquantitative justification for the square root dependence was developed by Koenig,[10] based upon the time dependence of k_d, which must compete with the return process k_r. He obtained the expression $k_d = r/(\rho - R_0)t$, where r is the root mean square displacement distance for a particle in a time t, ρ is an effective collision diameter, and R_0 is the initial distance of separation. Using the relationship $r = (2Dt)^{1/2}$, obtained from theories of Brownian motion, where D is the relative diffusion coefficient for the pair, he obtained the expression in eq 10 for k_d in units of sec^{-1}.

$$k_d = \left(\frac{2D}{t}\right)^{1/2} \frac{1}{\rho - R_0} \quad (10)$$

This expression predicts that k_d becomes smaller as the viscosity of the solution is increased. The effect due to the viscosity of dibenzylamine can be considered in this light. The radicals formed in the dissociative process can undergo many collisions with surrounding molecules before either diffusion or reaction has occurred.[1,18b,41] If many collisions between the benzylamino radical and dibenzylamine occur for each reaction encounter, then for the nonreactive encounters the dibenzylamine has the same effect as any solvent, *i.e.*, to prevent the radical from escaping the "cage." An increase in the dibenzylamine concentration under these conditions increases the return process, k_r, by inhibiting the diffusion process, k_d.

Following the initial dark reaction (*i.e.*, the abstraction of a hydrogen atom by the benzylamino radical), a pair of radicals remains which are also subject to reaction under "cage" conditions (eq 11). The effect

$$(PhCH_2)_2NH \underset{k_r}{\overset{h\nu}{\rightleftharpoons}} [PhCH_2\cdot, \dot{N}HCH_2Ph] \quad (11a)$$

$$[PhCH_2\cdot, \dot{N}HCH_2PH] + (PhCH_2)_2NH \xrightarrow{k_s} [PhCH_2\cdot + PhCH_2NH_2 + (PhCH_2)_2N\cdot] \quad (11b)$$

$$[PhCH_2\cdot \,||\, \cdot N(CH_2Ph)_2 \xrightarrow{k_d} PhCH_2\cdot + (PhCH_2)_2N\cdot \quad (11c)$$
$$\xrightarrow{k_p} \text{products}$$

of reaction 11b is to produce a benzyl radical and a dibenzylamino radical under conditions where they are not statistically distributed throughout the solution.[42] Therefore, the probability that these radicals will react with each other is greater than the probability that they will react with radicals of their own type. Once, however, diffusion has occurred, there is a statistical chance of encounter with either type of radical. Consequently, for reaction 11c a distinction can be made between the process involving the benzyl radical and the dibenzylamino radical, which leads directly to products, and the diffusion process, which leads to the radicals being distributed evenly throughout the solution. Both events ultimately lead to the formation of toluene, tribenzylamine, and the imine, but bibenzyl can only be formed after the second event, *viz.*, diffusion.

If the formation of toluene occurs largely *via* this "quasi-cage" type of mechanism, the ratio of toluene ("cage" product) to bibenzyl ("noncage" product) should reflect k_d and should be affected by viscosity. The formation of products from the radical pair discussed in the model above is given in Scheme I. If

SCHEME I

$$[PhCH_2 \,||\, (PhCH_2)_2N]$$

$$\swarrow^{k_p} \qquad \searrow^{k_d}$$

$$PhCH_3 + PhCH{=}NCH_2Ph + (PhCH_2)_3N \qquad PhCH_2\cdot + (PhCH_2)_2N\cdot$$

$$2PhCH_2\cdot \xrightarrow{k_1} (PhCH_2)_2$$

$$(PhCH_2)_2N\cdot + PhCH_2\cdot \xrightarrow{k_2} PhCH_3 + PhCH_2N{=}CHPh + (PhCH_2)_3N$$

$$2(PhCH_2)_2N\cdot \xrightarrow{k_3} (PhCH_2)_2NH + PhCH_2N{=}CHPh$$

we assume that $k_1 = k_2/2 = k_3$[43] and the concentrations of benzyl and dibenzylamino radicals are the same, then a straightforward steady-state treatment gives the rates of formation of toluene and bibenzyl as $r[PhCH_3] = (3k_pA + 2k_dA)/3$ and $r[(PhCH_2)_2] = k_dA/3$, where $A = [PhCH_2\|(PhCH_2)_2N]$. Equation 12 results if the relative amounts of products are taken

$$\frac{PhCH_3}{(PhCH_2)_2} = \frac{3k_p}{k_d} + 2 \quad (12)$$

to represent the rate ratios. The rate constant k_d is assumed to be the only viscosity-dependent term,[10] since k_p is the rate constant for reaction of the two species produced in the absence of bulk solvent effects. From eq 10 it follows that $PhCH_3/(PhCH_2)_2$ is proportional to $(1/D)^{1/2}$ or the square root of viscosity.

The data for this relationship are listed in Table VI.

TABLE VI

EFFECT OF VISCOSITY ON THE RATIO OF TOLUENE TO BIBENZYL[a]

$(PhCH_2)_2NH$[b]	$\frac{PhCH_3}{(PhCH_2)_2}$	$\eta^{1/2}$	Solvent[c]	$\frac{PhCH_3}{(PhCH_2)_2}$	$\eta^{1/2}$
0.20	5.0	0.86	Pentane	3.75	0.46
0.25	5.5	0.89	Hexane	4.3	0.54
0.50	7.0	0.94	Heptane	4.9	0.60
0.75	8.0	0.97	Isooctane	5.8	0.66
1.00	8.25	1.01	Nonane	6.3	0.78
1.50	9.5	1.08	Cyclohexane	7.0	0.88

[a] Photolysis time, 60 min; 253 nm. [b] Molar concentration in cyclohexane. [c] 0.5 *M* $(PhCH_2)_2NH$.

(41) E. Rabinowitch and W. Wood, *Trans. Faraday Soc.*, **32**, 1381 (1936).

(42) The representation of the benzyl and dibenzylamino radical pair by the slash marks in eq 11c is to distinguish it from the initial pair in 11a. In a strict sense, the benzyl radical and dibenzylamino radical probably do not represent a "caged" pair; however, in our operational definition a "cage" is construed as a radical pair in a measurably nonstatistical distribution. Hydrogen bond aggregates should also be included in this context.

(43) This may not be a valid assumption, however, since the self-reaction of amino radicals shows rather large steric effects. For example, the rate constant for diethylamino radicals is $7 \times 10^9\ M^{-1}\ sec^{-1}$ at $-90°$, but for the isopropyl analog it is $5 \times 10^6\ M^{-1}\ sec^{-1}$ at $-10°$ [J. R. Roberts and K. U. Ingold, *J. Amer. Chem. Soc.*, **93**, 6686 (1971)]. The rate of the cross-association of benzyl and dialkylamino would, however, be more similar to the dimerization of benzyl radicals.

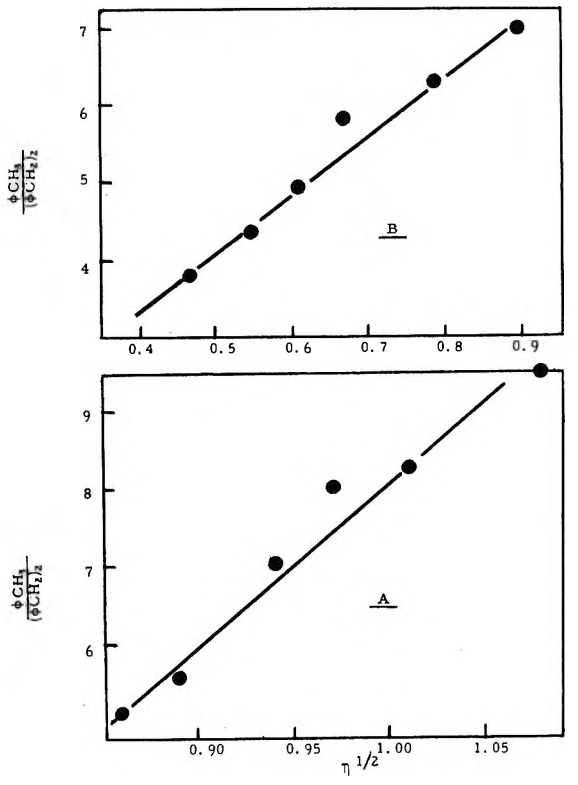

Figure 7.—Ratio of cage to noncage products *vs.* the viscosity: (A) dibenzylamine in cyclohexane; (B) hydrocarbon solvents.

As shown in Figure 7A for various concentrations of dibenzylamine in cyclohexane, the ratio of the two products does vary as predicted for the model being considered. Unlike the initial step in the reaction 11b where both viscosity and concentration were concerned, step 11c should show a linear relationship with the viscosity function alone. This linearity was found to hold, and in Figure 7B the same quantities are plotted for the data obtained in the series of hydrocarbon solvents. The slopes for the two plots are 8.3 and 21.6 for the hydrocarbon solvents and dibenzylamine, respectively. The higher value for the dibenzylamine is predictable, even though the viscosity effects of the two solutions may be similar. Thus, when dibenzylamine is the solvent, the reaction of the benzylamino radical with dibenzylamine (eq 11) (which is less available in the hydrocarbon solvent) results in the formation of the radical pair that is in closer proximity than that predicted by viscosity effects alone. Under these circumstances, there is a greater probability for encounter of the radical pair, and it is reflected in a higher ratio of "cage" to "noncage" products. The ratio of toluene to bibenzyl is only a crude measure of the cage effects, and additional studies of "cage" and "noncage" recombinations using stereochemical probes and chemically induced dynamic polarization would be desirable.

Disproportionation of benzyl radicals and dibenzylamino radicals can also be examined directly from the photolysis of *N,N,N*-tribenzylamine (Table VII). If radicals formed in the homolysis of tribenzylamine were randomly distributed in solution, the probability of encounter of a benzyl radical with another benzyl radical is one-half that with an amino radical. The low yields of bibenzyl, however, suggest that the radicals are not distributed statistically (provided there is no or little selectivity in the combination processes). A cage mechanism (eq 14) offers the most reasonable

TABLE VII
PHOTOLYSIS OF *N,N,N*-TRIBENZYLAMINE

Amine[a]			Product, mmol				
Start[e]	Recover	Solvent	$PhCH_3$	$(Ph-CH_2)_2$	$PhCH{=}NCH_2-Ph$	Ph-CHO[d]	$(Ph-CH_2)_2-NH$
1.76[c]	0.73	*c*-C_6H_{12}	0.78	0.08	0.75	0.80	0.26
4.65[b]		*c*-C_6H_{12}	0.65	0.09	0.65		0.22
1.76[c]	0.71	CH_3CN	0.66		0.80	0.74	0.21
1.75[c]	0.86	CH_3CN	0.66	0.09	0.70	0.76	0.21

[a] Millimoles. [b] Photolysis time, 200 min. [c] Photolysis time, 400 min. [d] Only after acid hydrolysis. [e] In 10 ml of solvent.

$$(PhCH_2)_3N \rightleftharpoons [Ph\dot{C}H_2, (PhCH_2)_2\dot{N}] \quad (13)$$

$$[Ph\dot{C}H_2, (PhCH_2)_2\dot{N}] \begin{cases} \rightarrow PhCH_3 + PhCH_2N{=}CHPh & (14a) \\ \rightarrow PhCH_2\cdot + (PhCH_2)_2N\cdot, \text{ etc.} & (14b) \end{cases}$$

explanation for the high yields of toluene and *N*-benzylbenzaldimine generated by the cross-disproportionation of benzyl and dibenzylamino radicals.

This mechanism is consistent with that proposed for the secondary steps in the photodecomposition of dibenzylamine. A major difference between them, however, lies in the idea that the two radicals are produced directly by this photochemical process, with the consequence that the initial distance of separation is probably less than that for the same pair of radicals derived from the photolysis of dibenzylamine. This difference is reflected in a higher ratio of toluene relative to bibenzyl (about 10). A value this large in the photolysis of dibenzylamine is only attained in highly viscous media.

Factors involved in the disproportionation of benzylamino radicals are also noteworthy. The mechanism presented in eq 11 does not explicitly include the cross-disproportionation of the benzyl radical and the benzylamino radical (eq 15).[44] On the other hand, the dis-

$$Ph\dot{C}H_2 + H\dot{N}CH_2Ph \longrightarrow PhCH_3 + HN{=}CHPh \quad (15)$$

proportionation of benzyl and dibenzylamino radicals is the principal process (eq 14b) in the photolysis of *N,N,N*-tribenzylamine and other tertiary benzylamines.[45] Similarly, the photolyses of a series of *N*-benzyl-*N*-alkylamines show no evidence of disproportionation of the benzyl and alkylamino radical pair. Furthermore, the quantum yields in the photolysis of *N*-benzyl-*N*-*tert*-butylamine (and benzylamine itself) is not significantly different from that of the other alkyl analogs,[45] despite the impossibility of cross-disproportionation. Apparently, the cross-disproportionation of the secondary dialkylamino radicals occurs readily, whereas that of the primary analogs does not.

There are several explanations for this selectivity. The cross disproportionations of benzyl and alkylamino radicals generally show high selectivity,[45] and

(44) Due to the instability of benzaldimine under reaction conditions, however, we cannot rigorously establish that cage disproportionation of this radical pair does not occur at all. Some of the results presented earlier may be attributed to contribution from such a disproportionation.

(45) M. A. Ratcliff and J. K. Kochi, *Tetrahedron*, in press.

a large degree of hydrogen transfer is indicated in the transition state. Accordingly, the low stability[46] of simple alkylidene imines (eq 15) relative to their *N*-alkyl analogs would discourage cross-disproportionation with the relatively unreactive benzyl radical. Finally, the facile hydrogen transfer from the N–H available in secondary amines would promote the competitive scavenging of the reactive alkylamino radicals over that of the more stable dialkylamino analogs.[47]

Experimental Section

All products were determined as previously described.[19] Solvents used in the photolyses were, when available, commercial Spectrograde solvents used without further purification. Other hydrocarbon solvents were purified for photolysis by passing them through a 10% silver nitrate on acid-washed alumina column.[48] Nujol (Plough, Inc.) was heated to 175° (1 mm) in a vacuum oven for 20 hr. It was then diluted with 4 equiv of pentane and passed through an alumina column as described above. The pentane was removed by rotary evaporation. Solvents purified by these methods showed absorbances of less than 0.05 in a 1-cm cell. Cyclohexene was prepared by the standard method of dehydrating cyclohexanol with H_2SO_4. Commercial cyclohexene contained impurities which absorbed strongly at 250 nm. A variety of methods to purify the commercial material failed. Prepared in this manner the cyclohexene had an absorbance of 0.1 in a 1-cm cell at 250 nm. All operations were carried out with syringes using degassed and capped vessels. Isopropyl ether was stirred vigorously with an aqueous ferrous solution for 2 hr. The ether layer was dried and distilled from lithium aluminum hydride into a second flask containing more lithium aluminum hydride. A nitrogen atmosphere was maintained throughout all operations. The ether after fractionation was kept in a sealed flask. Standard solutions of both cyclohexene and isopropyl ether in cyclohexane were prepared using degassed solutions and surgical syringes. Standard solutions of amine were prepared from these stock solutions for quantum yield studies.

Dibenzylamine was purified by methods previously described.[1] At 253 nm, dibenzylamine has ϵ 357, whereas *N*-benzylbenzaldimine has ϵ 18,000. To ensure 99% absorption of the incident light by the amine the molar ratio of the amine to the imine must be approximately 500:1. This condition was easily met by both procedures used for purification, as previously described.[1]

Quantum Yield Measurements.—Aliquots (3.0 ml) of standard solutions were transferred to 10 × 1 cm quartz tubes and degassed with a stream of nitrogen. For the more volatile solvents, the solutions were degassed in volumetric flasks sealed with rubber septa. After degassing, additional solvent, previously degassed, was added *via* a surgical syringe to compensate for solvent lost. Samples (3 ml) were then added to previously degassed and capped photolysis tubes with a surgical syringe.

The solutions were photolyzed in a precision merry-go-round apparatus (F. G. Moses, Co., Wilmington, Del.). A coiled low-pressure Hg lamp (Mr. Charles Shott, University of Alberta), operating at 100 mA from a 5000-V transformer, was placed in the center of the apparatus and the samples were rotated around it. A shutter allowed the system to be used only after the lamp was warmed up. A constant temperature of 32° was maintained in the reactor by the lamp.

Actinometry was carried out with chloroacetic acid using a value of 0.370 as the quantum yield for chloride formation at 32°.[49] The intensity of the lamp was found to be $7.22 \pm 0.08 \times 10^{-5}$ einstein hr^{-1} by this method. This value was obtained by averaging 20 separate runs. The consistency was a demonstration of the uniformity of the quartz tubes and the reproducibility of the merry-go-round method.

The quantum yields reported for the dibenzylamine photolysis were measured for reactions photolyzed to less than 0.1% conversion. This limitation was necessary to ensure against filtering from the *N*-benzylbenzaldimine formed during the reaction. For two cases (0.1 and 1.0 *M*) the quantum yield was obtained from the slope of a yield *vs.* time plot which was linear over the time period involved. Other values were obtained by averaging five runs carried out simultaneously.

Viscosities were determined at 32.0 ± 0.05° in modified Cannon-Fenske routine viscometers calibrated by the Cannon Instrument Co., State College, Pa. Densities were obtained from literature values[50] or by direct weighing.

Registry No.—Dibenzylamine, 103-49-1; tribenzylamine, 620-40-6; benzylamine, 100-46-9; cyclohexene, 110-83-8; diisopropyl ether, 108-20-3; toluene, 108-88-3; bibenzyl, 103-29-7.

Acknowledgment.—We wish to thank the National Science Foundation, The Petroleum Research Fund of the American Chemical Society, and the U. S. Army Edgewood Arsenal for financial support of this research.

(46) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. I, W. A. Benjamin, New York, N. Y., 1965, p 301.

(47) The reactivity sequence is $H_2\dot{N} > R_2\dot{N}$: B. G. Gowenlock and D. R. Snelling, *Advan. Chem. Ser.*, **No. 36**, 150 (1962).

(48) E. C. Murray and R. N. Keller, *J. Org. Chem.*, **34**, 2234 (1969).

(49) R. N. Smith, P. A. Leighton, and W. G. Leighton, *J. Amer. Chem. Soc.*, **61**, 2299 (1939).

(50) R. R. Breisback, *Advan. Chem. Ser.*, **No. 15** (1955); **No. 22** (1959).

Photochemistry of Dihydromayurone. Novel Solvent Participation in a Photoisomerization[1]

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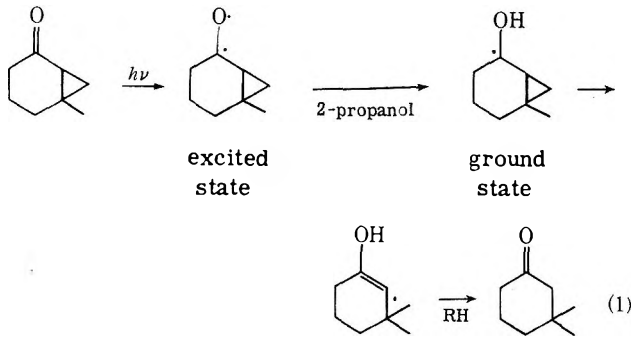
When irradiated in 2-propanol, both *cis*- and *trans*-dihydromayurone (**1** and **6**) react to give a mixture of isomerized (**2** and **3**) and reduced (**4** and **5**) products. The isomeric photoproducts (**2** and **3**) are unusual in that a reducing solvent is necessary for their formation although a net reduction has not occurred. An exchange of hydrogen atoms during isomerization was demonstrated by irradiation of dideuterio-*trans*-dihydromayurone (**8**) in 2-propanol to give monodeuterated hydrindanone **9** and irradiation of **1** in 2-propanol-d_1 to give monodeuterated hydrindanone **7**. Hydrindanone **2** is a secondary product derived from the photoisomerization of **3**. The difference between the photoreduction of **1** and that of simpler bicyclo[4.1.0]heptan-2-ones is attributed to the *gem*-dimethyl group, which sterically hinders hydrogen abstraction.

The photoreduction of conjugated cyclopropyl ketones in 2-propanol has been shown[2] to proceed with hydrogen abstraction by the n–π^* excited carbonyl oxygen atom, followed by a ground-state rearrangement of the α-hydroxycyclopropylcarbinyl radical. The products obtained from bicyclo[4.1.0]heptan-2-ones are cyclohexanones derived from the reductive opening of the cyclopropyl ring (eq 1). The alternate



(1)

products, cycloheptanones, are normally not observed owing to both the thermodynamic preference for opening to a six-membered ring as well as preference for opening of the outer cyclopropyl bond which is geometrically aligned for better overlap, as compared to the inside bond, with the adjacent carbonyl center.

The irradiation of either *cis*- or *trans*-dihydromayurone (**1** and **6**, respectively) in 2-propanol does not follow this simple reaction course, but rather gives a complex mixture of products (Scheme I).

The ketones were irradiated in 2-propanol with a Corex-filtered (>260 nm) 450-W Hanovia medium-pressure mercury lamp and the reaction progress was monitored by gas–liquid chromatography (glc). After removal of the solvent and oxidation of the total mixture to convert any alcohols to the corresponding ketones, the products were isolated by a combination of alumina and silica gel chromatography and recrystallization. The isolated yields are listed in Table I.

3a,7,7-Trimethyl-7a-vinylhexahydro-1-indanone (**2**) was identified on the basis of its spectral data. The nmr spectrum clearly shows a vinylic group at a quaternary center, three methyl singlets, and two hydrogens α to the carbonyl group (see Experimental Section). This ketone is isomeric with **1** (mol wt 206) and the ir

TABLE I

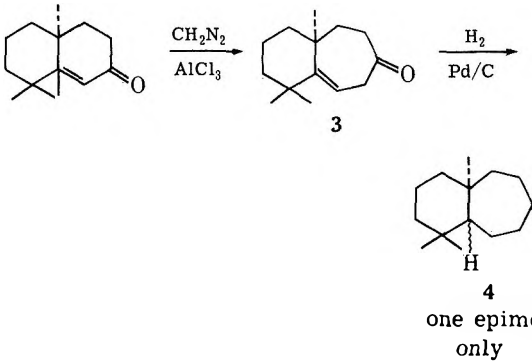
ISOLATED YIELDS FROM THE 2-PROPANOL IRRADIATIONS OF 1 AND 6

	Products, %						
Reactant	1	2	3	4	5	6	Non-monomeric material[a]
1	25	14	6	9	8	2	36
6	2	12.5	4	8.5	2	29	42

[a] Consists mainly of tertiary alcohols from dimerization and solvent addition.

carbonyl stretching frequency (1732 cm^{-1}) indicates a cyclopentanone moiety. The structure of **2** has not been proven by synthesis and the stereochemistry at C-7a is unknown.

7,11,11-Trimethylbicyclo[5.4.0]-1-undecen-4-one (**3**) was readily identified from spectral data and by comparison with an authentic sample prepared by diazomethane ring expansion of 8,8,10-trimethyl-1(9)-octal-2-one (eq 2).[3]



(2)

Further evidence for the structural assignment of **2** was obtained by isolation of **3** and reirradiation in 2-propanol. Ketone **2** was isolated in 23% yield and was identical with the sample of **2** obtained by direct irradiation of either **1** or **6**. The formation of α-vinyl ring-contracted ketones from the irradiation of cyclic β,γ-unsaturated ketones is well documented.[4]

7,11,11-Trimethylbicyclo[5.4.0]undecan-4-one (**4**) was isolated as a mixture of epimers from both the irradiations of **1** and **6** (80:20 ratio from **1**, 55:45 ratio from **6**). This was determined from the fact that **4** was partially resolved into two peaks on glc and the

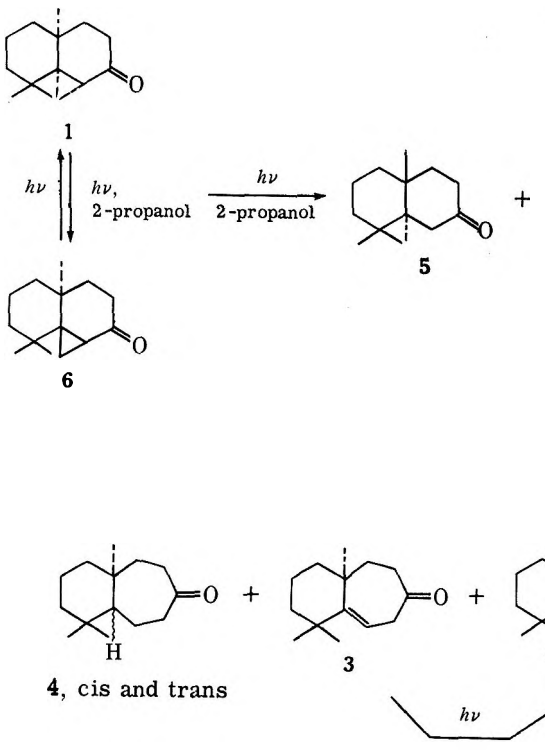
(1) The results of this research were first disclosed at the XXIII IUPAC Congress in Boston, July 1971, Abstracts, p 100.

(2) W. G. Dauben, L. Schutte, R. E. Wolf, and E. J. Deviny, *J. Org. Chem.*, **34**, 2512 (1969).

(3) C. Enzell, *Tetrahedron Lett.*, 185 (1962).

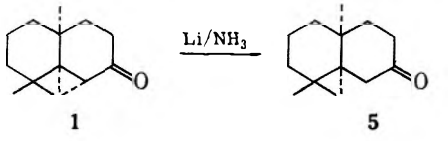
(4) L. A. Paquette and R. F. Eizember, *J. Amer. Chem. Soc.*, **89**, 6205 (1967); R. G. Carlson and J. H. Bateman, *Tetrahedron Lett.*, 4151 (1967); L. A. Paquette, R. F. Eizember, and O. Cox, *J. Amer. Chem. Soc.*, **90**, 5153 (1968); L. A. Paquette and G. V. Meehan, *J. Org. Chem.*, **34**, 450 (1969).

SCHEME I



nmr spectrum showed six methyl singlets whose relative intensities varied depending on whether **4** was isolated from the irradiation of **1** or **6**. Catalytic reduction of **3** gave one epimer of **4** (eq 2) which was identical with the major epimer of **4** isolated from the irradiation of **1**. The ring fusion stereochemistry of this epimer has not been determined.

cis-8,8,9,10-Tetramethyl-2-decalone (**5**), the expected product from the irradiation of **1** based on the work of Dauben,[2] was identified by comparison with **5** obtained as the sole product from lithium–ammonia reduction of **1** (eq 3).



(3)

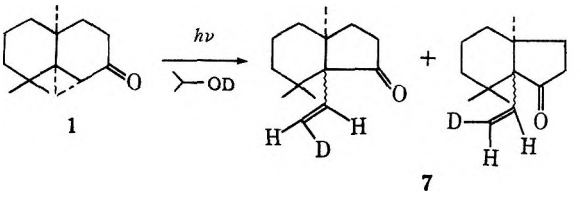
The interconversion of **1** and **6** was demonstrated only by glc retention times. The irradiation of either **1** or **6** gave a low yield (2%) of the epimer and isolation was not possible.

The interconversion of **1** and **6**, as well as formation of isomeric photoproducts **2** and **3**, suggested that for these products a hydrogen-donating solvent would not be necessary since a net photoreduction had not occurred. However, **1** was quite stable to irradiation in 2-methyl-2-propanol. Although small amounts of the same products were detected, the rate of reaction was very much slower than the rate in 2-propanol and probably the small amount of reaction that was observed was initiated by inefficient hydrogen abstraction from 2-methyl-2-propanol.

In the case of **6**, prolonged irradiation in 2-methyl-2-propanol afforded 10% **1** but none of the products **2**–**5**.

The absence of rapid formation of isomeric ketones **2** and **3** without the presence of a hydrogen-donating solvent demonstrated that a unique hydrogen abstraction–loss process must be involved to result in nonreduced products.

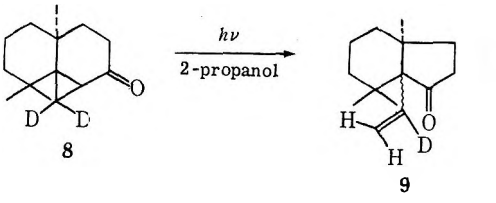
Confirmation of this hypothesis was obtained by two deuteration experiments. The hydrindanone product isolated from the irradiation of **1** in 2-propanol-d_1 contains one deuterium (mol wt 207) and the nmr spectrum shows conclusively that the deuterium is located at the terminal position of the double bond (eq 4). The nmr



(4)

spectrum of **7** is identical with that of **2** except for the vinylic region. Ketone **7** has one vinylic hydrogen at δ 5.65–6.13 (m), one-half of a terminal vinylic hydrogen at 5.21 (d, J = 11 Hz, cis coupling), and one-half of a terminal vinylic hydrogen at 4.90 (d, J = 18 Hz, trans coupling). This differs from the spectrum of **2** in that the vinylic hydrogen of **2** appears as a clean doublet of doublets at δ 5.91 (J = 11 Hz, J' = 17.5 Hz) instead of the multiplet obtained from **7** due to additional deuterium coupling, and the terminal methylene hydrogens of **2** appear as eight peaks (J_{cis} = 11 Hz, J_{trans} = 17.5 Hz, J_{gem} = 2 Hz) instead of the four peaks obtained from **7** due to the elimination of observable geminal coupling. The integration of the nmr spectrum of **7** allows the conclusion that the deuterium is equally substituted at both positions of the terminal methylene group.

The hydrindanone product isolated from the irradiation of *trans*-dideuteriodihydromayurone (**8**) (mol wt 208) also contains one deuterium (mol wt 207) and its location exclusively at the α position of the double bond (eq 5) can be unambiguously determined from



(5)

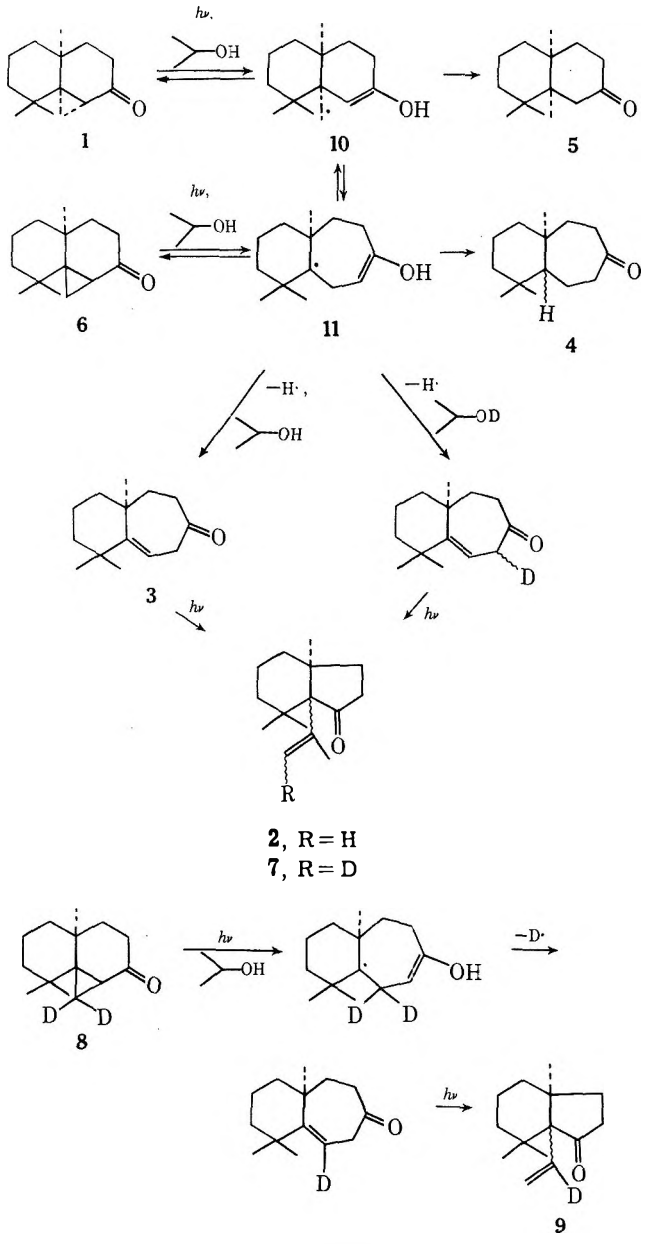
the nmr spectrum. Again, except for the vinylic region, the nmr spectrum of **9** is identical with that of **2**. Both the vinylic hydrogen absorption of **2** at δ 5.91 and the large vicinal coupling constants of the terminal methylene hydrogens of **2** are completely absent from the spectrum of **9**. The two terminal methylene hydrogens of **9** appear as two narrow multiplets (6–8-Hz width) at δ 5.26 and 4.94.

By glc, the irradiations of **8** in 2-propanol and **1** in 2-propanol-d_1 closely paralleled the original irradiations of **1** and **6**, although the products other than **7** and **9** were not isolated.

These experiments not only show an exchange of hydrogen during the isomerization of **1** or **6** to **2**, but the location of deuterium in **7** and **9** allows a reasonable

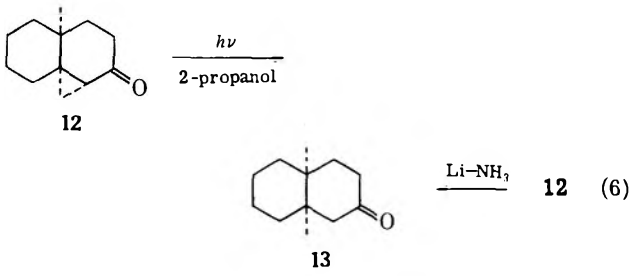
mechanism[5] to be proposed for the formation of **2** and **3** (Scheme II). The other products can also arise from the same radicals **10** and **11**.

SCHEME II



In the presence of a hydrogen-donating solvent *cis*-dihydromayurone opens the geometrically aligned cyclopropyl bond to give radical **10** which can abstract a second hydrogen to give **5**. However, the *gem*-dimethyl group sterically hinders **10** from hydrogen abstraction and allows the ground-state radical sufficient time to rearrange to tertiary radical **11**. In an inert solvent the same cyclopropyl bond probably opens but the excited-state diradical does not have the lifetime of ground-state radical **10** and therefore recloses to **1** rather than undergoes rearrangement.

The results from the reduction of *cis*-1,9-methano-10-methyl-2-decalone (**12**) are in support of this explanation involving the hindrance of radical **10** as the cause of these unusual products from the irradiation of dihydromayurone. Both photoreduction and lithium–ammonia reduction of **12** give only the expected *cis*-decalone (**13**) (eq 6). Without the *gem*-dimethyl

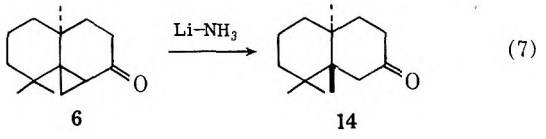


(6)

group of **1**, **12** reacts in the same manner as the simpler bicyclo[4.1.0]heptan-2-ones.

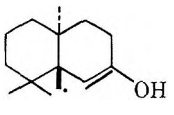
The formation of **2** and **3** from dihydromayurone represents the first example of a photoisomerization which occurs only under reducing conditions.

One aspect of the photochemistry of the dihydromayurones remains without a satisfactory explanation. *trans*-8,8,9,10-Tetramethyl-2-decalone (**14**), formed as the sole product from lithium–ammonia reduction of **6** (eq 7), was not present in the photomixture from **1** and,



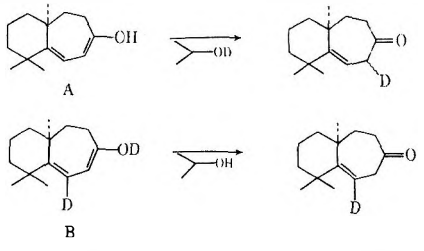
(7)

if formed at all in the irradiation of **6**, was present in only trace amounts. Inspection of molecular models shows little difference in steric hindrance toward hydrogen abstraction between radicals **10** and **15**; therefore, if radical **15** were formed in the sequence of photoreduction, then ketone **14** should have been present at least to the extent of a few per cent.



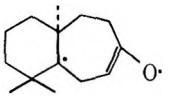
This implies that **6**, unlike its cis isomer **1**, directly opens to tertiary radical **11** although molecular models show that in both isomers the outside cyclopropyl bond should be the favored one for reductive cleavage. The irradiations in 2-methyl-2-propanol also support this conclusion. A substantial amount (10%) of ketone **6** photoisomerizes to **1** in 2-methyl-2-propanol; however, the reversibility of this reaction is not observed. This is consistent with the direct formation of tertiary

(5) A referee noted that the deuterium-labeling studies are also compatible with an alternate mechanism in which **1** or **8** undergo an internal rearrangement to enol A or B, respectively, followed by ketonization. The author



feels that the failure of rearrangement in 2-methyl-2-propanol argues decisively against this alternate mechanism; the referee further noted that differences in solvent acidities and dielectric constants make various solvent effects possible.

diradical **16** from the irradiation of **6**, followed by reclosure to either the cis or trans isomer.



16

Presently, we are studying a series of analogous cyclopropyl ketones without the *gem*-dimethyl group of the dihydromayurones (*e.g.*, **12** and its trans isomer) to elucidate the reasons for this differing behavior between cis and trans isomers.

Experimental Section

Preparative irradiations were carried out with a 450-W medium-pressure Hanovia mercury lamp in a quartz, water-cooled, immersion probe. The filter was a glass cylinder of Corex (>255 nm) insertable between the lamp and the probe. Solutions were outgassed with argon before and during the irradiations.

Infrared spectra were taken as neat samples (except where noted) on a Perkin-Elmer 457 and absorptions are reported as inverse centimeters, uv spectra were taken on a Beckman Acta III, nmr spectra were taken on a Varian A-60A as chloroform-d_1 solutions and are reported as δ units relative to TMS, and molecular weights were determined from mass spectra obtained with a Perkin-Elmer 270. Gas–liquid chromatography was done on a 10% Carbowax 20M (12 ft × 1/8 in.) column. Melting points are uncorrected.

Irradiation of *cis*-Dihydromayurone (1).—A solution of 4.00 g of 1[6] in 150 ml of 2-propanol (0.13 *M*) was irradiated for 3.75 hr. Glc showed six ketonic components with the following relative retention times: A, 0.33; B, 0.66; C, 0.73; D, 0.82; 1, 1.0; E, 1.1. The solvent was removed under reduced pressure, the residual oil (4.60 g) was oxidized at 0° with excess Jones reagent,[7] and the resulting mixture (4.02 g) was chromatographed on 300 g of alumina (neutral III, 2.5 × 60 cm column).

Compound A was eluted with hexane–benzene (10:1) and was identified as 3a,7,7-trimethyl-7a-vinylhexahydro-1-indanone (**2**): 0.552 g (14% yield); mol wt 206; λ_{max}^{MeOH} 301 nm (ϵ 40); ir (CCl_4) 1732 (s), 1620 (w), 1002 (m), 992 (w), 928 (s); nmr 5.91 (1 H, d of d, J = 11 Hz, J' = 17.5 Hz, vinylic H), 5.22 (1 H, d of d, J = 11 Hz, J' = 2 Hz, terminal methylene H), 4.90 (1 H, d of d, J = 17.5 Hz, J' = 2 Hz, terminal methylene H), 2.2 (2 H, m, α H), 1.18 , 1.15, 0.9 (9 H, 3 s, methyl H). The ketone was sublimed at 1 mm and recrystallized from aqueous ethanol, mp 196–199° (sealed capillary).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.45; H, 10.63.

Compounds C and D were eluted together with hexane–benzene (1:1). The early factions were enriched in C and identification was made on 80–90% pure material. Compound C gave two partially resolved peaks on glc and was identified as *cis*- and *trans*-7,11,11-trimethylbicyclo[5.4.0]undecan-4-one (**4**): 0.357 g, 9%; mol wt 208; ir 1704; nmr 1.05, 1.02, 0.98 (3 s, methyl H, major epimer), 0.95, 0.90, 0.82 (3 s, methyl H, minor epimer). The ratio of epimers was 4:1. The major epimer in this sample was identical (ir and nmr spectra, glc) with synthetic **4** obtained by low-pressure hydrogenation of 7,11,11-trimethylbicyclo[5.4.0]-1-undecen-4-one (**3**) prepared according to the procedure of Enzell.[3] Synthetic **4** consisted of only one epimer (nmr singlets at 1.05, 1.02, 0.98).

Compound D (0.299 g, 8%) was isolated pure (mp 149–150°) by two recrystallizations from hexane of fractions containing *ca.* equal amounts of C and D. Crystalline D was identified as *cis*-8,8,9,10-tetramethyl-2-decalone (**5**) by comparison (ir and nmr spectra, glc, mmp 148.0–150.5°) with **5** obtained by lithium–ammonia reduction of **1**.

Starting material 1 (1.0 g, 25%) and E were eluted together with benzene and benzene–ether (50:1). Compound E (0.08 g, 2%) was identified as *trans*-dihydromayurone (**6**) on the basis of an identical glc retention time with that of synthetic material.

Compound B was not very stable on alumina but was isolated (>90% pure, 0.24 g, 6%) from a silica gel chromatogram by elution with benzene–ether (100:1 and 50:1) and was identified as 7,11,11-trimethylbicyclo[5.4.0]-1-undecen-4-one (**3**): mol wt 206; ir 1708; nmr 5.52 (1 H, broadened t, J = 6 Hz, vinyl H), 3.20 (2 H, d, J = 6 Hz, one peak further split into d, J' = 2 Hz, allylic H), 2.38–2.66 (2 H, m, H α to carbonyl), 1.10, 1.14, 1.19 (9 H, 3 s, methyl H). This sample was identical (ir and nmr spectra, glc) with synthetic **3**.[3]

The remaining 36% included trace ketonic products but was mainly very polar material including a large amount of tertiary alcohols (dimers and 2-propanol addition products) whose structures were not investigated.

Extended irradiation of 1 in 2-methyl-2-propanol (0.590 g of 1, 150 ml of 2-methyl-2-propanol, 0.02 *M*, 15 hr) and chromatography as above gave 3% **2** (ir and nmr spectra, glc), 3% **5** (glc), trace amounts of **3** and **4** (glc), 78% **1**, and 16% nonmonomeric alcoholic material. The presence of **6** could not be detected in the irradiation mixture.

Isolation of **3** and reirradiation in 2-propanol (0.13 g, 5 ml of 2-propanol, 0.13 *M*, 8-RUL 3000-Å Rayonet lamps, 10 hr) gave **2** in 23% yield after isolation by alumina chromatography. The sample was identical (glc retention time, nmr spectrum) with **2** isolated from the direct irradiation of **1**.

Isolation of **2** and reirradiation in 2-propanol (0.81 g, 150 ml of 2-propanol, 0.026 *M*, 3 hr) rapidly gave a product whose glc retention time was identical with that of **3**. This glc peak remained at constant percentage (5–10%) throughout the irradiation as the glc peak for **2** decreased very slowly.

Irradiation of *trans*-Dihydromayurone (6).—A solution of 1.08 g of 6[8] in 150 ml of 2-propanol (0.035 *M*) was irradiated for 3 hr. The reaction was worked up and the products were isolated as described above. The products (yields) follow: **2**, 12.5%; **3**, 4%; **4**, 8.5% (55–45% mixture of epimers); **5**, 2%; **1**, 2%; **6**, 29%. The remaining 42% was nonoxidizable alcoholic material and was not investigated. The identification of **1**, **3**, and **5** was made solely on the basis of identical glc retention times with those of authentic samples. In addition to 1–6, the irradiation mixture contained a trace component with an identical glc retention time with that of synthetic *trans*-8,8,9,10-tetramethyl-2-decalone (**14**).

Extended irradiation of *trans*-dihydromayurone (**6**) in 2-methyl-2-propanol (0.046 *M*) for 9 hr gave none of the products **2**–**5**, 10% **1** (identified only by glc retention time), 84% unreacted **6**, and ~6% nonmonomeric material (percentages determined by equal volume glc injections).

Irradiation of *cis*-1,9-Methano-10-methyl-2-decalone (12).—A solution of 1.96 g of **12** (95% cis, 5% trans), prepared by Jones oxidation[7] of *cis*-1,9-methano-10-methyl-2-decalol,[9] in 150 ml of 2-propanol (0.073 *M*) was irradiated for 1.5 hr. The reaction was worked up as described above and the products were isolated by chromatography of the crude mixture (1.82 g) on 250 g of alumina (neutral III, 2.5 × 44 cm column).

Benzene eluted 0.582 g (32%) of crystalline material identified after recrystallization from hexane (mp 128–131°) as *cis*-9,10-dimethyl-2-decalone (**13**, mol wt 180) by comparison (ir and nmr spectra, glc, mmp 127.5–132.0°) with **13** obtained by lithium–ammonia reduction of **12**. Further elution with benzene gave recovered **12**, 0.640 g (35%).

By glc, there were several other ketonic photoproducts but all were present in very low yield and could not be isolated pure. Most of the remaining 33% was a mixture of tertiary alcohols including one crystalline alcohol (0.198 g) eluted with ether–methanol (100:1): mol wt 238; mp 125–130° recrystallized from hexane; ir 3360; nmr 1.40, 1.26, 0.93 (3 s, methyl H). This alcohol was tentatively identified as 1,9-methano-2-(1-hydroxy-1-methylethyl)-10-methyl-2-decalol.

Irradiation of *trans*-Dideuteriodihydromayurone (8).—A solution of 0.385 g of 8[8] in 150 ml of 2-propanol (0.012 *M*) was irradiated for 1 hr. The hydrindanone product was isolated by alumina chromatography and identified as 3a,7,7-trimethyl-7a-(1-deuteriovinyl)-hexahydro-1-indanone (**9**): 0.057 g (15%

(6) S. Nagahama, H. Kobayashi, and S. Akiyoshi, *Bull. Chem. Soc. Jap.*, **35**, 140 (1962); T. Nozoe, *et al.*, *Chem. Pharm. Bull.*, **8**, 936 (1960).

(7) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(8) *trans*-Dihydromayurone (**6**) was prepared from 8,8,10-trimethyl-$\Delta^{1,9}$-octalin by the following sequence: allylic bromination with *N*-bromosuccinimide, followed by hydrolysis with aqueous acetone, followed by the Simmons–Smith reaction and Jones oxidation (W. G. Dauben and E. I. Aoyagi, private communication). *trans*-Dideuteriodihydromayurone (**8**) was prepared by the same sequence using dideuteriomethylene iodide in the Simmons–Smith reaction.

(9) W. G. Dauben, P. Lang, and G. H. Berezin, *J. Org. Chem.*, **31**, 3869 (1966).

yield); mol wt 207; ir (CCl_4) 1734 (s), 928 (m); nmr 5.26 and 4.94 (2 H, 2 m, terminal vinylic H), 2.2 (2 H, m, α H), 1.19, 1.15, 0.92 (9 H, 3 s, methyl H). Except for the vinylic region (4.6–6.2), the nmr spectrum of **11** was identical with that of **2**.

The other photoproducts from **8** were not isolated but according to glc the irradiation of **8** closely paralleled the irradiations of **1** and **6**.

Irradiation of *cis*-Dihydromayurone (1) in 2-Propanol-d_1.—A solution of 0.200 g of **1** in 10 ml of 2-propanol-d_1 (Stohler Isotopes, deuteration on oxygen) (0.097 *M*) was irradiated for 11 hr using 8-RUL 3000-Å Rayonet lamps. The hydrindanone product was isolated by alumina chromatography and identified as 3a,7,7-trimethyl-7a-(2-deuteriovinyl)-hexahydro-1-indanone (**7**): 0.015 g (8% yield); mol wt 207; nmr 5.65–6.13 (1 H, m, vinylic H), 5.21 (0.5 H, d, J = 11 Hz, terminal vinylic H), 4.90 (0.5 H, d, J = 18 Hz, terminal vinylic H), 2.2 (2 H, m, α H), 1.18, 1.15, 0.92 (9 H, 3 s, methyl H). Except for the vinylic region (4.6–6.2), the nmr spectrum of **7** was identical with that of **2**.

The other photoproducts were not isolated, but, according to glc, the irradiation closely paralleled the undeuterated 2-propanol irradiation. By mass spectroscopy, no deuterium incorporation could be detected in recovered **1**.

***cis*-8,8,9,10-Tetramethyl-2-decalone (5).**—From lithium–ammonia reduction[10] of **1** there was obtained **5**: mp 150–151° recrystallized from hexane; mol wt 208; ir 1702; nmr 1.10, 1.05, 0.88, 0.81 (4 s, methyl H).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.60; H, 11.47.

***trans*-8,8,9,10-Tetramethyl-2-decalone (14).**—From lithium–ammonia reduction[10] of **6** there was obtained **14**: mol wt 208; ir 1705; nmr 1.37, 1.07, 0.81 (3 s, methyl H), 0.92 (d, J = 1 Hz, methyl H).

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.67; H, 11.79.

***cis*-9,10-Dimethyl-2-decalone (13).**—From lithium–ammonia reduction[10] of **12** there was obtained **13**, isolated by benzene elution from an alumina (neutral III) chromatogram: mp 132–134° recrystallized from hexane (lit.[11] mp 108–118°); mol wt 180; ir 1705; nmr 1.04, 0.90 (2 s, methyl H) (lit.[11] nmr 1.05, 0.90).

Registry No.—**1**, 7129-16-0; **2**, 35342-07-5; **3**, 35342-08-6; ***cis*-4**, 35342-09-7; ***trans*-4**, 35342-10-0; **5**, 35342-11-1; **6**, 31090-36-5; **8**, 35342-13-3; **9**, 35342-14-4; **12**, 35340-22-8; **13**, 5523-99-9; **14**, 35340-24-0; 1,9-methano-2-(1-hydroxy-1-methylethyl)-10-methyl-2-decalol, 35340-25-1.

Acknowledgments.—The author would like to thank W. G. Dauben and A. R. Hochstetler for helpful discussions regarding this research and J. Fischer for excellent technical assistance.

(10) W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966).

(11) J. A. Marshall, W. I. Fanta, and H. Roebke, *ibid.*, **31**, 1016 (1966).

Sterically Controlled Syntheses of Optically Active Organic Compounds. XV. Syntheses of Optically Active Aspartic Acid through β-Lactam[1]

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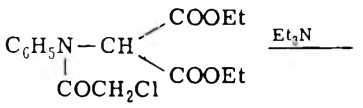
Optically active *N*-alkyl-*N*-chloroacetamidoacetonitriles were prepared and were converted to their corresponding β-lactams by treatment with sodium hydride. The β-lactams were hydrolyzed and hydrogenolyzed to form optically active aspartic acid. When (*R*)-α-alkylbenzylamines were used, (*S*)-aspartic acid was the result. The yield of aspartic acid from aminoacetonitriles ranged from 36 to 96%. The optical purity of aspartic acid ranged from 21 to 67%. A temperature effect on the sterically controlled reaction was examined. The effect of temperature on the optical purity and yield was found to be small. To examine whether the sterically controlled reaction is due to an asymmetric induction or to a first-order asymmetric transformation, equilibration reactions were carried out using three solvents (dioxane, benzene, acetonitrile). The results indicate that the formation of optically active aspartic acid is largely due to an asymmetric induction.

The cyclization of diethyl *N*-phenyl-*N*-chloroacetamidomalonate (I) to β-lactam (II) has been reported by Sheehan and Bose.[2] Hydrolysis and decarboxylation of the β-lactam yielded *N*-phenylaspartic acid (III).



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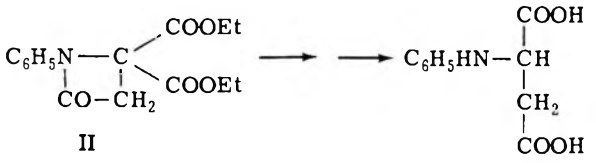


II III

This reaction is similar to that of cyclization of diethyl ω-bromopropylmalonate in the presence of sodium ethoxide.[3] Several similar β-lactam formations have been recorded.[4-6] Recently, Martin, *et al.*,[7] reported the synthesis of *N*,2-diphenylaspartic acid in a similar way from β-lactam that was formed by cyclization of *N*-chloroacetyl-*N*,2-diphenylglycine ethyl ester. The preparation of β-lactams is summarized in a review by Sheehan and Corey.[8]

In the present study, the β-lactams were prepared from *N*-alkyl-*N*-chloroacetamidoacetonitriles by the cyclization reaction. Hydrolysis and subsequent hydrogenolysis of the β-lactams yielded aspartic acid. When the *N*-alkyl groups were chiral, optically active aspartic acid was obtained. The reaction scheme of this study is shown in Scheme I.

The optically active moieties used were (a) racemic α-

(1) Contribution no. 198 of the Institute for Molecular and Cellular Evolution, University of Miami. Part XIV: K. Harada and K. Matsumoto, *Bull. Chem. Soc. Jap.*, **44**, 1068 (1971).

(2) J. C. Sheehan and A. K. Bose, *J. Amer. Chem. Soc.*, **72**, 5158(1950).

(3) H. M. Walborsky, *ibid.*, **71**, 2941 (1949).

(4) J. C. Sheehan and A. K. Bose, *ibid.*, **73**, 1261 (1951).

(5) A. K. Bose, B. N. Ghosh-Mazumdar, and B. G. Chatterjee, *ibid.*, **82**, 2382 (1960).

(6) B. G. Chatterjee, V. V. Rao, and B. N. Ghosh-Mazumdar, *J. Org. Chem.*, **30**, 4101 (1965).

(7) T. A. Martin, W. T. Comer, C. M. Combs, and J. R. Corrigan, *ibid.*, **35**, 3814 (1970).

(8) J. C. Sheehan and E. J. Corey, *Org. React.*, **9**, 388 (1957).

Table I

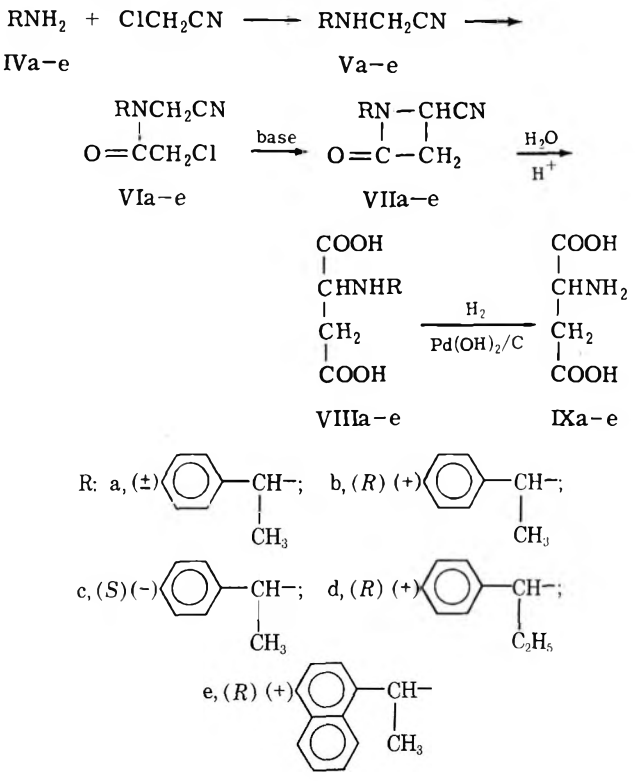
N-Alkylaminoacetonitriles and Their Hydrochlorides[a]

Compd no.	$[\alpha]^{25}D$[b] (benzene)	Bp, °C (mm)	Yield, %	Hydrochloride $[\alpha]^{25}D$[b] (H_2O)	Mp, °C	Formula	Calcd (found), % C	H	N
Va		118–119 (3.0)	64		181–182 dec	$C_{10}H_{12}N_2 \cdot HCl$	61.06 (61.25)	6.66 (6.76)	14.24 (14.13)
Vb	+238.8 (*c* 5.3)	112 (2.2)	50	+50.9 (*c* 1.4)	184–185 dec	$C_{10}H_{12}N_2 \cdot HCl$	61.06 (60.89)	6.66 (6.59)	14.24 (13.84)
Vc	−248.8 (*c* 4.7)	112 (2.2)	51	−50.7 (*c* 2.0)	184–185 dec	$C_{10}H_{12}N_2 \cdot HCl$	61.06 (61.09)	6.66 (6.69)	14.24 (14.23)
Vd	+218.4 (*c* 5.3)	109–110 (0.8)	53	+41.6 (*c* 1.9)	154–155 dec	$C_{11}H_{14}N_2 \cdot HCl$	62.70 (62.98)	7.18 (7.18)	13.30 (13.26)
Ve	+201.4 (*c* 4.9)	163–165 (1.2)	44	−44.4 (c 1.3)	200–201 dec	$C_{14}H_{14}N_2 \cdot HCl$	68.15 (68.05)	6.13 (6.17)	11.35 (11.14)

[a] Optically active amines used were (*R*)(+)-α-methylbenzylamine ($[\alpha]^{25}D$ +41.5°, benzene), (*S*)(−)-α-methylbenzylamine ($[\alpha]^{25}D$ −42.3°, benzene), (*R*)(+)-α-ethylbenzylamine ($[\alpha]^{25}D$ +21.7°, benzene), (*R*)(+)-α-(1-naphthyl)ethylamine ($[\alpha]^{25}D$ +88.0°, benzene). [b] The specific rotations were measured by the use of JASCO-ORD/UV-5 optical rotatory dispersion recorder using a 10-mm cell.

Scheme I

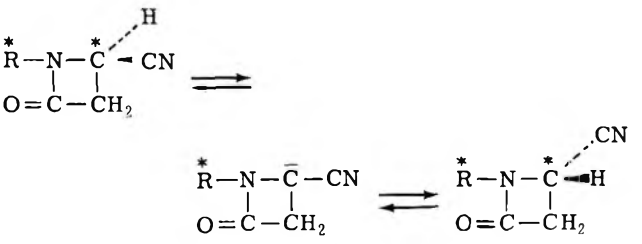
Synthesis of Aspartic Acid *via* β-Lactam



methylbenzylamine, (b) (*R*)(+)-α-methylbenzylamine, (c) (*S*)(−)-α-methylbenzylamine, (d) (*R*)(+)-α-ethylbenzylamine, and (e) (*R*)(+)-α-(1-naphthyl)-ethylamine. The *N*-alkylaminoacetonitriles Va-e were prepared from amines IVa–e and chloroacetonitrile. The yields and physical properties of Va–e are summarized in Table I. These free *N*-alkylaminonitriles have a large optical rotatory power even at the D line. The melting points, specific rotations, and elemental analyses of these aminonitrile hydrochlorides are also listed in Table I. The aminonitriles were acylated with chloroacetic anhydride to form the *N*-alkyl-*N*-chloroacetamidoacetonitriles (VIa–e). The yields, physical properties, and elemental analyses of the *N*-chloroacetylated aminoacetonitriles (VIa–e) are summarized in Table II.

Acylated *N*-alkylaminoacetonitriles (VIa–e) were treated with sodium hydride in dioxane at various temperatures (25, 50, 75°) to form corresponding β-lactams (VIIa–e). The intermediate lactam VIIa was isolated by distillation and was analyzed for elemental composition. This shows that the lactam is a rather stable compound. The lactam VIIa was hydrolyzed with hydrochloric acid and *N*-α-methylbenzyl-(±)-aspartic acid (VIIIa) was isolated. In the synthesis of optically active aspartic acid, the resulting β-lactams were hydrolyzed with 6 *N* hydrochloric acid without isolation. The resulting *N*-alkylaspartic acids (VIIIa–e) were isolated by the use of a Dowex 50 column and were then hydrogenolyzed using palladium hydroxide on charcoal to yield aspartic acid (IX). The yields of the synthesized aspartic acid are rather high (70 ∼ 95%) and the optical purities ranged from 21 to 67%. When (*R*)(+)- and (*S*)(−)-amines were used, (*S*)- and (*R*)-aspartic acids were formed. When α-methylbenzylamine was used, the optical purity of aspartic acid ranged from 41 to 49%. The use of α-ethylbenzylamine resulted in a decrease in the optical purity (19–29%). However, when α-(1-naphthyl)ethylamine was used, the optical purity of the resulting aspartic acid increased considerably (54–67%). The temperature effect on the asymmetric synthesis results in a rather small change in the yield and also in optical activity of the resulting aspartic acid. However, the optical purities of aspartic acid prepared at 50° seemed a little higher than those of aspartic acid prepared at 25 and 75°. The results are summarized in Table III.

Few asymmetric syntheses of four-membered carbocyclic or heterocyclic ring systems have been reported[9] and it was important to establish that asymmetric induction occurred during ring closure rather than by epimerization of the α-carbon atom. To examine the possibility of the formation of optically active aspartic acid by asymmetric transformation, three different solvents (dioxane, benzene, and acetonitrile) were used



(9) L. A. Paquette and J. P. Freeman, *J. Amer. Chem. Soc.*, **91**, 7548 (1969), have reported the asymmetric synthesis of a thiete 1,1-dioxide.

TABLE II

N-ALKYL-*N*-CHLOROACETAMIDOACETONITRILES

Compd no.	$[\alpha]^{25}D$[a] (dioxane)	Bp (mm) or mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
VIa		184–185 (1.5)	89	$C_{12}H_{13}N_2OCl$	60.89	5.54	11.84	61.09	5.46	11.87
VIb	+95.0 (*c* 1.9)	91–92	87	$C_{12}H_{12}N_2OCl$	60.89	5.54	11.84	60.60	5.71	11.74
VIc	−95.8 (*c* 1.5)	91–92	89	$C_{12}H_{13}N_2OCl$	60.89	5.54	11.84	60.71	5.63	11.69
VId	+129.5 (*c* 2.7)	183–184 (1.9)	79	$C_{13}H_{15}N_2OCl$	62.55	6.09	10.85	62.29	6.03	11.17
VIe	+60.2 (*c* 1.7)	92–94	82	$C_{16}H_{15}N_2OCl$	67.26	5.29	9.77	67.01	5.26	9.80

[a] The specific rotations were measured by the use of a JASCO ORD/UV-5 optical rotatory dispersion recorder using a 10-mm cell.

TABLE III

SYNTHESIS OF OPTICALLY ACTIVE ASPARTIC ACID

Starting material[a]	Confign of asymmetric moiety[b]	Temp, °C	Time, hr	Confign	Aspartic acid yield, %[c]	DNP-aspartic acid, $[\alpha]^{25}D$ (1 *N* NaOH)[d]	Optical purity, %[e]
VIa	±	25	12	±	36		
	±	25	36	±	92		
	±	50	5	±	94		
VIb	(*R*)(+)-Me	25	36	*S*	96	+39.8 (*c* 1.7)	43
	(*R*)(+)-Me	50	5	*S*	54	+42.8 (*c* 1.5)	47
	(*R*)(+)-Me	75	5	*S*	75	+41.3 (*c* 1.5)	45
VIc	(*S*)(−)-Me	25	36	*R*	75	−37.7 (*c* 1.7)	41
	(*S*)(−)-Me	50	5	*R*	72	−44.8 (*c* 1.6)	49
	(*S*)(−)-Me	75	5	*R*	44	−40.7 (*c* 1.4)	44
VId	(*R*)(+)-Et	25	36	*S*	76	+19.4 (*c* 1.5)	21
	(*R*)(+)-Et	50	5	*S*	67	+28.9 (*c* 1.5)	31
	(*R*)(+)-Et	75	5	*S*	75	+26.8 (*c* 1.5)	29
Ve	(*R*)(+)-Naph	25	36	*S*	69	+58.7 (*c* 1.4)	64
	(*R*)(+)-Naph	50	5	*S*	75	+62.0 (*c* 1.6)	67
	(*R*)(+)-Naph	75	5	*S*	68	+49.3 (*c* 1.6)	54

[a] In each reaction, 0.0025 mol of VI and 0.0025 mol of sodium hydride in 20 ml of dioxane were used. [b] (*R*)(+)-Me, (*R*)(+)-α-methylbenzylamine ($[\alpha]^{25}D$ +41.5°, benzene); (*S*)(−)-Me, (*S*)(−)-α-methylbenzylamine ($[\alpha]^{25}D$ −42.3°, benzene); (*R*)(+)-Et, (*R*)(+)-α-ethylbenzylamine ($[\alpha]^{25}D$ +21.7°, benzene); (*R*)(+)-Naph, (*R*)(+)-α-(1-naphthyl)ethylamine ($[\alpha]^{25}D$ +88.0°, benzene). [c] The yields were calculated from the data obtained from an amino acid analyzer and are based on the starting N,N-disubstituted aminoacetonitriles (VIa–e). [d] The specific rotations were measured by the use of a JASCO ORD/UV-5 optical rotatory dispersion recorder using a 10-mm cell. [e] The optical purity is defined as $[\alpha]D^{obsd}/[\alpha]D^{lit.} \times 100$. DNP-(*S*)-aspartic acid, $[\alpha]^{25}D$ +91.9° (1 *N* NaOH).

to detect the epimerization process. After normal β-lactam formation using dioxane and sodium hydride, the reaction mixture was divided into three parts. The first part was kept standing at room temperature under agitation for 24 hr; the other two parts were evaporated almost to dryness under reduced pressure. To these residues, benzene and acetonitrile were added and the mixtures were kept standing under agitation for 24 hr at room temperature. If first-order asymmetric transformation took place during the agitation in these different solvents, the optical purities of the resulting aspartic acid would be expected to be different. The results are summarized in Table IV.

TABLE IV

OPTICAL PURITIES OF DNP-ASPARTIC ACID PREPARED BY EQUILIBRATION IN VARIOUS SOLVENTS

Solvent	Dielectric constant	$[\alpha]^{25}D$ (*c* 1.6–1.9, 1 *N* NaOH)[a]	Optical purity, %[a]
Dioxane	2.2	+38.0 (+37.9)	41.4 (40.8)
CH_3CN	37.5	+34.3 (+34.2)	37.4 (37.2)
Benzene	2.3	+35.2 (+33.6)	38.5 (36.6)

[a] The values in parentheses are results obtained in the repeated experiment.

The results show that the optical purities of aspartic acid in various solvents are similar; however, the value obtained using dioxane seems a little higher than those obtained by the use of benzene and acetonitrile. This slight difference might be due to experimental error or epimerization during the equilibration. However, the values obtained by the use of benzene (ε 2.27) and acetonitrile (37.5) are almost the same. If the equilibration in acetonitrile took place, the optical purity of the aspartic acid would be expected to be different from those obtained by the use of dioxane and benzene. Therefore, the equilibration reactions suggest that the effect of first-order asymmetric transformation is not great and that the optical activity of aspartic acid is largely due to asymmetric induction during the lactam formation.

It is of crucial importance in sterically controlled syntheses to measure optical activities of the product without any fractionation of the optical isomers. The ion-exchange separation of the synthesized amino acid is a preferred technique of isolation. However, the method usually does not give chemically pure amino acids. Therefore, further purification without fractionation of optical isomers is usually necessary. In the present work, all amino acids isolated by ion exchange were dinitrophenylated by the use of 2,4-dinitrofluorobenzene.[10,11] The resulting DNP-amino acids were

(10) F. Sanger, *Biochem. J.*, **39**, 507 (1945).
(11) K. R. Rao and H. A. Sober, *J. Amer. Chem. Soc.*, **76**, 1328 (1954).

chromatographically purified[12] and isolated without fractionation of the optical isomers.[13]

Experimental Section

[*N*-(*S*)(−)-α-Methylbenzyl]aminoacetonitrile (Vc).—(*S*)(−)-α-Methylbenzylamine (12.1 g, 0.10 mol), triethylamine (10.1 g, 0.10 mol), and chloroacetonitrile (7.6 g, 0.10 mol) were dissolved in 60 ml of absolute alcohol. The solution was refluxed gently for 4 hr in an oil bath. After the reaction was over, the ethanol was evaporated *in vacuo*. The residue was dissolved in 100 ml of ethyl acetate and the solution was washed with water. The solution was dried with anhydrous sodium sulfate and the solvent was evaporated. The residual oil was distilled under reduced pressure: bp 121° (2.2 mm); yield, 8.23 g (51.4%); $[\alpha]^{25}D$ −248.8° (*c* 4.7, benzene).

Other *N*-alkylaminonitriles were prepared in a similar way. The yields and physical properties of the free *N*-alkyl-aminonitriles (Va–e) and the physical properties and elemental analyses of their hydrochlorides are summarized in Table I.

***N*-(*S*)(−)-α-Methylbenzyl-*N*-chloroacetamidoacetonitrile (VIc).**—Vc (8.0 g, 0.05 mol) was dissolved in 120 ml of dry benzene. To this solution, chloroacetic anhydride, 8.6 g (0.05 mol) was added slowly. The solution was then refluxed for 3 hr in an oil bath. After the reaction was over, the benzene solution was washed with 0.1 *N* hydrochloric acid, 3% sodium hydrogen carbonate, and water. The benzene solution was dried with anhydrous sodium sulfate and the solvent was evaporated. The residual crystals were recrystallized from ethanol: yield, 10.5 g (88.5%); mp 91–92°; $[\alpha]^{25}D$ −95.8° (*c* 1.5, dioxane). Elemental analyses are shown in Table II.

Other *N*-alkyl-*N*-chloroacetamidoacetonitriles were prepared in a similar way. The physical properties, yields, and elemental analyses are shown in Table II.

(*R*)-Aspartic Acid (IXc).—Sodium hydride (0.10 g, 0.0025 mol, 60% suspension in mineral oil) was suspended in 30 ml of anhydrous dioxane. To this mixture, 0.59 g (0.0025 mol) of VIc in 20 ml of anhydrous dioxane was added slowly at room temperature for a period of 2 hr under agitation. After the addition was over, the reaction mixture was stirred for 34 hr. In the cyclization reactions (VI → VII) at 50 and at 75°, the reaction mixtures were stirred for 3 hr at the temperatures after the addition of VI was over. The precipitated salt was then removed by filtration and the solvent was evaporated under reduced pressure. The residue was hydrolyzed with 50 ml of 6 *N* hydrochloric acid for 6 hr. The solution was extracted twice with ether, and the aqueous solution was evaporated to dryness *in vacuo*. The residue was dissolved in a small amount of water and the solution was applied to a Dowex 50 column (H^+ form, 1.9 cm × 23 cm). The column was eluted with 1.5 *N* aqueous ammonia and the fractions containing amino acid were combined and evaporated under reduced pressure. The residual product (VIIIc) was dissolved in water and was hydrogenolyzed by the use of 0.5 g of palladium hydroxide on charcoal for 12 hr. After the reaction was over, the catalyst was removed by filtration. A part of the solution was diluted in a proper way, and was analyzed on an automatic amino acid analyzer to determine accurately the yield of aspartic acid. Aspartic acid (IXc) was obtained by evaporation of the water. The yield of aspartic acid was found to be 74.9%. A part of the aspartic acid was recrystallized from water and ethanol for elemental analysis. Calcd: N, 10.52. Found: N, 10.40. The rest of the aspartic acid was converted to DNP-aspartic acid in the usual way, and the resulting DNP-aspartic acid was purified by the use of a Celite column treated with a pH 4 citrate–phosphate buffer.[10,11] DNP-(*R*)-aspartic acid had $[\alpha]^{25}D$ −37.7° (*c* 1.7, 1 *N* NaOH); optical purity, 41%.

(12) J. C. Perrone, *Nature* (London), **167**, 513 (1951).

(13) K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967).

Isolation of (±)-Lactam (VIIa).—Sodium hydride (60%, 0.40 g, 0.01 mol) was suspended in 50 ml of anhydrous dioxane. To this suspension, 2.36 g (0.01 mol) of VIa in 20 ml of anhydrous dioxane was added dropwise at room temperature under agitation over a period of 2 hr. After the addition was over, the reaction mixture was stirred at room temperature for an additional 36 hr. The solvent was then removed under reduced pressure. The residue was dissolved in 50 ml of ethyl acetate and the solution was washed with 30 ml of 1 *N* hydrochloric acid, with 2% sodium hydrogen carbonate, and then with water. The ethyl acetate solution was dried with anhydrous sodium sulfate. After evaporation of the solvent under reduced pressure, the residual oil was distilled under reduced pressure and VIIa, 1.40 g (70%), was obtained, bp 151–152° (1.5 mm).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04. Found: C, 71.94; H, 6.61.

***N*-α-Methylbenzyl-(±)-aspartic Acid (VIIIa).**—Lactam VIIa (0.8 g, 0.004 mol) was refluxed with 20 ml of 6 *N* hydrochloric acid for 6 hr. The hydrolysate was extracted with ether to remove colored material and the aqueous solution was evaporated to dryness under reduced pressure. The residue was dissolved in a small amount of water and the solution was applied to a Dowex 50 column (hydrogen form) and was eluted with 1 *N* aqueous ammonia. The fractions containing the amino acid were combined and evaporated under reduced pressure. The pH of the concentrated aqueous solution was adjusted to about 2.8; *N*-alkylaspartic acid (VIIIa) crystallized. Then VIIIa was recrystallized from water–alcohol; VIIIa, 0.75 g (73%), was obtained, mp 181–183° dec.

Anal. Calcd for $C_{12}H_{15}NO_4 \cdot H_2O$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.71; H, 6.84; N, 5.65.

Equilibration Reaction of Lactam VIIb Using Various Solvents.—Sodium hydride (60%, 0.3 g, 0.0075 mol) was suspended in 80 ml of anhydrous dioxane. To this, 1.78 g (0.0075 mol) of VIb in 30 ml of absolute dioxane was added dropwise in the manner described above. The reaction mixture was stirred for 36 hr. The reaction mixture was then divided equally into three portions. A dioxane portion was kept at room temperature for an additional 24 hr under agitation. The other two portions were evaporated to dryness under reduced pressure avoiding contamination by moisture. To one of the dried residues, 35 ml of dry benzene was added, and, to the other residue, 35 ml of acetonitrile was added. These solutions were then kept at room temperature for 24 hr under agitation. The three reaction mixtures were then evaporated under reduced pressure. As described earlier, the residues were then hydrolyzed and hydrogenolyzed to yield optically active aspartic acid. The specific rotations and optical purities of DNP-aspartic acid obtained by the use of various solvents are summarized in Table IV.

Registry No.—Va, 35341-72-1; Va HCl, 35341-73-2 Vb, 35341-74-3; Vb HCl, 35341-75-4; Vc, 35341-76-5; Vc HCl, 35341-77-6; Vd, 35341-78-7; Vd HCl, 35341-79-8; Ve, 35341-80-1; Ve HCl, 35341-81-2; VIa, 35341-82-3; VIb, 35341-83-4; VIc, 35341-84-5; VId, 35341-85-6; VIe, 35341-86-7; VIIa, 35341-87-8; VIIIa, 17196-56-4; (*R*)-aspartic acid, 1783-96-6; (*S*)-aspartic acid, 56-84-8; DNP-(*R*)-aspartic acid, 7690-55-3.

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The Synthesis of O^2,2′-Anhydro-5,6-dihydro Nucleosides

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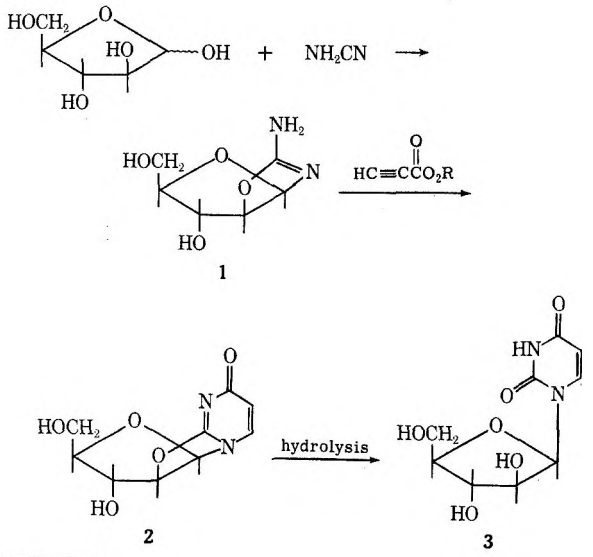
When 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (1) was allowed to react with α,β-unsaturated esters, the previously unknown O^2,2′-anhydro-5,6-dihydrouridines were produced in moderate yield. The synthesis and spectral properties of three members of this class of compounds, O^2,2′-anhydro-5,6-dihydrouridine (**5a**), O^2,2′-anhydro-5-methyl-5,6-dihydrouridine (**5b**), and O^2,2′-anhydro-6-carbomethoxy-5,6-dihydrouridine (**5c**), are discussed.

Anhydro nucleosides have been studied extensively and are frequent intermediates along the synthetic pathway to novel nucleoside systems.[1] They also have been postulated[2] as naturally occurring intermediates in the biological conversion of the more common nucleosides to the less common ones and vice-versa. In contrast, there are very few reports of anhydrodihydro nucleosides in spite of the fact that dihydro nucleosides have been found to occur in some tRNAs.[3] In their synthesis of thio analogs of 5,6-dihydrouridine, Škarić, Gašpert, and Hohnjec reported the synthesis and spectral properties of O^2,5′-anhydro-2′,3′-*O*-isopropylidine-5,6-dihydrouridine.[4] To our knowledge no other reports of anhydrodihydro nucleosides have appeared. In this report, we describe the facile synthesis and spectral properties of several O^2,2′-anhydro-5,6-dihydrouridines, a potentially useful class of compounds in the study of dihydrouridines.

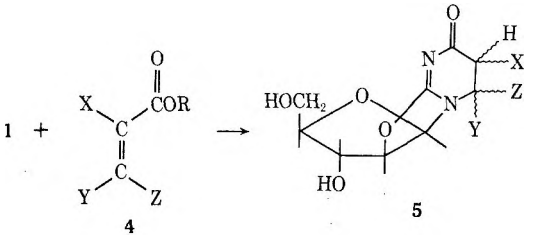
Recently, Sanchez and Orgel[5] described a novel, high yield synthesis of several arabino and ribo nucleosides. They found that the reaction of cyanamide with arabinose gave a good yield of 2-amino-β-D-arabinofurano-[1′,2′:4,5]-2-oxazoline (1). The aminooxazoline **1** was in turn allowed to react with ethyl propiolate to give O^2,2′-anhydrouridine (2) in good yield (Scheme I).

SCHEME I



We found that a similar reaction took place when the aminooxazoline **1** was allowed to react with several activated olefins (Scheme II). When a solution of **1**

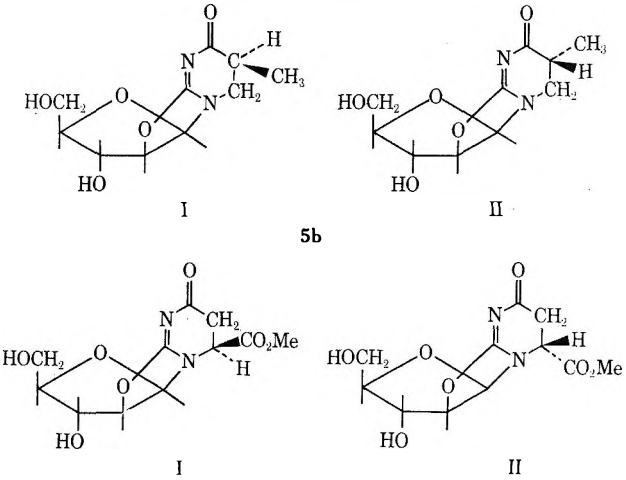
SCHEME II



a, X = Y = Z = H; R = CH_3
b, X = CH_3; Y = Z = H; R = CH_3
c, X = H; Y = CO_2CH_3; Z = H; R = CH_3
d, X = Y = H; Z = $CO_2C_2H_5$; R = C_2H_5

was heated with methyl acrylate (**4a**), a glassy solid was obtained after removal of the solvent. Chromatography of the residue gave the desired O^2,2′-anhydro-5,6-dihydrouridine (**5a**) in 57% yield as white needles after recrystallization.

The nmr spectrum of **5a** contained a typical A_2B_2 pattern with triplets centered at δ 2.45 and 3.57. The remainder of the spectrum was similar to that of O^2,2′-anhydrouridine. Likewise, when methyl methacrylate was allowed to react with the aminooxazoline, O^2,2′-anhydro-5-methyl-5,6-dihydrouridine (**5b**) was



isolated in 36% yield. *A priori* a mixture of two diastereoisomers (epimeric at C-5) would be expected. Thin layer chromatography (tlc) (silica gel, 5% MeOH in $CHCl_3$, eight passes) indicated that the material was homogeneous. Likewise, the sharp melting point,

(1) Leading reference: "The Chemistry of Nucleosides and Nucleotides," A. M. Michelson, Academic Press, New York, N. Y., 1963; J. J. Fox and I. Wempen, *Advan. Carbohyd. Chem.*, **14**, 283 (1959).

(2) (a) L. I. Pizer and S. S. Cohen, *J. Biol. Chem.*, **235**, 2387 (1960); (b) D. M. Brown, D. B. Parihar, C. B. Reese, and A. Todd, *J. Chem. Soc.*, 3035 (1958).

(3) R. W. Holley, G. A. Everett, J. T. Madison, and A. Zamir, *J. Biol. Chem.*, **240**, 2122 (1965).

(4) V. Škarić, B. Gašpert, and M. Hohnjec, *J. Chem. Soc. C*, 2444 (1970).

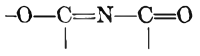
(5) R. A. Sanchez and L. E. Orgel, *J. Mol. Biol.*, **47**, 531 (1970).

196.5–198.0°, was consistent with a single component. However, the nmr spectrum showed two sets of peaks, ABC splitting, for the 6α and the 6β protons, indicating that both of the two possible epimers, **5b**-I and **5b**-II, were present but in unequal amounts. The possibility that the two sets of peaks were due to slowly interconverting conformers was eliminated because a large axial–axial coupling was observed for both components—a condition that could not exist in the case of conformers since one conformer would not have an axial proton in the 5 position.

The reaction of the aminooxazoline **1** with dimethyl fumarate gave a complex product mixture containing two major components. Chromatography on silica gel gave an oil which contained only the two major components. Treatment of this oil with hot methanol gave one of the isomers of **5c** as white needles. The configuration of the carbomethoxy group about C-6 has not been determined. All attempts to isolate the other major reaction product were unsuccessful.

When the aminooxazoline **1** was allowed to react with diethyl maleate, two major reaction products were observed by tlc. Chromatography on silica gel separated the major components from minor contaminants. The residual oil, after solvent removal, failed to crystallize from ethanol; however, when the oil was treated with hot methanol and allowed to stand at room temperature, white needles precipitated. This material was not the expected product **5d**, but the corresponding methyl ester **5c** as shown by ir, nmr, melting point, and mixture melting point. Apparently transesterification had occurred. More noteworthy is the fact that both the fumarate and the maleate add to the aminooxazoline **1** to give the same major product or, at least, a mixture of the two C-6 epimers. Very careful tlc (silica gel, 5% MeOH in $HCCl_3$ eight passes) of the analytically pure product from the reaction of **1** with **4c** and with **4d** indicated the presence of a small amount (~10–20%) of a second component with a similar R_f value. This minor component may well be the other epimer, but it could not be detected by nmr at 100 MHz. The mechanistic implications of this product distribution will be discussed later.

Spectral Properties. Infrared.—The ir spectrum of each of the anhydro-5,6-dihydrouridines **5a**, **5b**, and **5c** showed three absorptions which are apparently due to the system



These frequencies and intensity of these absorptions are given in Table I. It should be noted that the only

Table I

Compd	Frequency, cm^{-1}		
5a	1690 (m)	1605 (vs)	1490 (sh)
5b	1690 (m)	1605 (vs)	1490 (sh)
5c	1685 (m)	1610 (vs)	1490 (sh)

other anhydrodihydrouridine reported[4] in the literature O^2,5′-anhydro-5,6-dihydrouridine absorbed at 1681 and 1546 cm^{-1}. The relative intensities of the peaks at 1690 and 1605 cm^{-1} are unusual and apparently characteristic of this system.

Nmr Spectra.—Nmr spectra were measured at 60 and 100 MHz on samples dissolved in deuterium oxide or d_6-dimethyl sulfoxide and calibrated against internal tetramethylsilane.

Compound **5a** showed the expected signals for the arabinoside portion plus A_2B_2-type triplets for the cyclic methylenes of the dihydrouracil. The apparent vicinal coupling constant of 8.0 Hz indicated either a deceptively simple AA′BB′ system or a rapidly averaging AA′BB′ system. The parameters are listed in Table II. Compound **5b** gave an nmr spectrum that

Table II

Nmr Data Determined on Anhydrodihydro Nucleosides

Parameter	Shift, δ			
	5a[a]	**5b** major[b]	**5b** minor[b]	**5c**[a]
$\delta_{1'}$	5.88	6.07		6.04
$J_{1',2'}$	5.5	5.5		5.5
$\delta_{2'}$	5.08	5.32		5.23
$J_{2',3'}$	0.5[c]	0.5[c]		0.5[c]
$\delta_{3'}$	4.32	4.57		4.38
$J_{3',4'}$	1.0[c]	2.0		2.0
$\delta_{4'}$	4.03[d]	4.3[d]		4.09[e]
$J_{4',5'a}$	6.0	4.5		6.0
$J_{4',5'b}$				4.0
$\delta_{5'a}$	3.32[f]	3.59[f]		3.38[g]
$\delta_{5'b}$				3.49[g]
$J_{5'a,5'b}$				−12.5
$\delta_{5_{ax}}$	2.45[h]	2.82[i]	2.79[i]	2.65[g]
$J_{5_{ax},5_{eq}}$				−16.6
$J_{5_{ax},6_{ax}}$	8.0	12.5	12.5	8.6
$J_{5_{ax},6_{eq}}$	8.0	7.0	7.0	
$\delta_{5_{eq}}$	2.45[h]			2.84[g]
$J_{5_{eq},6_{ax}}$	8.0			4.4
$J_{5_{eq},6_{eq}}$	8.0			
$\delta_{6_{ax}}$	3.57[h]	3.40[j]	3.38[j]	4.80
$J_{6_{ax},6_{eq}}$		−12.0	−12.0	
$\delta_{6_{eq}}$	3.57[h]	3.87[j]	3.83[j]	

[a] 60-MHz spectrum, DMSO solvent, TMS reference. [b] 100-MHz spectrum, D_2O solvent, DSS reference. [c] Unresolved. Estimated from line width. [d] Apparent as two partly overlapped triplets of an A_2B subspectrum but probably actually a deceptive AA′B subspectrum. [e] Two four-line, partly overlapped X patterns of ABX subspectrum. [f] Apparent as a doublet of an A_2B subspectrum but probably actually a deceptive AA′B subspectrum. [g] Eight lines for the AB part of an ABX subspectrum. [h] Apparent as a triplet of an A_2B_2 system but probably actually a deceptive AA′BB′ system. [i] Two four-line partly overlapped C patterns of ABC system. [j] Eight lines for the AB part of an ABC system.

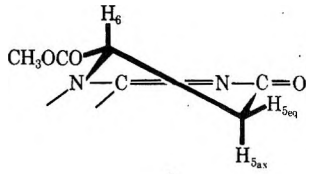
indicated it was a mixture. In addition to the typical signals for the arabinoside portion there were two sets of ABC patterns assigned to the uracil 5 and 6 hydrogens of two epimers **5b**-I and **5b**-II present in amounts of 55 and 45%. Both epimers showed a large diaxial vicinal coupling for the 5 hydrogen suggesting conformations having the 5 methyl exclusively equatorial in each. The parameters are listed in Table II.

Compound **5c** gave an nmr spectrum that showed no evidence of a mixture. In addition to the usual signals for the arabinoside portion there was one ABX subspectrum attributed to the three uracil hydrogens. The parameters are listed in Table II.

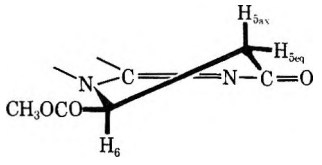
To determine the conformation of the uracil portion the ABX subspectrum was analyzed[6] with the aid of the LAOCN program.[7] The spectrum was first factored by construction methods to determine the line number

(6) G. Slomp, *Appl. Spectrosc. Rev.*, **2**, 263 (1969).
(7) S. Castellano and A. A. Bothner-By, *J. Chem. Phys.*, **41**, 3863 (1964).

assignments. The observed line frequencies were then fitted by iteration and the root mean square error of the fit was reduced from 0.393 to 0.069. The parameters are shown in Table II. The spectrum was judged to be a like-sign narrow-coupled case from the agreement of line intensities in the observed and calculated spectra. The magnitude of the $5_{ax},6$ coupling constant indicates that these vicinal hydrogens are diaxial; hence the structure is either **5c**-I or **5c**-II and a choice cannot be made from these data.



I



II

5c

Circular Dichroism.—The CD spectrum of **5a**, **5b**, and **5c** were measured and the results are tabulated in Table III. Although the CD spectra showed what appeared to be characteristic differences, sufficient data to assign the absolute configuration was not available.

TABLE III

CIRCULAR DICHROISM SPECTRAL DATA

Compd	λ_{max}, mμ	$[\theta]_{max}$
5a	235	+11,800
5a	255	+11,400
5b	235	+23,700
5c	256.5	−9,350
5c	230	+48,500

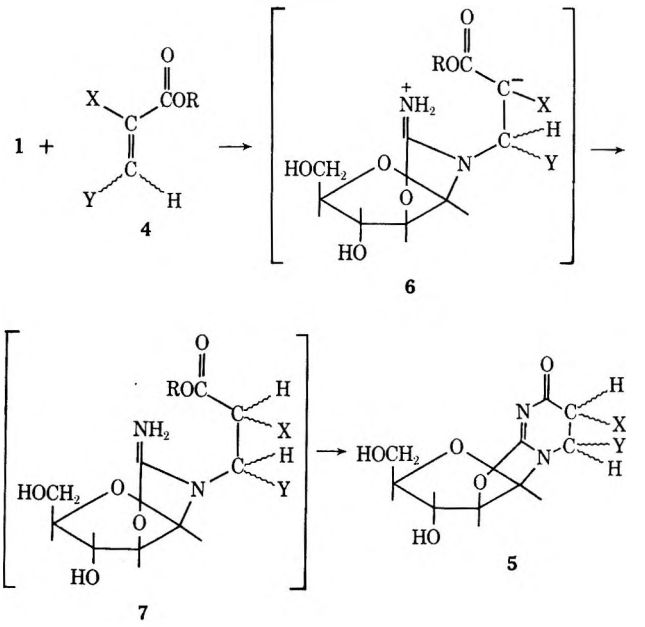
Discussion

A mechanism which is consistent with the product formation and with the known mode of addition of the aminooxazoline **1** to activated triple bonds[5,8] is presented in Scheme III. The endocyclic nitrogen of the aminooxazoline **1** adds to the β carbon of the activated double bond in a Michael-type addition, followed by proton migration and ring closure to give the observed products. The anion generated at the 5 carbon in the intermediate **6** is protonated nonstereoselectively. This results in an almost equimolar mixture of the two epimers of **5b**. An alternate, but less likely, explanation for the formation of the epimeric mixture is the loss of the configurational identity of the product during work-up and isolation. The inverse mode of ring formation, *i.e.*, addition of the exocyclic amine to the ester carbonyl followed by ring closure, would also explain the observed products **5a–c**. This mechanism seems unlikely in view of the regiospecificity generally observed in the addition of amines to α,β-unsaturated esters.[9]

(8) C. M. Hall and A. J. Taylor, unpublished work.

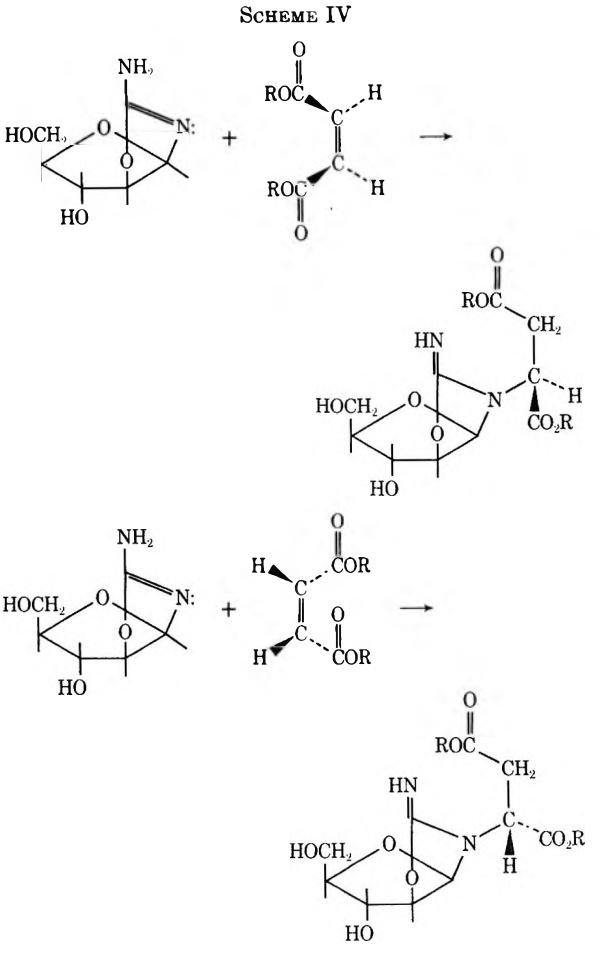
(9) S. Patai and Z. Rapport in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, Chapter 8.

SCHEME III



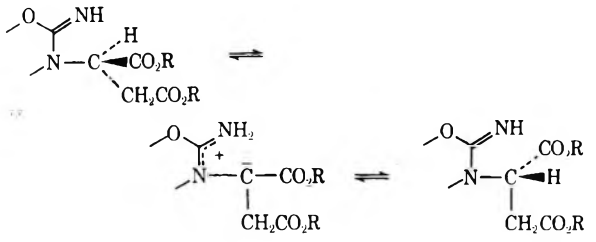
The apparent stereoselectivity observed in the formation of **5c** and **5d** can be accounted for in one of several fashions. (1) The aminooxazoline **1** must approach the ester in a preferred fashion—from either the front or the back. The direction of approach is determined by the carboxyl group attached to the β carbon since the product ratio from the maleate and fumarate is the same. This is shown schematically in Scheme IV. (2) The initial adduct **7** (Scheme III)

SCHEME IV



undergoes epimerization to give an epimeric mixture in which one of the epimers predominates. Epimerization is followed by cyclization to give the observed distribution of diastereomers. Epimerization at C-6 might occur as shown in Scheme V.[10] (3) The product

Scheme V



distribution of diastereomers may represent the equilibrium mixture which was achieved during the product isolation. It is not apparent from models that one diastereomer should be favored over the other.

Experimental Section

O_2,2-Anhydro-5,6-dihydrouridine (5a). A mixture of 2-amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (1, 2.0 g, 0.0115 mol), methyl acrylate (4.0 g, 0.044 mol), and dimethylacetamide (70 ml) was heated at 75° for 2 hr, then allowed to stand for 18 hr at room temperature. Removal of the solvent left a glassy residue which failed to crystallize. The residue was chromatographed on a silica gel column (200 g). The column was eluted with 1 l. of 10% MeOH in CH_2Cl_2 and 2 l. of 15% MeOH in CH_2Cl_2. The majority of the product was eluted in the first 750 ml of 15% MeOH in CH_2Cl_2 eluate. Removal of the solvent left a solid which was recrystallized from absolute ethanol to give white needles (1.30 g, mp 177–179°). The total yield was 57%. The ir, nmr, and uv spectra were consistent with the proposed structure of O^2,2′-anhydro-5,6-dihydrouridine: the ir and nmr results are reported in Tables I and II; uv max (95% EtOH) 237 nm (ε 14,150), 273 (114, sh).

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 47.37; H, 5.30; N, 12.28. Found: C, 47.40; H, 5.40; N, 12.04.

O^2,2′-Anhydro-5-methyl-5,6-dihydrouridine (5b). A mixture of the aminooxazoline 1 (2.0 g, 0.0115 mol), methyl methacrylate (4.0 g, 0.040 mol), and dimethylacetamide (70 ml) was heated at 70° for 3 hr and then it was allowed to stand at room temperature for 18 hr. Tlc (silica gel, 25% MeOH in $CHCl_3$) indicated that some aminooxazoline 1 was still present. An additional 4 g of methyl methacrylate was added, and the reaction mixture was heated an additional 8 hr at 75°. The solvent was removed to leave a glassy residue which was slurried in MeOH. An insoluble solid was collected by filtration (844 mg). This material was shown to be identical with the starting aminooxazoline 1 by tlc (silica gel 25% MeOH in $CHCl_3$). The residue from the filtrate was chromatographed on a silica gel column (100 g) using 10% MeOH in CH_2Cl_2 as the eluent. The desired product began to appear in the eluate after about 1.0 l. had been collected. The next 2 l. of eluate were combined and the solvent was removed to leave a crystalline solid (670 mg). This material was recrystallized from isopropyl alcohol to give a white solid in 36% yield (based on recovered 1, 582 mg, mp 196.5–198°). The nmr, ir, and uv spectra were consistent with the proposed structure 5b: the ir and nmr results are reported in Tables I and II; uv (95% EtOH) 236 nm (ε 13,900), 273 (164, sh).

Anal. Calcd for $C_{10}H_{14}O_5N_2$: C, 49.58; H, 5.83; N, 11.57. Found: C, 49.72; H, 5.88; N, 11.51.

(10) We are indebted to the referee for first suggesting this possibility.

Reaction of 2-Amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline (1) with Dimethyl Fumarate. A mixture of the aminooxazoline 1 (4.0 g, 0.023 mol), dimethyl fumarate (6.4 g, 0.044 mol), and dimethylacetamide (140 ml) was heated at 95–100° for 6 hr and then was allowed to stir at room temperature for 72 hr. Tlc (silica gel, 15% MeOH in CH_2Cl_2, uv or $KMnO_4$ solution) showed that considerable starting material remained. An additional 6.4 g of dimethyl fumarate was added and the mixture was heated for an additional 8 hr at 95–100°. Removal of the solvent left an oil which was chromatographed on a silica gel column (400 g). The column was eluted with 4 l. of 5% MeOH in CH_2Cl_2 followed by 1 l. of 15% MeOH in CH_2Cl_2 at which point a uv-absorbing material began to appear in the eluate (tlc, silica gel, 5% MeOH in $HCCl_3$). Ten 60-ml fractions were collected. Removal of the solvent from these fractions left an oil (1.99 g combined), which failed to crystallize. The oil was rechromatographed on silica gel (200 g) using 5% MeOH in CH_2Cl_2. After 6 l. of eluate had been eluted, 20 150-ml fractions were collected. Fractions 1–15 were combined and the residual oil crystallized from methanol to give white needles (225 mg, mp 185–186° dec). A second crop of 322 mg was also obtained (mp 185–186° dec; total yield 8%). The ir, uv, and nmr spectra were consistent with those expected for O^2,2′-anhydro-6-carbomethoxy-5,6-dihydrouridine (5c): the ir and nmr results are reported in Tables I and II (the $J_{5,6}$ indicated that the carbomethoxy group assumed an equatorial position, but the configuration about C-6 could not be determined with the available data); uv max (95% EtOH) 236 nm (ε 13,400), 269.5 (135, sh).

Anal. Calcd for $C_{11}H_{14}O_7N_2$: C, 46.15; H, 4.93; N, 9.79. Found: C, 46.47; H, 5.36; N, 10.21.

Reaction of 2-Amino-β-D-arabinofurano[1′,2′:4,5]-2-oxazoline with Diethyl Maleate. A mixture of the aminooxazoline 1 (4.0 g, 0.023 mol), diethyl maleate (7.60 g, 0.044 mol), and dimethylacetamide (140 ml) was heated at 95° for 6 hr and was stirred at room temperature for 18 hr. An additional 7.6 g of diethyl maleate was added and the reaction mixture was heated at 95° for 4 hr. Removal of the solvent left a viscous syrup. The excess diethyl maleate was separated by chromatography on silica gel (400 g, 2 l. of 5% MeOH in $CHCl_3$ followed by 2 l. of 15% MeOH in $CHCl_3$). The fractions which contained the reaction products (one minor and two major spots on tlc, 2% MeOH in $CHCl_3$) were combined and rechromatographed (silica gel, 200 g, MeOH in CH_2Cl_2). Tlc of the eluted fractions indicated that no significant degree of separation had been achieved. The fractions were combined and the solvent was removed to leave a syrup (3.52 g). This residue was dissolved in hot methanol and the resulting solution was allowed to stand for 18 hr in a draft to give colorless needles (395 mg, mp 183.5–184.5° dec). A portion of this material was recrystallized for analysis. Several additional crops were obtained from the mother liquor (887 mg, mp 186–187° dec), whose spectral properties were identical with those of the first crop. The total yield was 19%. The ir, nmr, and uv spectrum and elemental analysis indicated that this material was not the expected O^2,2′-anhydro-6-carboethoxy-5,6-dihydrouridine (5d), but the corresponding methyl ester: the ir and nmr results are reported in Tables I and II; uv max (95% EtOH) 236 nm (ε 14,350), 269 (180, sh). The melting point of an admixture of this material and the product obtained from the reaction of the aminooxazoline 1 and dimethyl fumarate was undepressed. Both materials had identical R_f values on tlc (silica gel, 2% MeOH in $CHCl_3$). Nmr showed no evidence for 5d in the crystallized material.

Anal. Calcd for $C_{11}H_{14}N_2O_7$: C, 46.15; H, 4.93; N, 9.79. Found: C, 46.32; H, 4.95; N, 9.65.

Registry No.—5a, 35324-11-9; 5b, 35324-12-0; 5c, 35324-13-1.

Acknowledgment.—We are indebted to Dr. W. C. Krueger and his coworkers for the CD and uv measurements and to Mr. P. Meulman for measuring and interpreting the ir spectra.

Favorskii Rearrangement and Grob Fragmentation of Carvone Tribromides

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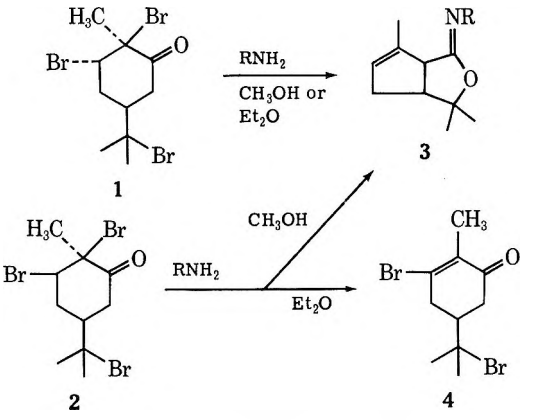
The reaction of *trans*-carvone tribromide (1) and *cis*-carvone tribromide (2) with bases is shown to depend on the base, solvent, and configuration of the β-bromo group. Products derived from Favorskii rearrangement are formed when 1 or 2 are treated with sodium methoxide in methanol or ether. An epoxy ether (11) also results from the reaction of 1 with sodium methoxide in ether. Grob fragmentation occurs when 1 and 2 are treated with sodium hydroxide in water. Vinyl bromides 19, 20, and 21, along with epoxycarone 22, are formed from 2, whereas 1 gives homoterpenyl methyl ketone (27), keto acid derivatives 25 and 26, and 4-methyl-3-pentenoic acid (46).

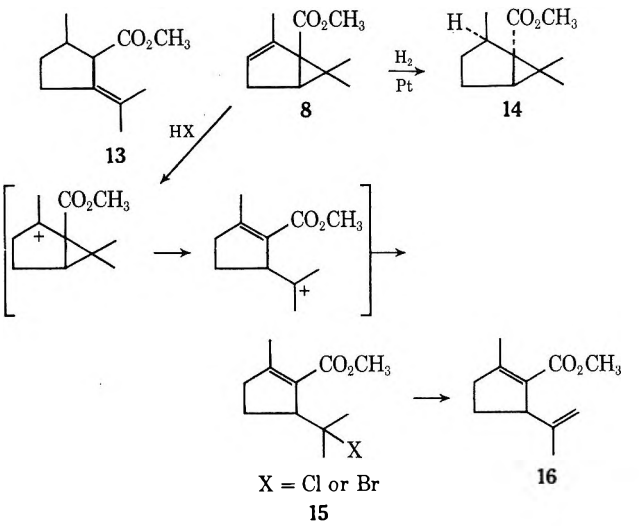
trans-Carvone tribromide (1)[2a,3] undergoes a Favorskii rearrangement to afford iminolactone 3 when treated with primary amines in methanol or ether. *cis*-Carvone tribromide (2)[2a] likewise yields 3 when treated with isopropylamine in methanol, but affords the dehydrobromination product 4 when the reaction is conducted in ether.[2b] In view of the divergent paths followed by 2, it became of interest to study the reaction of 1 and 2 with methoxide and hydroxide ions in various solvents.



Sodium Methoxide.—In solvent methanol, sodium methoxide converted 1 and 2 into complicated mixtures of products from which the compounds shown in Chart I were isolated and identified. Qualitatively, the two bromides yield the same major products, except for the formation of 17% of bicyclo[3.1.0]hexane derivative 8 in the reaction with 2.

In ether, the reaction with sodium methoxide takes a new path for each isomer (see Chart II). Both 1 and 2 yield substantial amounts of bicyclic ester 8. In addition, 1 also affords the dibromo hydroxy ketone 12 if the reaction is worked up with water, or the dibromo epoxy ketone 11 if water is excluded in the isolation step.

The structures assigned 5–12 are based on spectral data (see Experimental Section) and conversion, where possible, into known compounds. Thus, unsaturated ester 5 was transformed by partial catalytic hydrogenation into methyl *cis*-pulegenate (13).[4] Bicyclic ester 8 absorbed 1 equiv of hydrogen in the presence of platinum to yield 14, whose stereochemistry is assigned on the assumption that hydrogenation occurs from the least hindered side of the molecule. Treatment of 8 with hydrogen chloride or hydrogen bromide gave halo esters 15 which were dehydrobrominated to the known 16.[5]



Carvenolide (7) and carvacrol (10) were identified by spectral comparison with authentic samples. Complete characterization of 6 and 9 was not achieved because of the instability of 6 and the small amount of 9 isolated.

Epoxy ether 11 lacks carbonyl absorption in the infrared and shows a methoxy signal at 3.46 ppm in its nmr spectrum. An apparent one-proton triplet at 4.53 ppm (J = 2.5 Hz) suggests an equatorial orientation for the C-3 proton and, hence, an axial position for the C-3 bromine. The crystalline epoxy ether 11 is stable in solution in the absence of acid, but on standing at room temperature for a few days is converted into vinyl ether 17. Vinyl ether 17 displays a strong olefin stretching vibration at 6.10 μ and an nmr doublet at 4.76 ppm attributed to a vinyl proton. Hydrolysis of 17 with hydrobromic acid or sodium hydroxide solution gave hydroxy ketone 18. The assignment of an equatorial hydroxyl group in 18 was substantiated by an ultraviolet maximum at 283 nm (ε 37.4) and by an upfield shift of 16.2 Hz for the C-2 methyl group when the nmr spectrum was determined in benzene rather than $CDCl_3$.[6] Similar spectral properties were shown by acetate 18a.

(1) David Ross Research Fellow, Purdue University, 1964–1966.

(2) (a) J. Wolinsky, J. J. Hamsher, and R. C. Hutchins, *J. Org. Chem.*, **35**, 207 (1970); (b) J. Wolinsky, R. O. Hutchins, and T. W. Gibson, *ibid.*, **33**, 407 (1968).

(3) Unless otherwise indicated all the reactions were carried out with racemic products.

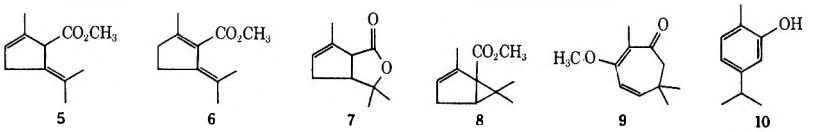
(4) J. Wolinsky, H. Wolf, and T. W. Gibson, *J. Org. Chem.*, **28**, 274 (1963); J. Wolinsky and D. Chan, *ibid.*, **30**, 41 (1965).

(5) J. Wolinsky and D. Nelson, *Tetrahedron*, **25**, 3767 (1969).

(6) J. Ronayne and D. H. Williams, *J. Chem. Soc. B*, 540 (1967).

CHART I

REACTION OF 1 AND 2 WITH SODIUM METHOXIDE IN METHANOL[a]

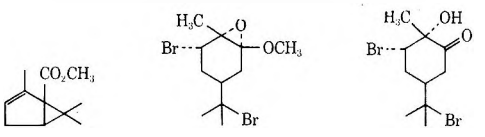


Bromide	5	6	7	8	9	10
1	36%	Trace	12.9%			4.6%
2	49%	14%	4%	22%	7%	

[a] The reaction yields were determined by glpc and are not corrected for detector response differences.

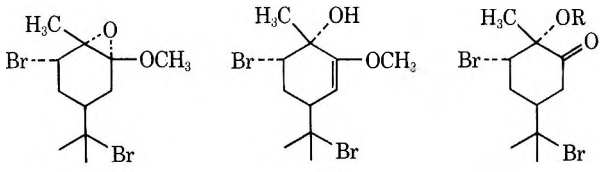
CHART II

REACTION OF 1 AND 2 WITH SODIUM METHOXIDE IN ETHER



Bromide	8	11	12
1	36-47%	(29-33%)[a]	(21%)[b]
2	59-67%		

[a] Isolated when care is taken to avoid moisture in the reaction work-up. [b] Isolated when water is added during work-up.



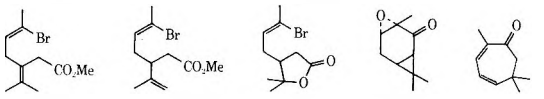
11 17 18, R = H; 18a, R = Ac

NaOH.—The reactions of carvone tribromides **1** and **2** with sodium hydroxide in water and ether were conducted under a nitrogen atmosphere at room temperature. Since these systems are heterogeneous, one experiment was performed in dioxane–water in order to examine the effect of homogeneity on the reaction course. The acidic products were converted to methyl esters with diazomethane in order to facilitate their separation and isolation.

The action of sodium hydroxide on *cis*-carvone tribromide (**2**) produced the array of products shown in Chart III. The reaction proved to be qualitatively

CHART III

ACTION OF SODIUM HYDROXIDE ON *cis*-CARVONE TRIBROMIDE (**2**)[a]



Solvent	19	20	21	22	23
Water	4-9%	3-8%	39-56%	25-27%	
Water–dioxane	8%	2%	12%	41%	
Ether[b]	11%	22%	25%		13%

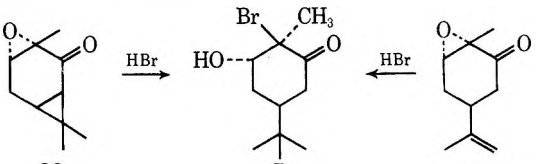
[a] Reaction yields were determined by glpc and are not corrected for detector response differences. [b] Carvenolide (**7**) (3.5%) and unsaturated ester **16** (5.3%) were also isolated.

similar in water, dioxane–water, or ether. However, in ether, epoxide **22** was not found and eucarvone **23** was isolated in low yield.

Little or no Favorskii rearrangement occurs in the reaction of **2** with sodium hydroxide; instead the carbonyl group of **2** is attacked, leading to compounds **19**, **20**, and **21** by a Grob fragmentation[7] or to epoxide **22** by a multistep process.

The reaction of sodium hydroxide with **1** changes dramatically with solvent (see Chart IV). In ether a Favorskii rearrangement prevails, while in water compounds **24**, **25**, **26**, and **27** are formed by way of a Grob fragmentation.[7]

Methyl homoterpenyl ketone (**27**), eucarvone (**23**), unsaturated ester **24**, and keto ester **25** were identified by comparison with authentic samples. Keto ester **26**, bromo esters **19** and **20**, and bromolactone **21** were identified by elemental analyses and spectral data (see Experimental Section). Treating epoxycarone **22**[8] with hydrobromic acid gave dibromo ketohydrin **29**, which proved to be identical with an authentic sample prepared from epoxycarvone (**30**).[2]



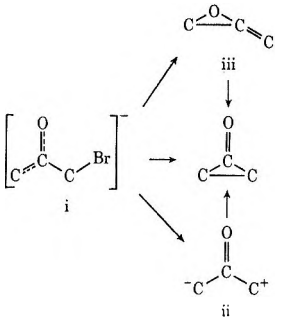
22 29 30

The skeletal rearrangement of α-halo ketones induced by bases which leads to carboxylic acid derivatives is known as the Favorskii rearrangement. The use of this transformation as a synthetic tool, as well as studies of its mechanism, are complicated by the multifunctional nature of the α-halo ketone, which permits a variety of competing reactions, such as dehydrohalogenation, substitution, and epoxy ether formation, sometimes to the exclusion of the Favorskii rearrangement.[9]

(7) C. A. Grob and P. W. Schiess, *Angew. Chem.*, **6**, 1 (1967), and references cited therein.

(8) W. D. P. Burns, M. S. Carson, W. Cocker, and P. V. R. Shannon, *J. Chem. Soc. C*, 3073 (1968).

(9) It is now generally acknowledged that the Favorskii rearrangement proceeds by way of a cyclopropanone intermediate. The exact path to the cyclopropanone intermediate may vary with the reaction conditions, and may involve a direct intramolecular displacement of enolate i, collapse of dipolar ion ii, or rearrangement of an allene oxide iii.[10]

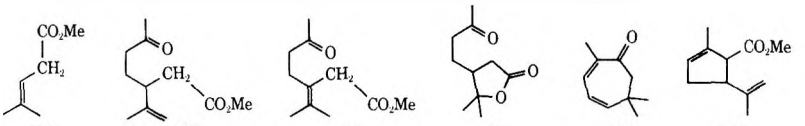


i ii iii

(10) A. Kende, *Org. React.*, **11**, 261 (1960); F. G. Bordwell and M. W. Carlson, *J. Amer. Chem. Soc.*, **92**, 3377 (1970), and references cited therein.

CHART IV

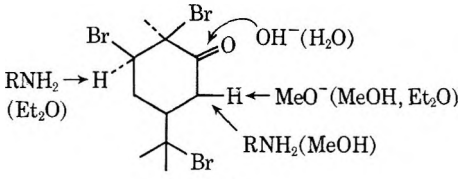
ACTION OF SODIUM HYDROXIDE ON *trans*-CARVONE TRIBROMIDE (1)[a]



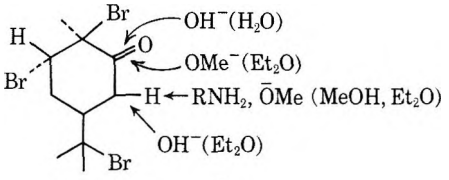
Solvent	24	25	26	27	23	28
H_2O	31%	2.6%	10%	36.5%	7%	0%
Et_2O[b]	1%					10%

[a] Reaction mixture was esterified with diazomethane prior to analysis and isolation of products was by preparative glpc. Yields were determined by glpc and are uncorrected for detector response differences. [b] Products: carvenolide (7) (3.5%), unsaturated ester 5 (5.3%), and bicyclic ester 8 (4.6%).

A spectrum of these transformations is observed with the multifunctional carvone tribromides 1 and 2. The product determining attack of base, summarized in A and B, appears to depend upon the nature of the base, the solvent, and the configuration of the β-bromine atom.



A

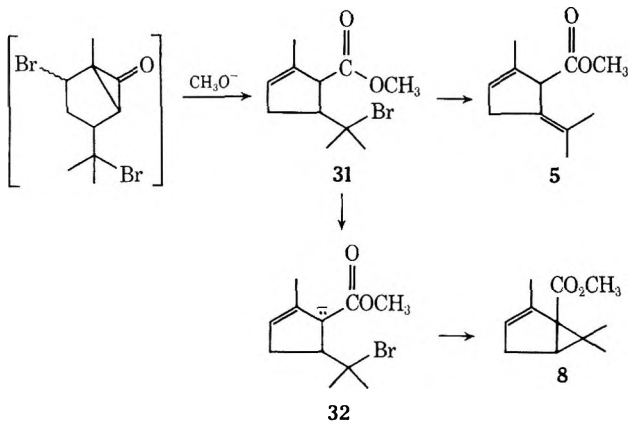


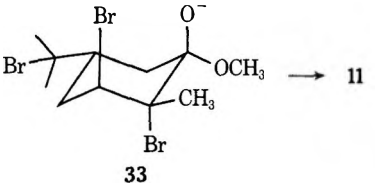
B

The reaction of *cis*-carvone tribromide (2) with the strong base sodium methoxide in methanol or ether favors the removal of the α' proton and subsequent Favorskii rearrangement. The initially formed product is most likely 31, which loses hydrogen bromide to yield 5 and 6 or affords 8 *via* the anion 32. Carvenolide 7 most likely is formed by lactonization, during reaction work-up, of the acid corresponding to 5. In ether, the 1,2 elimination of hydrogen bromide is minimized and cyclization of anion 32 to 8 becomes the favored pathway.

The mechanism shown in Scheme I also accounts for the reaction of *trans*-carvone tribromide (1) with sodium methoxide when the reaction is conducted in methanol; however, in ether concurrent attack at the carbonyl group, formation of the axial alkoxide 33, and subsequent intramolecular displacement of the α-bromo group leads to epoxy ether 11.

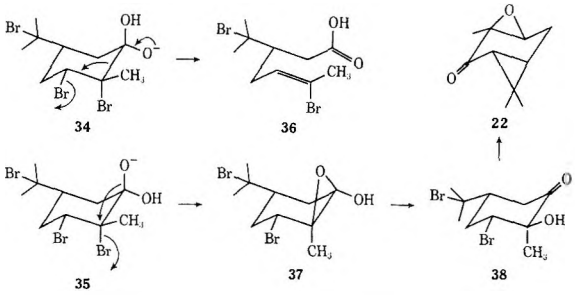
SCHEME I





33

On using the weaker base, hydroxide ion in water, the products appear to arise exclusively from attack at the carbonyl group. The reaction of *cis*-carvone tribromide (2) can be rationalized assuming axial and equatorial attack at the carbonyl group generating 34 and 35. Alkoxides 34 and 35 have the trans antiperiplanar configuration[11] required for a Grob type of fragmentation generating 36, which is ultimately transformed into the observed products 19, 20, and 21. The failure to observe Grob fragmentation products in ether or methanol may be attributed to the lower polarity of these solvents.[12]



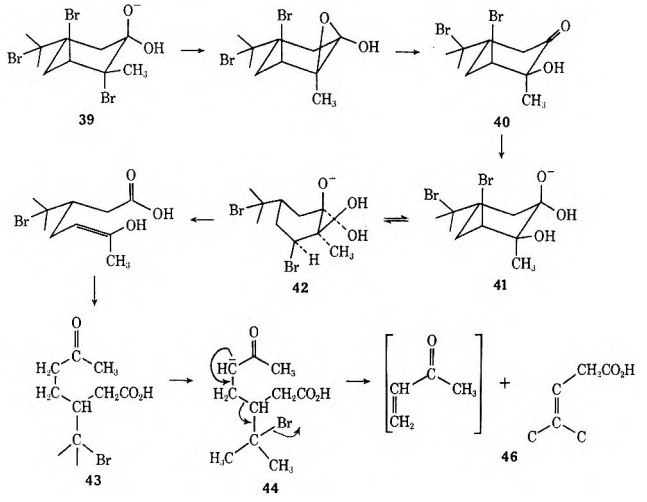
Alkoxide 35 also possesses a configuration permitting intramolecular displacement of the α-bromine atom, resulting in the formation of epoxy alcohol 37. Hydrolysis of 37 results in 38, which can cyclize to epoxycarone 22. It is not clear whether epoxide formation precedes or follows the formation of the cyclopropane ring in these last steps.

Hydroxide ion addition to the carbonyl group of *trans*-carvone tribromide (1) affords alkoxide 39, which lacks the necessary antiperiplanar configuration for a Grob fragmentation, but which can undergo intramo-

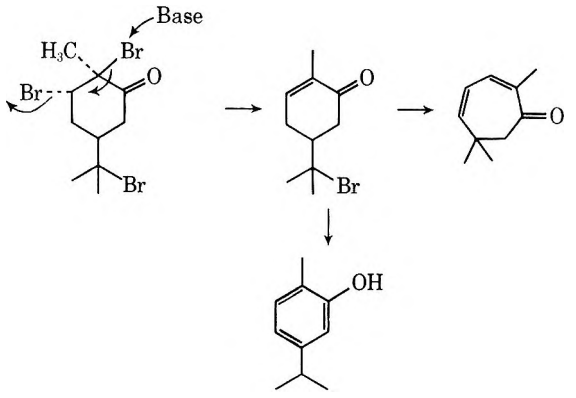
(11) C. A. Grob, H. R. Kiefer, H. J. Lutz, and H. J. Wilkens, *Helv. Chim. Acta*, **50**, 416 (1967).

(12) *Cf.* P. Brenneisen, C. A. Grob, R. A. Jackson, and M. Ohta, *Helv. Chim. Acta*, **48**, 146 (1965).

lecular displacement and subsequent hydrolysis to yield hydroxy ketone **40**.[13] Competing Favorskii rearrangement and epoxide formation is no longer possible for **40**, but alkoxide **41** may undergo a Grob fragmentation by way of a high-energy conformation such as **42** to yield **43**, which subsequently is transformed into **24**, **25**, **26**, and **27**. The conversion of **43** to **46**, which yields **24** during the reaction work-up, is most easily visualized as another Grob fragmentation proceeding by way of anion **44**.



Finally, it is worth noting that eucarvone (**23**) or carvacrol (**10**) are among the products of reaction of **1** with bases under a variety of conditions. These compounds probably result by debromination of **1**, followed by cyclization or decomposition of carvone hydrobromide.



Experimental Section[14]

Reaction of *cis*-Carvone Tribromide (2) with Sodium Methoxide. A. Methanol.—To a stirred solution of 6.90 g (0.1275 mol) of sodium methoxide in 150 ml of absolute methanol was added 5.0 g (0.1275 mol) of *dl-cis*-carvone tribromide (**2**). The mixture was stirred for 20 hr, 500 ml of water was added, and the mixture was then extracted with ether. The ether solution was dried, the ether was removed, and the residue was distilled, affording 1.70 g of liquid, bp 60–110° (1.2 mm). Analysis by glpc using a 3-m DEGS column at 150° indicated the presence of 22.5% of 1-carbomethoxy-2,6,6-trimethylbicyclo[3.1.0]-2-hexene (**8**), 48.6% of 3-carbomethoxy-2-methyl-4-isopropylidene-1-cyclopentene (**5**), 14% of 2-carbomethoxy-1-methyl-3-isopropylidene-1-cyclopentene (**6**), 6.7% of 3-methoxyeucarvone (**9**), 3.5% of carvenolide (**7**), and a total of 4.8% of several unidentified components.

The aqueous layer remaining after ether extraction was acidified with concentrated hydrochloric acid and extracted with ether to yield 134 mg of dark tar.

Pure samples of **5**, **6**, **7**, **8**, and **9** were collected by preparative glpc. Carvenolide (**7**) was identified by comparison with glpc retention time and ir and nmr spectra of an authentic sample.[4]

1-Carbomethoxy-2,6,6-trimethylbicyclo[3.1.0]-2-hexene (**8**) showed $n^{20}D$ 1.4709; ir 5.78 μ; nmr (CCl_4) δ 0.94 and 1.23 (s, 6, CH_3CCH_3), 1.83 (s, 3, $CH_3CH=$), 1.72–2.5 (m, 3), 3.65 (s, 3, OCH_3), and 5.15 ppm (m, 1, CH=C).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.31; H, 8.95. Found: C, 73.40; H, 9.28.

3-Carbomethoxy-2-methyl-4-isopropyl-1-cyclopentene (**5**) displayed $n^{20}D$ 1.4789; ir 5.75 μ; nmr (CCl_4) δ 1.66 (broad s, 9, $CH_3C=C$), 3.00 (m, 2, $C=CCH_2C=C$), 3.66 (s, 3, OCH_3), 3.89 [m, 1, $(C=C)_2CHC=O$], and 5.61 ppm (m, 1, CH=C).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.31; H, 8.95. Found: C, 72.98; H, 9.16.

Since only a small quantity of 3-methoxyeucarvone (**9**) and the unstable 2-carbomethoxy-1-methyl-3-isopropylidene-1-cyclopentene (**6**) were isolated, they were not completely characterized. 3-Methoxyeucarvone (**9**) exhibited strong carbonyl absorption at 6.1 μ; nmr (CCl_4) 1.08 (s, 6, CH_3CCH_3), 1.79 (s, 3, $CH_3C=C$), 2.54 (s, $O=CCH_2C=C$), 3.69 (s, 3, $-OCH_3$), and 5.98 ppm (AB q, 2, -CH=CH-). A glpc pure sample of **6** showed nmr signals at δ 1.54, 1.67 and 1.82 (s, 9, 3 $CH_3C=C$) and 2.43 (broad s, 4, $C=CCH_2CH_2C=C$).

B. Diethyl Ether.—A mixture of 6.90 g (0.1275 mol) of sodium methoxide, 75 ml of anhydrous ether, and 5.00 g (0.01275 mol) of *dl-cis*-carvone tribromide (**2**) was stirred for 24 hr. The resulting pink-brown mixture was diluted with 200 ml of ether and 500 ml of water and the layers were separated. The aqueous phase was extracted with ether, the combined ether fractions were dried, and the ether was removed, affording 2.03 g of orange oil. Distillation *in vacuo* gave 1.31 g (67%) of 1-carbomethoxy-2,6,6-trimethylbicyclo[3.1.0]-2-hexene (**8**), bp 40–42° (0.5 mm). Analysis of the distillate by glpc showed only the presence of bicyclic ester **8**.

Work-up of the basic aqueous layer gave only a small amount (186 mg) of tar.

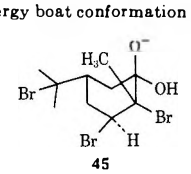
Hydrogenation of 8.—A solution of 1.5 g of bicyclic ester **8** in 25 ml of ethanol was hydrogenated over 150 mg of PtO_2. The uptake of 1 equiv of hydrogen required 3 hr. The catalyst and solvent were removed and analysis of the residue by glpc indicated the presence of one product contaminated by a small amount of **8**. Distillation *in vacuo* gave 1.4 g of 1-carbomethoxy-2,6,6-trimethylbicyclo[3.1.0]hexane (**14**), bp 63–65° (2 mm). The analytical sample was prepared by distillation: bp 55° (1.3 mm); $n^{20}D$ 1.4646; ir 5.81 μ; nmr (CCl_4) δ 1.08 and 1.27 (s, 6, CH_3C-CH_3), 1.12 and 1.27 (d, 3, $CHCH_3$), 1.4–2.9 (m), and 3.58 ppm (s, 3, OCH_3).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.50; H, 9.93. Found: C, 72.72; H, 10.08.

Reaction of 8 with Hydrohalides. A. HBr.—A solution of 1.027 g of bicyclic ester **8** in 7 ml of chloroform and 12 ml of fuming hydrobromic acid was stirred at ambient temperature for 1 hr. The mixture was diluted with water, the layers were separated, and the aqueous phase was extracted with methylene chloride. The combined organic phases were washed with water and 5% sodium bicarbonate solution, and dried. The solvents were removed under diminished pressure, affording 1.21 g of a light tan oil which darkened rapidly on standing, ir 5.80 and 6.05 μ. Attempts to purify this material led to extensive decomposition.

A solution of 380 mg of the crude product in 10 ml of 2,6-lutidine was refluxed for 48 hr. Ether was added and the mixture was extracted with 5% hydrochloric acid. The ether phase was dried and evaporated to give 253 mg of tan oil. Evaporative

(13) It is not surprising that the conversion **39** → **40** occurs more rapidly than a Grob fragmentation, since the latter transformation requires the ring to assume the high-energy boat conformation **45**.



(14) All boiling and melting points are uncorrected. Nuclear magnetic resonance spectra were measured at 60 MHz with a Varian Associates A-60 spectrometer. Chemical shifts are given as δ values in parts per million with reference to tetramethylsilane as an internal standard. Microanalyses were performed by Dr. C. S. Yeh and associates. The reactions of **1** and **2** were conducted under an atmosphere of nitrogen at ambient temperature, and drying of organic solutions was accomplished with anhydrous $MgSO_4$.

distillation gave a liquid whose infrared spectrum and glpc retention time were identical with those of authentic methyl 5-isopropenyl-2-methyl-1-cyclcpentene carboxylate (16).[5]

B. HCl.—A mixture of 1.050 g of bicyclic ester **8** in 7 ml of chloroform and 12 ml of concentrated hydrochloric acid was stirred vigorously at ambient temperature for 1 hr. The mixture was worked up as described above to give 1.18 g of pale yellow liquid. Evaporative distillation gave a colorless liquid which rapidly darkened on standing. An accurate microanalysis could not be obtained due to the instability of the compound.

A solution of 508 mg of the chloro ester in 10 ml of 2,6-lutidine was refluxed for 38 hr. The mixture was cooled, diluted with ether, and extracted with 5% hydrochloric acid. The ether solution was dried and concentrated, affording 388 mg of an orange oil. Distillation *in vacuo* gave a liquid whose infrared and nmr spectra as well as glpc retention time were identical with those of an authentic sample of **16**.

Hydrogenation of 3-Carbomethoxy-2-methyl-4-isopropylidene-1-cyclopentane (5).—A solution of 100 mg of **5** in 15 ml of methanol and 2 ml of acetic acid was hydrogenated over 10 mg of platinum oxide until a slight excess of 1 equiv of hydrogen had been absorbed (1 hr). The mixture was filtered and the solvents were removed. The glpc retention time and infrared spectrum of the residue were identical with those of an authentic sample of *cis*-methyl pulegenate (**13**).[4]

Reaction of *trans*-Carvone Tribromide (1) with Sodium Methoxide. A. Methanol.—A solution of 6.30 g (0.1275 mol) of sodium methoxide and 4.94 g (0.127 mole) of *dl-trans*-carvone tribromide (**1**) in 50 ml of methanol was stirred for 20 hr. After 500 ml of water was added, the mixture was extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated. The residue was distilled *in vacuo* and the material distilling at 60–200° (0.5 mm) was collected. A small amount of solid distilled at the higher temperature, but was not investigated further.

Analysis of the liquid distillate (1.35 g) using a 3-m DEGS column at 170° indicated the presence of a number of compounds. The major products, 3-carbomethoxy-2-methyl-4-isopropylidene-1-cyclopentene (**5**) (62%), carvenolide (**7**) (22.4%), and carvacrol (**10**) (4.6%), were isolated by glpc and identified by comparison of glpc retention times and nmr spectra. Trace amounts of 2-carbomethoxy-1-methyl-3-isopropylidene-1-cyclopentene (**6**) and 3-methoxyeucarvone (**9**) were also detected.

B. Diethyl Ether.—A mixture of 20.7 g (0.383 mol) of sodium methoxide, 15.0 g (0.0383 mol) of *dl-trans*-carvone tribromide (**1**), and 225 ml of anhydrous ether was stirred for 25 hr. Water (1 l.) was added and the aqueous phase was extracted with ether. The ether solution was dried and evaporated to afford 8.21 g of orange oil. When kept at −20° the oil partially solidified. The solid was removed by filtration and washed with cold pentane. This process was repeated again to give a total of 2.08 g of solid. Recrystallization from hexane gave the analytical sample of dibromo hydroxy ketone **12**: mp 100.5–101.5°; ir (melt) 2.85 and 5.80 μ; λ_{max} 283 nm (ϵ 37.4); nmr ($CDCl_3$) δ 1.60 (s, 3, CH_3CO), 1.82 and 1.86 (s, 6, CH_3CBrCH_3), 2.1–3.0 (m), 3.96 (s, 1, –OH), and 3.96 ppm (t, 1, J = 2.5 Hz, HCBr). In benzene, the CH_3CO signal was shifted upfield by 16.2 Hz, indicating the presence of an axial methyl group.

Anal. Calcd for $C_{10}H_{16}Br_2O_2$: C, 36.61; H, 4.92; Br, 48.72. Found: C, 36.40; H, 4.70; Br, 49.02.

The filtrate obtained after removing **12** was distilled *in vacuo* to afford 2.90 g of liquid bp 45–55° (0.6 mm). Glpc analysis of this product indicated the presence of 91% of bicyclic ester **8** and a total of 9% of four unidentified compounds. A sample of **8** was collected and identified by ir and nmr comparison with that of an authentic sample.

Recrystallization of the distillation residue from hexane afforded an additional 0.61 g of hydroxy ketone **12**.

The acetate derivative of 3-bromo-2-hydroxy-2-methyl-5-(2-bromoisopropyl)cyclohexanone (**12**) was prepared by stirring with magnesium and acetyl chloride and after the usual work-up was purified by recrystallization from hexane: mp 91–92°; ir 5.75 μ; λ_{max}^{EtOH} 283 nm (ϵ 43.5); nmr ($CDCl_3$) δ 1.77 and 1.82 [2, s, 6, $(CH_3)_2CBr$], 1.90 (s, 3, CH_3COAc), 2.16 (s, 3, $O{=}CCH_3$), and 5.35 ppm (t, 1, J = 3 Hz, –CHBr). In benzene, the nmr signal assigned to the α-methyl group was shifted 19.8 Hz upfield, indicative of an axial methyl group.

Anal. Calcd for $C_{12}H_{18}Br_2O_3$: C, 38.75; H, 4.89; Br, 43.19. Found: C, 39.06; H, 4.94; Br, 43.18.

C. Diethyl Ether. Work-Up without Water.—A mixture of 20.7 g (0.383 mol) of sodium methoxide, 20.7 g (0.0383 mol) of *dl-trans*-carvone tribromide (**1**), and 210 ml of anhydrous ether was stirred for 38.5 hr and then filtered. The ether was removed under diminished pressure, pentane was added to the residue, and the mixture was kept at −20° to yield 4.33 g (33.8%) of white solid (two crops). Several recrystallizations from hexane gave the analytical sample of epoxy ether **11**: mp 85–87°; ir ($CHCl_3$) no –OH or carbonyl absorption; nmr ($CDCl_3$) δ 1.44 (s, 3, CH_3-CO), 1.76 and 1.79 [2 s, 6, $(CH_3)_2CBr$], 3.46 (s, 3, $-OCH_3$), and 4.53 ppm (t, 1, J = 2.5 Hz, –CHBr).

Anal. Calcd for $C_{11}H_{18}Br_2O_2$: C, 38.64; H, 5.29; Br, 46.72. Found: C, 38.71; H, 5.33; Br, 46.60.

Epoxy ether **11** liquified upon standing at room temperature for a few hours, and after several days resolidified. Recrystallization from hexane gave hydroxy enol ether **17**: mp 43–45°; ir 6.1 μ; nmr ($CDCl_3$) δ 1.54 (s, 3, CH_3CO), 1.76 and 1.85 [2 s, 6, $(CH_3)_2CBr$], 3.64 (s, 3, $CH_3OC{=}C$), 4.60 (m, 1, $W_{1/2}$ = 7.5 Hz, –CHBr), and 4.76 ppm (d, 1, J = 2.8 Hz, $-C{=}CH-$).

Anal. Calcd for $C_{11}H_{18}Br_2O_2$: C, 38.64; H, 5.29; Br, 46.72. Found: C, 38.64; H, 5.43; Br, 47.02.

Distillation of the mother liquors obtained from the crystallization of epoxy ether **11** gave 2.60 g of bicyclic ester **8**, bp 63–65° (1.8 mm).

A solution of epoxy ether **11** in chloroform was stirred vigorously at ambient temperature with 3 ml of fuming hydrobromic acid. The chloroform layer was washed with 5% sodium bicarbonate, dried, and evaporated under diminished pressure. The solid residue was crystallized from hexane to afford colorless crystals of hydroxy ketone **18**,[2] mp 101–103°.

Hydroxy ketone **18** was also obtained from epoxy ether **11** by shaking an ether solution of **11** with 1.0 N sodium hydroxide solution.

D. Hexane—A mixture of 13.80 g (0.256 mol) of sodium methoxide, 10.0 g (0.0256 mol) of *dl-trans*-carvone tribromide (**1**), and 150 ml of spectroscopic grade hexane was stirred for 24 hr. The mixture was diluted with 500 ml of water and 200 ml of ether. The aqueous layer was extracted with ether and the combined organic layers were dried. The solvents were removed *in vacuo*, leaving 4.81 g of orange oil. Distillation *in vacuo* gave 2.10 g of liquid, bp 44–48° (0.2 mm), $n^{20}D$ 1.4726. Analysis by glpc indicated this material was largely (90%) bicyclic ester **8**.

The distilland was recrystallized from hexane and afforded 440 mg of hydroxy ketone **12**, mp 101–103°.

Reaction of *cis*-Carvone Tribromide (2) with Sodium Hydroxide in Water.—A mixture of 30.0 g (0.0765 mol) of *dl-cis*-carvone tribromide (**2**) and 49.2 g (1.23 mol) of sodium hydroxide in 300 ml of water was stirred for 71 hr. The mixture was extracted with ether, and the ether solution was dried and distilled to give 3.23 g (25.4%) of α-3,4-epoxycaran-2-one (**22**): bp 59–63° (0.5 mm); nmr (CCl_4) δ 0.95, 1.18, and 1.28 (3 s, 9, CH_3C- and CH_3-CO), and 3.08 ppm (m, 1, $W_{1/2}$ = 5 Hz, epoxide H).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.25; H, 8.48. Found: C, 71.92; H, 9.01.

The basic aqueous solution remaining after the ether extraction described above was saturated with carbon dioxide to pH 6 and extracted with ether. The ether solution was washed with saturated salt solution and dried, and an ethereal solution of diazomethane was added. The solvent was removed, leaving 1.6 g of oil. Analysis by glpc indicated that this material was composed of 51% of methyl 3-isopropenyl-6-bromo-5-heptenoate (**20**), 40% of methyl 3-isopropylidene-6-bromo-5-heptenoate (**19**), and 9% of 3-(4-bromo-2-butenyl)-4,4-dimethylbutyrolactone (**21**).

The aqueous solution remaining after ether extraction described above was acidified with hydrochloric acid to pH 1 and extracted with ether. The ether solution was dried and concentrated to afford 11.2 g of orange oil. Distillation gave 10.5 g of lactone **21**, bp 126–128° (0.24 mm). An analytical sample of lactone **21** was obtained by glpc: $n^{20}D$ 1.4985; ir (neat) 5.70 μ; nmr (CCl_4) δ 1.27 and 1.43 (2 s, 6, CH_3COCH_3), 2.29 (s, 3, $CH_3BrC{=}C-$), 5.63 ppm (m, 1, $-C{=}CH-$). A sample of lactone **21** prepared from *d-cis*-carvone tribromide in the manner described above showed mp 44–45°.

Anal. Calcd for $C_{10}H_{15}BrO_2$: C, 48.61; H, 6.09; Br, 32.24. Found: C, 48.38; H, 6.26; Br, 32.00.

A pure sample of methyl 3-isopropylidene-6-bromo-5-heptenoate (**19**) was obtained by glpc: ir 5.7 and 6.0 μ; nmr (CCl_4) 1.71 and 1.77 (2 s, 6, $CH_3C{=}C-$), 2.30 (d, 3, J = 1.5 Hz, CH_3-$C{=}C-$), 2.97 (s, 2, $-C{=}CCH_2CO$), 2.92 (d, 2, $C{=}CHCH_2$-$C{=}C-$), 3.58 (s, 3, CH_3O-), and 5.46 (t of d, 1, J = 7, 1.5 Hz, $CH_3C{=}CHCH_2-$).

Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.58; H, 6.57; Br, 30.60. Found: C, 50.70; H, 6.47; Br, 30.40.

A pure sample of methyl 3-isopropenyl-6-bromo-5-heptenoate (**20**) was obtained by glpc: ir 5.7 and 6.05 μ; nmr (CCl_4) δ 1.70 (m, 3, J = 0.5 Hz, CH_3C=C-), 2.24 (m, 3, J = 0.5 Hz, CH_3Br-C=C-), 3.56 (s, 3, CH_3O-), and 5.46 ppm (m, 1, BrC=CH-).

Anal. Calcd for $C_{11}H_{17}BrO_2$: C, 50.58; H, 6.57; Br, 30.60. Found: C, 50.17; H, 6.54; Br, 30.32.

Reaction of Sodium Hydroxide with *cis*-Carvone Tribromide (2) in Aqueous Dioxane.—A solution of 10 g (0.0256 mol) of *dl-cis*-carvone tribromide (**2**) and 16.4 g (0.411 mol) of sodium hydroxide in 70 ml of pure dioxane and 40 ml of water was stirred for 45 hr. After the usual work-up, distillation of the neutral fraction gave 1.73 g (40.8%) of epoxy ketone **22**, bp 55–58° (0.25 mm).

Work-up of the acidic fraction and treatment with diazomethane, followed by distillation *in vacuo*, gave 0.80 g of a mixture (glpc analysis) of 16.4% of isopropyl ester **20**, 60% of isopropylidine ester **19**, and 24% of several unidentified products, bp 65–90° (0.4 mm), and 0.32 g of bromolactone **21**, bp 100–110° (0.4 mm). The yields of **20**, **19**, and **21** were 2, 8, and 41%, respectively.

Reaction of Sodium Hydroxide with *cis*-Carvone Tribromide in Ether.—A mixture of 16.4 g (0.410 mol) of powdered and vacuum dried sodium hydroxide, 10.0 g (0.0256 mol) of *dl-cis*-carvone tribromide (**2**), and 150 ml of anhydrous ether was stirred for 64 hr. The usual work-up gave 447 mg of a neutral fraction. Analysis by glpc showed only one major component, which was collected and identified as eucarvone (**23**) on the basis of its ir and nmr spectra.

Work-up of the acid fraction and treatment with diazomethane gave 4.83 g of liquid. Distillation in *vacuo* afforded 2.36 g, bp 74–90° (0.55 mm), and 1.47 g, bp *ca.* 120° (0.45 mm). Analysis of the first fraction by glpc indicated the presence of 55% of the isopropenyl ester **20** and 28% of the isopropylidene ester **19**. The second fraction was comprised of bromo lactone **20**. The yields of **20**, **19**, and **21** were 22, 11, and 23%, respectively.

Reaction of *trans*-Carvone Tribromide with Sodium Hydroxide in Water.—A mixture of 20.0 g (0.0512 mol) of *d-trans*-carvone tribromide (**1**) and 32.8 g (0.82 mol) of sodium hydroxide in 200 ml of water was stirred for 70 hr. The mixture was extracted with ether. The ether solution was dried and evaporated to afford 1.2 g of liquid. Analysis by glpc indicated the presence of eucarvone (**23**) (49%), carvacrol (**10**) (28%), and small amounts of several unidentified substances.

The basic solution remaining after ether extraction was acidified with hydrochloric acid and extracted with ether. The ether solution was dried and treated with diazomethane, and then concentrated under diminished pressure to afford 6.73 g of liquid. Analysis by glpc indicated the presence of methyl 4-methyl-3-pentenoate (**24**) (30%), methyl 3-isopropenyl-6-ketoheptenoate (**25**) (4%), methyl 3-isopropylidene-6-ketoheptanoate (**26**) (15%), and homoterpenyl methyl ketone (**27**) (51%).

Pure samples of eucarvone (**23**), carvacrol (**10**), **24**, **25**, and **26** were obtained by preparative glpc. Carvacrol, eucarvone (n^{20}D 1.5068), and keto ester **25**[15] were identified by spectral comparison with known samples. Pure homoterpenyl methyl ketone was obtained by recrystallization from pentane at −20°, and showed mp 43–44° and ir and nmr spectra identical with those of an authentic sample.

Methyl 4-methyl-3-pentenoate (24) showed carbonyl absorption at 5.74 μ; nmr (CCl_4) δ 1.63 and 1.74 [2 s, 6, $(CH_3)_2C$=C], 2.92 (d, 2, J = 7 Hz, $-CH_2C$=C), 3.59 (s, 3, $-OCH_3$), and 5.22 ppm (t, 1, J = 7 Hz, C=CH).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.36; H, 9.43. Found: C, 65.40; H, 9.48.

Reaction of *trans*-Carvone Tribromide with Sodium Hydroxide in Ether.—A mixture of 32.8 g (0.822 mol) of powdered and dried sodium hydroxide, 20.0 g (0.0512 mol) of *dl-trans*-carvone tribromide (**1**), and 300 ml of anhydrous ether was stirred for 79 hr. The resulting brown mixture was diluted with water and the layers were separated. The aqueous phase was extracted with ether and the combined ether fractions were washed with water, dried, and distilled *in vacuo* to yield 1.51 g (19.7%) of liquid, bp 34–36° (0.25 mm), which was identified as eucarvone (**23**) on the basis of its infrared spectrum.

The aqueous phase remaining after ether extraction was acidified with hydrochloric acid and extracted with ether. The ether solution was washed with water, dried, and treated with excess diazomethane. Distillation under reduced pressure gave 110 mg (1.4%) of methyl 4-methyl-3-pentenoate (**24**), bp 45° (10 mm), and 2.5 g of liquid, bp 55–90° (0.25 mm). Preparative gas chromatography (Carbowax at 190°) gave 17% of bicyclic ester **8**, 19% of 3-carbomethoxy-4-isopropenyl-2-methylcyclopentene (**28**), 38% of unsaturated ester **5**, and 12% of carvenolide (**7**).

3-Carbomethoxy-4-isopropenyl-2-methylcyclopentene (**28**) displayed n^{20}D 1.4722; ir 5.75 and 6.05 μ; nmr (CCl_4) δ 1.69 (s, 6, CH_3C=C), 3.65 (s, 3, CO_2CH_3), 4.68 (m, 2, C=CH_2), and 5.38 ppm (m, 1, CH=C).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.53; H, 8.99.

Reaction of Epoxycarone 22 with Hydrobromic Acid.—A solution of 240 mg of epoxycarone **22** in 5 ml of chloroform was stirred vigorously for 1 hr with 5 ml of fuming hydrobromic acid. The layers were separated and the aqueous phase was extracted with methylene chloride. The combined organic layers were dried and the solvents were removed under diminished pressure to afford 345 mg of pale yellow oil. Recrystallization from hexane at −20° gave flat needles, mp 95–97°. The analytical sample of hydroxy ketone **29** was obtained by repeated recrystallization from hexane: mp 96–97°; ir ($CHCl_3$) 2.7 and 2.85 μ; λ_{max}^{EtOH} 307 nm (ϵ 95); nmr ($CDCl_3$) δ 1.77, 1.79, and 1.83 (3 s, 9, CH_3CBr), 2.03–3.5 (m), and 4.38 ppm (t, 1, J = 2.5 Hz, -CH—O). In benzene, the nmr signal of the α-methyl group was only shifted to higher field by 5.4 Hz, indicating an equatorial α-methyl group.

Anal. Calcd for $C_{10}H_{16}Br_2O_2$: C, 36.61; H, 4.97; Br, 48.72. Found: C, 36.90; H, 4.97; Br, 48.45.

The acetate of hydroxy ketone **29** was prepared by treatment with magnesium and acetyl chloride. Repeated recrystallization from hexane at −20° gave an analytical sample: mp 47–50°; ir 5.72 and 5.8 μ; λ_{max}^{EtOH} 306 nm (ϵ 153); nmr ($CDCl_3$) δ 1.75 and 1.77 (2 s, 9, CH_3CBr), 2.04 (s, 3, $OCOCH_3$), and 5.51 ppm (t, 1, J = 3 Hz, -CHOAc).

Anal. Calcd for $C_{12}H_{18}Br_2O_3$: C, 38.95; H, 4.89; Br, 43.19. Found: C, 39.04; H, 5.10; Br, 43.52.

Reaction of Epoxycarvone (30) with Hydrobromic Acid.—A solution of 1.0 g of epoxycarvone (**30**)[16] in 5 ml of chloroform was stirred vigorously at ambient temperature, with 10 ml of fuming hydrobromic acid. The layers were separated, the purple chloroform solution was washed with 5% sodium bicarbonate solution and dried, and the solvent was removed under diminished pressure. The deep purple solid was recrystallized from hexane, Norit, to afford 0.56 g of colorless needles, mp 94–96°, whose ir spectrum was identical with that of hydroxy ketone **29** obtained from epoxycarone **22**.

When 1 ml of acetic acid saturated with hydrogen bromide was added to an ice-cooled solution of 200 mg of epoxycarvone (**30**) in 1 ml of acetic acid and the solution was stirred for 2 min and then worked up, there was obtained 96 mg of hydroxy ketone **29**.

When the reaction of epoxycarvone (**30**) with hydrogen bromide in acetic acid was allowed to proceed for 1 hr at 0°, work-up and recrystallization from hexane gave *cis*-carvone tribromide (**2**), mp 112–116°.

Registry No.—**1**, 22249-53-2; **2**, 22249-55-4; **5**, 35324-51-7; **8**, 35427-26-0; **11**, 35324-04-0; **12**, 35324-05-1; **12** acetate, 35324-06-2; **14**, 35324-07-3; **17**, 35324-08-4; **19**, 35324-52-8; **20**, 35324-53-9; **21**, 35324-54-0; **22**, 35324-55-1; **24**, 2258-65-3; **28**, 35324-57-3; **29**, 35324-09-5; **29** acetate, 35324-10-8.

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The Preparation of Deuterated Organic Compounds from Activated Organic Halides by Reduction with Zinc–Deuterium Oxide[1]

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Reductive elimination of halogen from α-halo esters with zinc and deuterium oxide in polar aprotic solvents provides a convenient method for the preparation of the corresponding α-deuterated substances. The procedures developed for carrying out these transformations can be applied to the synthesis of large quantities of either mono- or dideuterated esters with good isotopic purity. Several isolated experiments suggest that this method should also be applicable to the conversion of α-halogenated nitriles and amides to the corresponding α-deuterated materials; when applied to the reductive deuteration of α-halogenated ketones and acid chlorides, the isotopic purities of the deuterated products are lower. This technique for the synthesis of α-deuterated esters is superior to the base-catalyzed exchange techniques in general use when the prerequisite α-halogenated analogs are available, both in its economical use of deuterium oxide and in its ability to introduce a single deuterium atom into a methyl or methylene group containing multiple equivalent exchangeable protons.

The acid- or base-catalyzed exchange of enolizable protons for deuterons is a widely used technique in isotopic synthesis.[3] Despite its simplicity and convenience, this technique suffers from two important disadvantages. First, the achievement of high isotopic purity by exchange requires multiple treatments of the substrate with deuterium oxide, itself of high isotopic purity, and is accordingly intrinsically wasteful of deuterium. Second, it is not suitable for the introduction of a specified number of deuterium atoms into a position containing a larger number of equivalent exchangeable hydrogens.[4]

In the course of other work, we required quantities of mono- and dideuterated alkyl halides having high isotopic purity. In an effort to circumvent exchange procedures for the preparation of these materials, we investigated the utility of synthetic methods for introducing deuterium based on the reductive elimination of halogen from α-halo carbonyl and nitrile derivatives with metallic zinc in the presence of deuterium oxide.[5] Here we report that this procedure provides a useful method for the preparation of esters, and probably of amides and nitriles, containing deuterium next to the unsaturated group; when applied to ketones the isotopic purity of the product is lower, and other procedures for the introduction of deuterium are presumably preferable to that described here.[3,6]

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(2) National Institutes of Health Predoctoral Fellow, 1967–1970.

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(5) Dehalogenation of α-halo ketones with zinc–acetic acid-*O*-*d* has been used previously to prepare α-deuterio ketones; *cf.*, for example, E. J. Corey and G. A. Gregoriou, *J. Amer. Chem. Soc.*, **81**, 3127 (1959); E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956); R. R. Sauers and C. K. Hu, *J. Org. Chem.*, **36**, 1153 (1971).

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Results and Discussion

Reductions were carried out by adding the organic halide (1 equiv) and deuterium oxide (~2–4 equiv) to zinc powder (~2 equiv) at 80° in diglyme or dimethoxyethane. Traces of exchangeable protons present in the reaction apparatus or on the zinc powder were exchanged for deuterium before addition of the organic halide by addition of deuterium oxide to the reaction flask containing the zinc and azeotropic distillation of this small initial charge of deuterium oxide from the reaction flask with benzene. The surface of the zinc was cleaned before this exchange by a brief washing with 5% hydrochloric acid; it was sometimes activated immediately before addition of the organic halide by reaction with iodine or 1,2-dibromoethane. The reductions frequently showed an induction period, particularly with less reactive organic chlorides; in certain instances, particularly those involving nitriles, these induction periods were capable of contributing to a significant decrease in the isotopic purity of the products if sufficiently prolonged, presumably by permitting isotopic exchange in the starting materials; further, accumulation of an excessive quantity of unreacted halide in the reaction flask during a lengthy induction period occasionally led to embarassingly exothermic reactions when initiation finally did take place. Thus, cleaning and activating the zinc surface, and checking to make certain that the reaction was initiated early in the addition of the organic halide (with appropriate use of 1,2-dibromoethane or iodine as initiating agents if necessary), were important in achieving high yields and isotopic purities.

Representative yields and isotopic purities obtained following this procedure are listed in Table I. To avoid obtaining inaccurate mass spectroscopic isotopic compositions as a result of exchange of deuterium for hydrogen in the mass spectrometer inlet system, the substances isolated directly from the reductions were converted to nonexchangeable derivatives more suitable for isotopic analysis (and for several types of further synthetic manipulation). These derivatives are also listed in Table I, and appropriate details of their preparation are described in the Experimental Section.

The significant conclusion to be drawn from the data of Table I is that the reductive dehalogenation of activated organic halides provides an attractive synthetic route to deuterated organic compounds. The

TABLE I

YIELDS AND ISOTOPIC PURITIES OF PRODUCTS OBTAINED ON DEHALOGENATION OF ACTIVATED ORGANIC HALIDES USING ZINC–DEUTERIUM OXIDE

Starting material	Yield,[a] %	Substrate[b]	Isotopic compn, % d_0	d_1	d_2	d_3
$ClCH_2CO_2$-*n*-C_3H_7	17	DCH_2CH_2I	2.5	96.0	1.5	
$Cl_3CCO_2CH_3$	63	$D_3CCH_2CH_2CH_2Br$		1.5	6.5	92.0
$BrCH_2CO_2$-*n*-C_3H_7	52	DCH_2CH_2I	2.0	98.0		
$CH_3CH_2CHBrCO_2C_2H_5$	50	$CH_3CH_2CHDCH_2Br$	1.4	98.6		
$CH_3CH_2CCl_2CO_2C_2H_5$	73	$CH_3CH_2CD_2CH_2Br$		2.4	97.6	
$C_2H_5OCO(CH_2)_3CHBrCO_2C_2H_5$	58	$Br(CH_2)_4CHDCH_2Br$	2.1	97.9		
$ClCH_2CN$	47	$DCH_2CH_2NH_2$	2.0	94.0	4.0	
$CH_3CH_2CCl_2CN$	76	$CH_3CH_2CD_2CH_2NH_2$		1.0	99.0	
$BrCH_2CON(C_6H_5)C_2H_5$	36	$DCH_2CH_2N(C_6H_5)C_2H_5$	7.0	93.0		
$ClCH_2COCl$	51[c]	DCH_2CH_2I	2.0	82.0	15.0	1.0
$ClCH_2COCH_3$	61	$DCH_2CHBrCH_3$	9.0	50.0	34.0	7.0

[a] Isolated yields of the products obtained by zinc–deuterium oxide reduction of the starting materials. [b] Substances on which the mass spectroscopic isotopic composition measurements were performed. [c] Acetic acid-d_2 was the isolated product.

procedure works best for esters,[7] and less well for the more acidic (and more rapidly exchangeable) ketones and nitriles. Since α-halogenated esters are relatively readily available using a number of synthetic techniques,[8] this procedure seems to provide the method of choice for preparation of specifically α-deuterated esters and derivatives.

Experimental Section

General Methods.—Nmr spectra were recorded using a Varian T-60 spectrometer in carbon tetrachloride solutions; chemical shifts are reported in parts per million (δ) from tetramethylsilane. Mass spectra were determined on a Hitachi Perkin–Elmer model RMU 6 spectrometer. Preparative glpc analyses were performed on a Hewlett–Packard Model 700 chromatograph with a thermal conductivity detector using the following columns: column A, 8-ft, 0.25-in. 10% DEGS on 60–80 mesh Chromosorb W; column B, 10-ft, 0.25-in. 10% Carbowax 20M on 60–80 mesh Chromosorb P; column C, 8-ft, 0.25-in. 5% SE-30 on 60–80 Chromosorb P; column D, 8-ft, 0.25-in. 10% XF-1150 on 60–80 mesh Chromosorb P.

Diglyme was distilled from calcium hydride, and degassed before use by bubbling a slow stream of nitrogen through it for 20 min. Dimethoxyethane (DME) was purified by distillation from a deep purple solution of sodium benzophenone dianion. The 2,2-dichlorobutyronitrile used was a gift of the Dow Chemical Co. Other halogenated ketones, esters, nitriles, and acid halides were obtained from Eastman Organic Chemicals, and were used without further purification. Reagent grade zinc dust (Mallinkrodt) was generally used without further purification, although activation with 10% hydrochloric acid is advisable for zinc dust which has been opened to air for considerable lengths of time.[9]

Isotopic compositions were determined mass spectrometrically on samples purified by preparative glpc. All spectra for isotopic analysis were obtained using ionizing voltages as close as possible to the appearance potential of the compound under examination. Isotopic compositions were normally obtained from peak area data; however, indistinguishable data resulted from analysis of peak heights. During collection of compounds from the glpc care was taken to collect all of the peak of interest, to avoid isotopic fractionation.[10]

Ethyl Butyrate-2-d_1.—Reagent zinc dust (130 g, 2 g-atoms), diglyme (300 ml) freshly distilled from calcium hydride, and benzene (200 ml) were placed in a 1-l., three-necked flask fitted with a Dean-Stark trap and a mechanical stirrer. One neck of the flask was sealed with a No-Air stopper. The mixture was heated to reflux and 15 ml of deuterium oxide was added dropwise over the course of 2 hr to exchange possible sources of protons. Recovery of water (15 ml) from the Dean-Stark trap was complete. The Dean-Stark trap was removed, benzene was separated from the reaction mixture by simple distillation, a reflux condenser was fitted to the apparatus, and 10 ml of deuterium oxide was added. The reaction mixture was heated to 80° and ethyl 2-bromobutyrate (2 ml) was added. An immediate 5–10° temperature rise indicated initiation of the reaction. The reaction flask was immersed in a large ice bath. The internal temperature of the reaction flask was maintained at 50–60° by cautious alternate addition of aliquots of ethyl 2-bromobutyrate (226 g, 1.16 mol) and deuterium oxide (80 g, 4.0 mol); each reagent was added in 12 equal portions.

Glpc analysis using column A at 100° showed that ethyl 2-bromobutyrate was reduced as rapidly as it was added to the reaction mixture. At the conclusion of the reaction, excess zinc and insoluble zinc salts were filtered from the reaction mixture and washed with two 100-ml portions of ether. The ether washes and diglyme solution were combined, and the product was isolated by a preliminary distillation. Material boiling between 50 and 160° was dried ($MgSO_4$) and carefully redistilled, yielding ethyl butyrate-2-d_1 (67 g, 0.58 mol, 50%) having bp 120–121°. The nmr spectrum was consistent with the proposed deuterium substitution.

1-Butanol-2-d_1 was prepared from ethyl butyrate-2-d_1 (67 g, 0.58 mol) dissolved in ether (50 ml) by dropwise addition to a solution of lithium aluminum hydride (25 g, 0.62 mol) in 300 ml of ether at 0°. The mixture was refluxed for 30 min, quenched with ethyl acetate (50 g, 0.56 mol), water (25 ml), 15% (w:w) aqueous sodium hydroxide (25 ml), and additional water (75 ml). The ether was decanted and the residual aluminum salts were refluxed with two 100-ml portions of ether. The ethereal solutions were combined, and distilled through a 120-cm platinum spinning band column to yield 1-butanol-2-d_1 (24 g, 0.32 mol, 55%) having bp 116–118°.

1-Butanol-2,2-d_2 was prepared from ethyl 2,2-dichlorobutyrate (145 g, 0.81 mol) and deuterium oxide (80 g, 4 mol) by zinc reduction and subsequent treatment with lithium aluminum hydride as described previously.[11]

Ethanol-2,2,2-d_3 was prepared from methyl trichloroacetate (176 g, 1.0 mol) and deuterium oxide (88 g, 4.4 mol) by zinc re-

(7) Side products formed in the reaction were not investigated; however, they are probably similar to those formed in the Reformatsky reaction. *Cf.* W. R. Vaughan, S. C. Bernstein, and M. E. Lorber, *J. Org. Chem.*, **30**, 1790 (1965); T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Amer. Chem. Soc.*, **89**, 5727 (1967); R. L. Shriner, *Org. React.*, **1**, 4 (1942); M. W. Rathke and A. Lindert, *J. Org. Chem.*, **35**, 3966 (1970).

(8) For representative references, see H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 155–156; A. Markovac and S. F. MacDonald, *Can. J. Chem.*, **43**, 3364 (1965); H. Reinheckel, *Chem. Ber.*, **93**, 2222 (1960); B. Castro, J. Villieras, and N. Ferracutti, *Bull. Soc. Chim. Fr.*, 3521 (1969); H. J. Ziegler, L. Walgraeve, and F. Binon, *Syn.*, **1**, 39 (1969); H. Reinheckel, *J. Prakt. Chem.*, **15**, 260 (1962); H. C. Brown, M. M. Rogic, M. W. Rathke, and G. W. Kabalka, *J. Amer. Chem. Soc.*, **90**, 1911 (1968); E. E. Smissman, *ibid.*, **76**, 5805 (1954); J. G. Gleason and D. N. Harpp, *Tetrahedron Lett.*, 3431 (1970); H. Staudinger, E. Anthes, and H. Schneider, *Chem. Ber.*, **46**, 3539 (1939); A. Roedig, N. Kreutzkamp, H. Meerwein, and R. Stroh, in "Methoden der Organischen Chemie," 4th ed, Vol. V/4, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1960, pp 197–212.

(9) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1276.

(10) For a discussion of the calculation of isotopic compositions by mass spectroscopy, see K. Biemann, "Mass Spectrometry, Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962.

(11) G. M. Whitesides, J. F. Gaasch, and E. R. Stedronsky, *J. Amer. Chem. Soc.*, **94**, 5258 (1972).

duction followed by lithium aluminum hydride reduction as described previously.[12]

1-Bromoethane-2,2,2-d_3, 1-bromobutane-2,2-d_2, and **1-bromobutane-2-d_1** were prepared from the analogous alcohols using a procedure similar to that described by Marvel and Kamm.[13] Thus, ethanol-2,2,2-d_3 (18 g, 0.36 mol) was added to a cooled mixture of 48% hydrobromic acid (82 g) and concentrated sulfuric acid (24 g) in a 250-ml single-necked flask. Concentrated sulfuric acid (40 g) was added, and the stirred mixture was warmed gently to distill the product as it formed into a trap cooled in a Dry Ice–acetone bath. The trap and its contents were warmed to 0° and the aqueous layer was removed using a Pasteur pipet. The organic layer was washed with two 10-ml portions of water and several 10-ml portions of concentrated sulfuric acid until the sulfuric acid layer remained clear and water white. Most of the sulfuric acid was removed using a Pasteur pipet, and the 1-bromoethane-2,2,2-d_3 (37 g, 0.33 mol, 91%) was separated from the residual concentrated sulfuric acid by bulb-to-bulb distillation at reduced pressure. The nmr of the distilled material consisted of a broadened singlet at δ 3.4.

1-Butanol-4,4,4-d_3 was prepared in 52% yield by reaction of ethyl-2,2,2-d_3-magnesium bromide with ethylene oxide, using a procedure analogous to that described by Huston and Langham.[14]

***n*-Propyl 2-Chloroacetate.**—*n*-Propyl alcohol (60 g, 1 mol) was placed in a 250-ml, three-necked, round-bottomed flask equipped with a dropping funnel, Teflon-coated magnetic stirring bar, and adaptor leading to a bubbler. The apparatus was flushed with nitrogen, and cooled to −15° in a Dry Ice–isopropyl alcohol bath. Chloroacetyl chloride (38 ml, 57 g, 0.5 mol) was added to the stirred reaction mixture over a period of 2 hr. The cooling bath was maintained at −20 to −10° by the occasional addition of Dry Ice. The mixture was allowed to warm to room temperature, then distilled through a 6-in. Vigreux column to yield *n*-propyl 2-chloroacetate (57.4 g, 0.42 mol, 84%): bp 75° (22 Torr) [lit.[15] bp 52.6–52.8° (10 Torr)]; nmr (CCl_4) δ 0.92 (t, 3, J = 6 Hz), 1.58 (m, 2, J = 6 Hz), 4.17 (m, 4, J = 6 Hz).

***n*-Propyl 2-bromoacetate** was prepared by a procedure analogous to that used in the synthesis of *n*-propyl 2-chloroacetate. From bromoacetyl bromide (100 g, 0.5 mol) and *n*-propyl alcohol (60 g, 1.0 mol), 67.8 g of *n*-propyl 2-bromoacetate (0.38 mol, 75%) was obtained: bp 79° (19 Torr) [lit.[16] bp 175–177° (762 Torr)]; nmr (CCl_4) δ 0.95 (t, 3, J = 6 Hz), 1.60 (m, 2, J = 6 Hz), 3.90 (s, 2), 4.07 (t, 2, J = 6 Hz).

***n*-Propyl Acetate-2-d_1.**—The experimental apparatus and procedure were similar to those described for ethyl butyrate-2-d_1. Zinc dust (32.7 g, 0.5 g-atom) was treated with 5 ml of deuterium oxide in a mixture of 60 ml of benzene and 100 ml of diglyme. After removal of the benzene and deuterium oxide, the reaction mixture was heated to 80°, and 5 ml of deuterium oxide, a crystal of iodine, and 2 ml of 1,2-dibromoethane were added. *n*-Propyl 2-chloroacetate (34.4 g, 0.25 mol) diluted with *ca.* 4 ml of 1,2-dibromoethane and additional deuterium oxide were added in 10 portions over 1 hr by syringe, *ca.* 1 ml of deuterium oxide being added after each 3.3-ml aliquot of ester; the total quantity of deuterium oxide used by the end of the reaction was 16.5 ml (15 g, 0.75 mol). The mixture was stirred and heated an additional 15 min. The apparatus was arranged for distillation and the first 35 ml of material distilling under an aspirator vacuum (~22 Torr) was collected. The distillate consisted of two phases; the aqueous phase was saturated with sodium chloride and extracted three times with 30-ml portions of ether. The organic phases were combined, dried ($MgSO_4$), and distilled through a 20-cm Nester-Faust Teflon spinning band column, yielding *n*-propyl acetate-2-d_1 (4.3 g, 0.042 mol, 17%): bp 100–102°; nmr (CCl_4) δ 0.92 (t, 3, J = 6 Hz), 1.52 (m, 2, J = 6 Hz), 1.92 (t, 2, J = 2 Hz), 3.95 (t, 2, J = 6 Hz).

n-Propyl acetate-2-d_1 (13.3 g, 0.13 mol, 52%) was also prepared from *n*-propyl 2-bromoacetate (45 g, 0.25 mol) using an analogous procedure.

Ethanol-2-d_1.—Lithium aluminum hydride (1.5 g, 0.04 mol) and ether (100 ml) were placed in a 250-ml, three-necked, round-bottomed flask equipped with a No-Air stopper, reflux condenser, and Teflon-coated magnetic stirring bar. To the stirred mixture was added dropwise through a syringe *n*-propyl acetate-2-d_1 (3.9 g, 0.038 mol) diluted with ether (15 ml). The mixture was refluxed an additional 2 hr, and water (1.5 ml), 15% (w:w) aqueous sodium hydroxide (1.5 ml), and additional water (4.5 ml) were cautiously added dropwise by syringe to the well-stirred slurry. The white aluminum salts were separated by suction filtration and washed with ether. The aluminum salts were then extracted overnight with an additional 50 ml of ether in a Soxhlet extractor. The ether portions were combined, dried ($MgSO_4$), and distilled to yield ethanol-2-d_1, (0.8 g, 0.017 mol, 45%), bp 78–79°.

1-Iodoethane-2-d_1 was prepared from ethanol-2-d_1 using a procedure based on that of Stone and Shechter,[17] and purified for isotopic analysis by preparative glpc using column C.

Diethyl 2-bromoadipate was synthesized in 77% yield using a literature procedure.[18] Its conversion to **diethyl adipate-2-d_1** was accomplished on a 30-g scale (58% yield) using a procedure analogous to that described for *n*-propyl acetate-2-d_1. **1,6-Hexanediol-2-d_1** and **1,6-dibromohexane-2-d_1** were obtained by procedures analogous to those described above for other alcohols and bromides.

Acetonitrile-d_1.—Zinc dust (43.5 g, 0.66 g-atom) was treated with 8 ml of deuterium oxide in a mixture of 100 ml of diglyme and 60 ml of benzene. After removal of the benzene and deuterium oxide by azeotropic distillation, 5 ml of deuterium oxide was added, the mixture was heated to 80°, and a crystal of iodine and 3 ml of 1,2-dibromoethane[19] were added. Chloroacetonitrile (18.8 g, 0.24 mol) and additional deuterium oxide (13 ml; the total quantity added was 18 ml, 20 g, 1 mol) were added in successive portions of 1 ml and 1.2 ml, respectively. The mixture was stirred and heated for an additional 15 min. The apparatus was arranged for distillation and the first 25 ml of material distilling under an aspirator vacuum (~22 Torr) was collected. Ether (20 ml) was added to this distillate, the organic layer was separated, and the aqueous layer was saturated with sodium chloride and extracted twice with 20-ml portions of ether. The organic fractions were combined, dried ($MgSO_4$), and distilled through a 20-cm Nester-Faust Teflon spinning band column to yield acetonitrile-d_1 (4.7 g, 0.11 mol, 47%), bp 81–82°, nmr δ 1.98 (t, J = 2 Hz).

Ethylamine-2-d_1.—Lithium aluminum hydride (4.5 g, 0.12 mol) and ether (100 ml) were placed in a 250-ml, three-necked, round-bottomed flask equipped with a reflux condenser and Teflon-coated magnetic stirring bar. One neck of the flask was fitted with a No-Air stopper. Acetonitrile-d_1 (4.6 g, 0.11 mol) diluted with ether (20 ml) was added dropwise from a syringe to the stirred mixture. After the mixture had refluxed an additional hour, the condenser top was fitted with an adaptor leading to a receiver cooled to −78°. Cautious addition of water (4.5 ml), 15% (w:w) aqueous sodium hydroxide solution (4.5 ml), and additional water (13.5 ml) resulted in the liberation of ethylamine-d_1, bp 17°, which condensed in the cold trap. Significant amounts of ether were also swept over. The cold ether solution of ethylamine-d_1 was treated with dry gaseous hydrogen chloride. Ethylamine hydrochloride, which precipitated as a fine white solid, was separated by filtration and dissolved in water (20 ml). The aqueous solution of the amine hydrochloride was transferred to a three-necked, 50-ml, round-bottomed flask equipped with a distillation take-off, and a Teflon coated magnetic stirring bar. One neck of the flask was fitted with a No-Air stopper. Addition of concentrated aqueous sodium hydroxide resulted in the liberation of ethylamine-d_1, which was swept into a receiver cooled with liquid nitrogen with a stream of nitrogen. The solid material in the receiver was contaminated with small amounts of water, but this impurity did not affect the mass spectral determination of the isotopic purity of the labeled ethylamine. Approximately 2.2 g (45%) of ethylamine-2-d_1 was obtained by this procedure.

Butyronitrile-2,2-d_2.—Zinc dust (65.4 g, 1 g-atom) suspended in a mixture of 125 ml of diglyme and 75 ml of benzene was treated with 8 ml of deuterium oxide using procedures described previously. After removing the initial charge of deuterium oxide and the benzene by azeotropic distillation, a Claissen adaptor and two 60-ml addition funnels were added to the apparatus. One funnel was charged with 36 ml of deuterium oxide (40 g, 2.0 mol), the other with 34.5 g (0.25 mol) of 2,2-

(12) G. M. Whitesides, E. J. Panek, and E. R. Stedronsky, *J. Amer. Chem. Soc.*, **94**, 232 (1972).

(13) C. S. Marvel and O. Kamm, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 25.

(14) R. C. Huston and C. C. Langham, *J. Org. Chem.*, **12**, 90 (1947).

(15) H. C. Brown and A. B. Ash, *J. Amer. Chem. Soc.*, **77**, 4019 (1955).

(16) A. I. Vogel, *J. Chem. Soc.*, 644 (1948).

(17) H. Stone and H. Shechter, *J. Org. Chem.*, **15**, 491 (1950).

(18) E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **70**, 3626 (1948).

(19) The elimination of the induction period by activation of the zinc is particularly important in obtaining satisfactory isotopic purities with nitriles.

dichlorobutyronitrile. Deuterium oxide (*ca.* 5 ml) was added, the mixture was heated to reflux, and 2 ml of 1,2-dibromoethane was added through the reflux condenser. Deuterium oxide and 2,2-dichlorobutyronitrile were added to the stirred mixture simultaneously at the rate of *ca.* 1 drop/sec, although the addition was stopped if the reaction became too vigorous. After addition was complete, the mixture was maintained at reflux for an additional 4 hr, cooled, and distilled at aspirator vacuum (~22 Torr). The first 60 ml of crude distillate was collected. The organic layer was separated from the aqueous layer, which was saturated with sodium chloride and extracted twice with 35-ml portions of ether. The organic fractions were combined, dried ($MgSO_4$), and distilled through a 20-cm Nester-Faust Teflon spinning band column to yield 13.5 g of butyronitrile-*2,2-d*$_2$ (0.19 mol, 76%): bp 116–118°; nmr δ 0.97 (t, 3, J = 6 Hz), 1.41 (q, 2, J = 6 Hz).

Buylamine-*2,2-d*$_2$.—Lithium aluminum hydride (2.85 g, 0.075 mol) and ether (100 ml) were placed in a 250-ml, three-necked, round-bottomed flask equipped with a No-Air stopper, reflux condenser, and Teflon-coated magnetic stirring bar. To the stirred mixture was added dropwise with a syringe 5.2 g (0.073 mol) of butyronitrile-*2,2-d*$_2$ diluted with ether (20 ml). The mixture was refluxed for an additional 2 hr and cooled, and water (2.8 ml), 15% (w:w) aqueous sodium hydroxide (2.8 ml), and additional water (8.4 ml) were cautiously added by syringe to the well-stirred slurry. The white aluminum salts were removed by suction filtration and washed with ether. The ether solution was dried ($MgSO_4$) and concentrated by rotary evaporation. A sample of the remaining yellow oil (~3.8 g, 70%) was purified by glpc on column C to yield a sample of butyronitrile-*2,2-d*$_2$ sufficiently pure for analysis by mass spectrometry.

***N*-Ethyl-*N*-phenyl-2-bromoacetamide** was prepared by a method analogous to that of Weaver and Whaley.[20] In a 1-l., three-necked, round-bottomed flask equipped with a mechanical stirrer and dropping funnel were placed 100 g of *N*-ethylaniline (0.84 mol) and 250 ml of 1,2-dichloroethane. The reaction vessel was cooled in a Dry Ice–isopropyl alcohol bath maintained between −20° and −30° and swept with nitrogen. Bromoacetyl bromide (85 g, 0.42 mol) was added from the dropping funnel to the well-stirred reaction mixture over a 4-hr period. At the conclusion of the reaction, the amine hydrochloride salts were separated by suction filtration and washed with 1,2-dichloroethane (50 ml). The filtrate was distilled at 22 mm to remove most of the 1,2-dichloroethane. The red liquid remaining was analyzed by glpc (column C) and nmr, and was found to contain a maximum of 80% (by weight) of *N*-ethyl-*N*-phenyl-2-bromoacetamide; almost all of the remaining 20% consisted of 1,2-dichloroethane. This crude material was used in the following step without further purification.

***N*-Ethyl-*N*-phenylacetamide-*2-d*$_1$** was prepared following procedures outlined above by reaction between zinc dust (32.7 g, 0.50 g-atom), *N*-ethyl-*N*-phenyl-2-bromoacetamide (~60 g of crude material, ~0.25 mol), and deuterium oxide (20 g, 1.0 mol) in 100 ml of diglyme. Following conventional work-up of the reaction mixture, the crude product was distilled through a 10-cm Vigreux column as an oily liquid, bp 82° (0.09 Torr), which solidified in the receiver. Recrystallization from warm ether yielded 14.8 g of *N*-ethyl-*N*-phenylacetamide-*2-d*$_1$ (0.09 mol, 36%): nmr δ 1.03 (t, 3, J = 6 Hz), 1.73 (*t*, 2, J = 2 Hz), 3.63 (q, 2, J = 6 Hz), 7.37 (m, 5).

***N*,*N*-Diethylaniline-*d*$_1$** was prepared by the reduction of *N*-ethyl-*N*-phenylacetamide-*2-d*$_1$ with lithium aluminum hydride using standard procedures.

(20) W. E. Weaver and W. M. Whaley, *J. Amer. Chem. Soc.*, **69**, 515 (1947).

Acetic acid-*d*$_n$ was prepared by reaction of zinc dust (32.7 g, 0.5 g-atom) suspended in 100 ml of diglyme with chloroacetyl chloride (28.2 g, 0.25 mol) and deuterium oxide (15.4 g, 0.75 mol) at 60°. The general procedure was that described previously; the chloroacetyl chloride and 9 ml of the deuterium oxide were added in nine portions during ~45 min to the reaction mixture. The apparatus was arranged for distillation and the first 40 ml of material distilling under an aspirator vacuum was collected. This crude distillate was carefully redistilled through a 20-cm Nester-Faust Teflon spinning band column, yielding a fraction boiling between 97 and 105°, as well as acetic acid-*d*$_n$ (5.4 g, 0.087 mol, 35%), bp 117–119°, nmr δ 1.98 (t, J = 2 Hz). The lower boiling fraction was saturated with sodium chloride and extracted three times with 30-ml portions of ether. The ether extracts were combined, dried ($MgSO_4$), and distilled through the spinning band column to yield an additional 2.5 g of acetic acid-*d*$_n$ (7.9-g total, 0.127 mol, 51%).[21]

Ethanol-*d*$_n$.—Sodium borohydride (3.65 g, 0.096 mol) and diglyme (20 ml) were placed in a 250-ml, three-necked, round-bottomed flask equipped with a No-Air stopper, Teflon-coated magnetic stirring bar, dropping funnel, and reflux condenser, with an adaptor leading to a mercury–acetone bubbler. The mixture was stirred for *ca.* 5 min, and a solution of acetic acid-*d*$_n$ (7.9 g, 0.127 mol) in diglyme (15 ml) was added slowly with a syringe. Frothing of the reaction mixture was evident during the addition. The reaction vessel was flushed with nitrogen, and boron trifluoride etherate (17.7 g, 0.125 mol) diluted with diglyme (20 ml) was added to the stirred reaction mixture from the dropping funnel over the course of 2 hr. The mixture was stirred an additional 0.5 hr and quenched with octyl alcohol (3 ml) and water (10 ml). The residual inorganic salts were removed by suction filtration and washed with ether (*ca.* 50 ml). The organic layer was separated and dried ($MgSO_4$), and the residue distilled through a 20-cm Nester-Faust Teflon spinning band column to yield ethanol-*d*$_n$ (4.2 g, 0.09 mol, 71%), bp 76–78°.

Acetone-*d*$_n$ was prepared by reduction of chloroacetone (21.6 g, 0.23 mol) with zinc powder (43.5 g, 0.67 g-atom) in diglyme using a procedure similar to that described previously. After removing the initial charge of deuterium oxide and benzene, the chloroacetone was added to the reaction flask, and the reaction mixture maintained at reflux temperature for 1 hr. After this time deuterium oxide (20 g, 1 mol) was added. The apparatus was arranged for distillation, and all material boiling below 150° was rapidly collected. This crude distillate was dried and redistilled to yield acetone-*d*$_n$ (8.4 g, 0.14 mol, 61%), having bp 56–57°.

This material was converted to isopropyl bromide for isotopic analysis by reduction to 2-propanol with lithium aluminum hydride, conversion to isopropyl tosylate, and treatment with calcium bromide in DMF.[22]

Registry No.—Ethylbutyrate-*2-d*$_1$, 13224-13-0; 1-butanol-*2-d*$_1$, 35223-78-0; 1-bromoethane-*2,2,2-d*$_3$, 7439-86-3; *n*-propyl 2-chloroacetate, 5396-24-7; *n*-propyl 2-bromoacetate, 35223-80-4; *n*-propyl acetate-*2-d*$_1$, 35223-81-5; ethanol-*2-d*$_1$, 1624-36-8; acetonitrile-*d*$_1$, 26456-53-1; ethylamine-*2-d*$_1$, 35223-83-7; butyronitrile-*2,2-d*$_2$, 35223-84-8; butylamine-*2,2-d*$_2$, 27847-12-7; *N*-ethyl-*N*-phenylacetamide-*2-d*$_1$, 35223-86-0; acetic acid-*2-d*$_1$, 35223-87-1; ethanol-*2-d*$_1$, 6181-08-4; acetone-*d*$_1$, 4468-52-4.

(21) A more efficient procedure for the synthesis of acetic acid-*d*$_2$ consists of the reaction of ketene with deuterium oxide: H. L. Mitchell, unpublished work.

(22) G. L. Jenkins and J. C. Kellett, *J. Org. Chem.*, **27**, 624 (1962).

A Case of Slow Nitrogen Inversion due to Intramolecular Hydrogen Bonding. Study of Slow Nitrogen Inversion in Diethyl 2-Aziridinylphosphonate from the Paramagnetic Induced Shifts in the Proton Magnetic Resonance Spectra Using Tris(dipivalomethanato)europium(III), and Solvent Shifts

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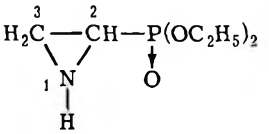
Retardation of pyramidal inversion of nitrogen was observed in diethyl 2-aziridinylphosphonate due to intramolecular hydrogen bonding. The presence of two invertomers has been shown by the nuclear magnetic resonance (nmr) studies using the paramagnetic shift reagent tris(dipivalomethanato)europium(III) [Eu(DPM)$_3$] and benzene solvent shift studies.

High barriers to pyramidal inversion of the nitrogen atom in aziridines has been proposed as early as 1939,[3] due to the strain in the three-membered ring. Since then several attempts have been made to resolve various substituted aziridines, without success.[3,4] However, the rates of nitrogen inversion in many derivatives of aziridine are measurable on the nmr time scale.[5] The temperature dependence of the nmr spectra of these aziridines have been used to calculate the activation parameters for nitrogen inversion.[5] Recently, diastereoisomeric forms of 1-chloro-2-methylaziridine have been separated by gas–liquid chromatography.[6] Similarly, separation of diastereoisomers of *N*-chlorocyclohexenimine by column chromatography has also been reported.[7] These reports suggest that some 1-haloaziridines will prove resolvable at room temperature. The slow inversion in *N*-haloaziridines has been attributed, besides the strain of the three-membered ring, to higher s character of the nitrogen lone pair due to the high electronegativity of the halogen substituent.[6,7] Conjugative destabilization by the repulsion between the nonbonding electron pairs of nitrogen and the halogen atom may also contribute to the enhancement of the barrier to inversion.[8] Synthesis of *N*-amino-[9] and *N*-methoxyaziridines[10a] and detection of very slow nitrogen inversion even at higher temperatures suggests that the presence of an adjacent heteroatom will decrease the rate of nitrogen inversion. So far the few examples of slow nitrogen inversion reported are in 1-substituted aziridines.[10b] Slow nitrogen inversion in aziridines without a substituent on nitrogen appears to have been reported in only one case.[10c]

This paper deals with the synthesis and nmr investigation of the aziridine **1**. Aziridine **1** has no substituent on nitrogen but has a structural feature which can contribute to the slow nitrogen inversion. This is the phosphoryl group at C-2, which can form an internal hydrogen bond with the hydrogen on nitrogen. This internal hydrogen bonding can be expected to be strong because it involves a five-membered ring as depicted in **2**. Evidence for the internal hydrogen bonding in



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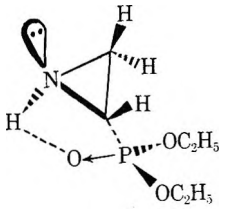

2

1 was obtained from ir studies. The ir spectrum of **1** in neat film showed two N–H stretching frequencies at 3450 and 3240 cm^{-1}. The peak at longer wavelength was attributed to the hydrogen-bonded N–H group. In the case of ethylenimine where no internal hydrogen bonding is possible, only one peak for N–H stretching is observed.[11] That the peak at 3240 cm^{-1} belongs to the internally bonded N–H was confirmed by ir dilution studies. The position of the band at 3240 cm^{-1} was found to be independent of concentration changes. Roberts and coworkers[4e,f] have shown that hydroxylic solvents decrease the rate of nitrogen inversion in the derivatives of aziridine. If that is the case, intramolecular hydrogen bonding, which will be stronger than a solvent–solute type hydrogen bonding, might decrease the rate of nitrogen inversion in the aziridine **1**.

(1) Research associate, 1969–1972.

(2) The senior author gratefully acknowledges support of this work by the Public Health Service, Cancer Institute, Grant CA 07202-09. This paper was presented in part at the 163rd National Meeting of The American Chemical Society, Boston, Mass., April 1972.

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(4) (a) T. L. Cairns, *J. Amer. Chem. Soc.*, **63**, 871 (1941); (b) H. M. Kissman and D. S. Tarbell, *ibid.*, **74**, 4317 (1952); (c) H. M. Kissman, D. S. Tarbell, and J. Williams, *ibid.*, **75**, 2959 (1953); (d) J. F. Kincaid and F. C. Henriques, Jr., *ibid.*, **62**, 1474 (1940); (e) A. T. Bottini and J. D. Roberts, *ibid.*, **78**, 5126 (1956); **80**, 5203 (1958), and references cited therein; (f) A. Loewenstein, J. F. Neumer, and J. D. Roberts, *ibid.*, **82**, 3599 (1960); (g) K. D. Berlin, S. Rengaraju, and P. E. Clark, *J. Heterocycl. Chem.*, **7**, 1095 (1970).

(5) M. Jautelat and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 642 (1969), and references cited therein.

(6) S. J. Brois, *ibid.*, **90**, 508 (1968).

(7) D. Felix and A. Eschenmoser, *Angew. Chem.*, **80**, 197 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 224 (1968).

(8) F. A. L. Anet, R. D. Trepka, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 357 (1967).

(9) S. J. Brois, *Tetrahedron Lett.*, 5997 (1968).

(10) (a) S. J. Brois, *J. Amer. Chem. Soc.*, **92**, 1079 (1970); (b) for a general review, see J. B. Lambert, "Topics in Phosphorus Chemistry," N. L. Allinger and E. L. Eliel, Ed., Vol. 6, Wiley, New York, N. Y., 1971; (c) T. J. Bardos, C. Szantay, and C. K. Navada, *J. Amer. Chem. Soc.*, **87**, 5796 (1965).

(11) R. W. Mitchell, J. C. Burr, Jr., and J. A. Merritt, *Spectrochim. Acta*, **23A**, 195 (1967).

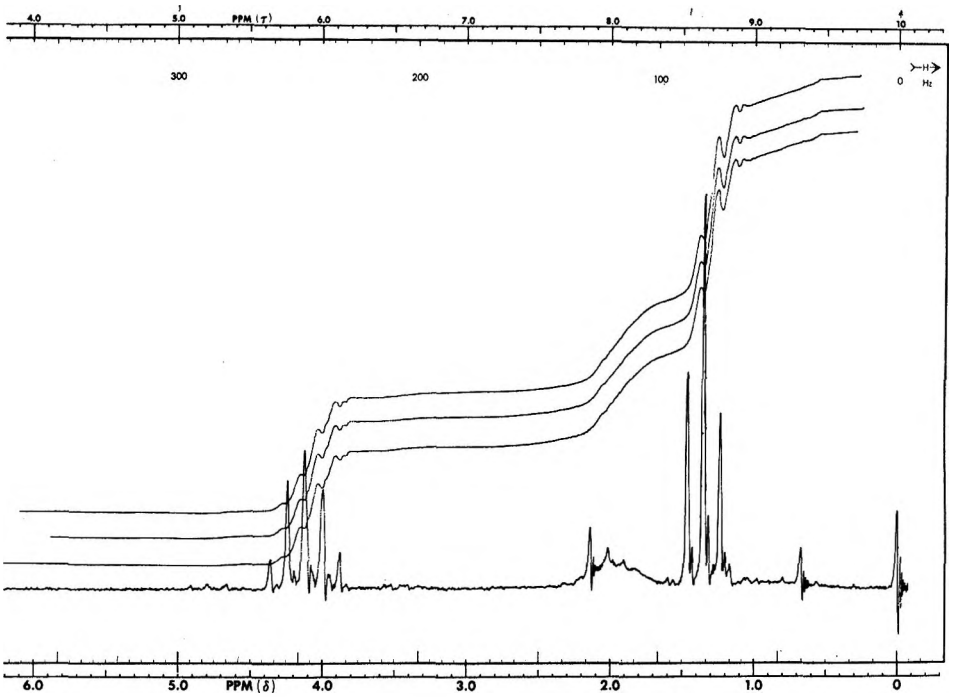
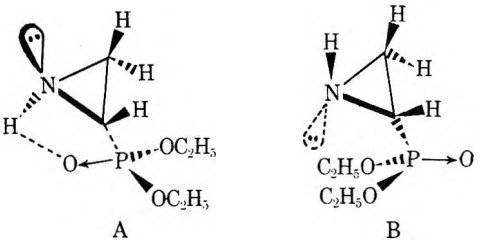


Figure 1.—60-MHz spectrum of diethyl 2-aziridinylphosphonate in $DCCl_3$.

The nmr spectrum of the aziridine **1** at 60 MHz in $DCCl_3$ (Figure 1) showed the aziridine ring protons as an envelope of unresolved peaks between δ 1.5–2.3. Analysis at 100 MHz also did not resolve the ring protons. In the 60-MHz spectrum methylene protons of the $P(O)(OC_2H_5)_2$ group displayed a quintet (due to common overlap of the two quartets arising from P–O–C–H coupling) at δ 4.12 (J = 7 Hz). The methyl protons absorbed at δ 1.35 as a triplet (J = 7 Hz). The presence of a smaller triplet at δ 1.33 indicated the presence of both invertomers of aziridine **1**. Further proof was obtained by the study of nmr spectra in $DCCl_3$ in the presence of paramagnetic shift reagent tris(dipivalomethanato)europium(III) [Eu(DPM)$_3$].

Eu(DPM)$_3$ has been used to effect paramagnetic induced shifts in the nmr spectra of alcohols.[12] Recently we have used this reagent in the study of syn–anti isomerism in oximes.[13] It was shown that the coordination of the Eu(DPM)$_3$ takes place on the oxime nitrogen lone pair and there is a steric effect in the coordination. This steric effect was useful in the analysis of syn–anti isomerism in oximes since the steric environments of the lone pair of electrons differs in the syn–anti forms of the oximes studied. Since syn–anti isomerism in oximes is due to an extreme case of high barrier to inversion of nitrogen lone pair, it is logical to expect similar paramagnetic induced shifts in the case of a slowly inverting aziridine.

In the case of aziridine **1**, the two invertomers can be represented as A and B. Intramolecular hydrogen bonding can take place between the N–H band P→O groups in invertomer A owing to the favorable cis arrangement of these groups. This will stabilize this form. In the invertomer B, unfavorable trans arrangement of N–H and P→O groups for intramolecular hydrogen bonding and the repulsion between the nitrogen lone pair and P→O group could make this invertomer less stable compared to A.



The nmr spectrum of the aziridine **1** in $DCCl_3$ (89 mg in 0.4 ml) containing 20 mg of Eu(DPM)$_3$ showed peaks corresponding to two invertomers A and B (Figure 2). A triplet at δ 1.37 (J = 7 Hz, OCH_2CH_3), unresolved multiplets approximately between 1.8 and 2.6 (aziridine ring protons), and a quintet (an overlap of two quartets due to P–O–C–H coupling in O←P-OCH_2) at 4.21 (J = 7 Hz, O←$POCH_2CH_3$) were attributed to the invertomer B. Corresponding peaks for the invertomer A are two triplets at δ 1.65 and 1.68 (J = 7 Hz, O←$POCH_2CH_3$), four partially resolved multiplets between 3.1 and 3.9 (aziridine ring protons), and two partly overlapping quintets at 4.8 and 4.87 (J = 7 Hz, O←$POCH_2CH_3$). The doubling of the signals for the methyl protons (δ 1.65 and 1.68) and methylene protons (4.8 and 4.87) of the OC_2H_5 group is attributed to the nonequivalence of the ethoxy groups due to restricted rotation of the C–P bond and the presence of the asymmetric center in invertomer A.

By increasing the concentration of the shift reagent Eu(DPM)$_3$, further downfield shifts of all the peaks of the invertomer A were observed as expected (Figure 3). However, overlap of ring methylene proton signals of invertomer A and the ethoxy methylene proton signals of the invertomer B occurs. The optimum concentration of Eu(DPM)$_3$ to observe all the peaks

(12) (a) C. C. Hinkley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969); (b) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *ibid.*, **92**, 5734, 5737 (1970); (c) J. K. M. Sanders and D. H. Williams, *Chem. Commun.*, 422 (1970).

(13) K. D. Berlin and S. Rengaraju, *J. Org. Chem.*, **36**, 2912 (1971).

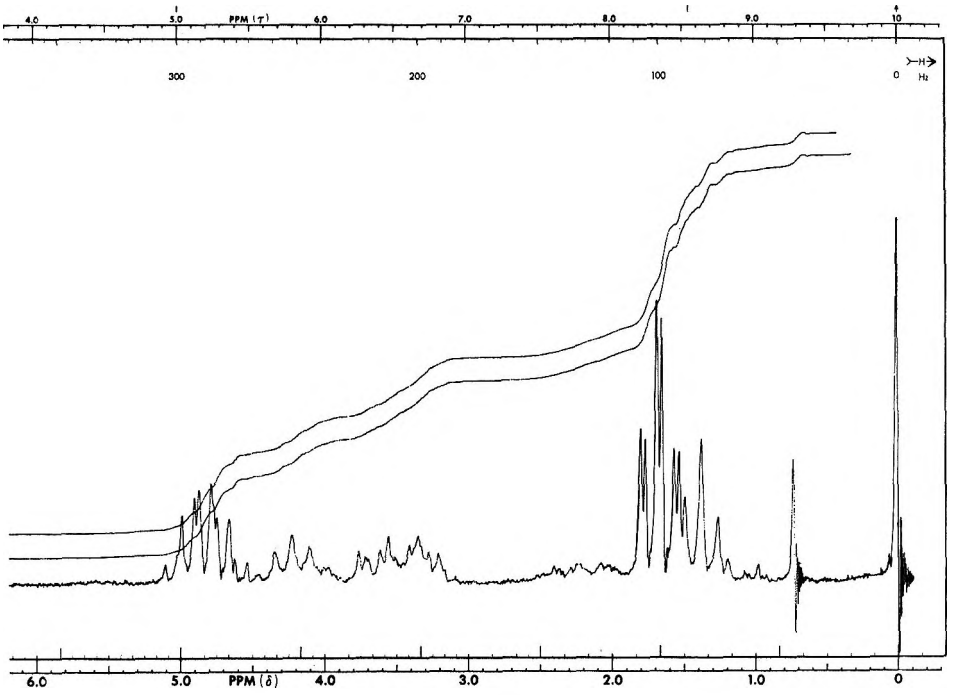


Figure 2.—60-MHz spectrum of diethyl 2-aziridinylphosphonate (0.0005 mol) in 0.4 ml of $DCCl_3$ containing 20 mg of $Eu(DPM)_3$.

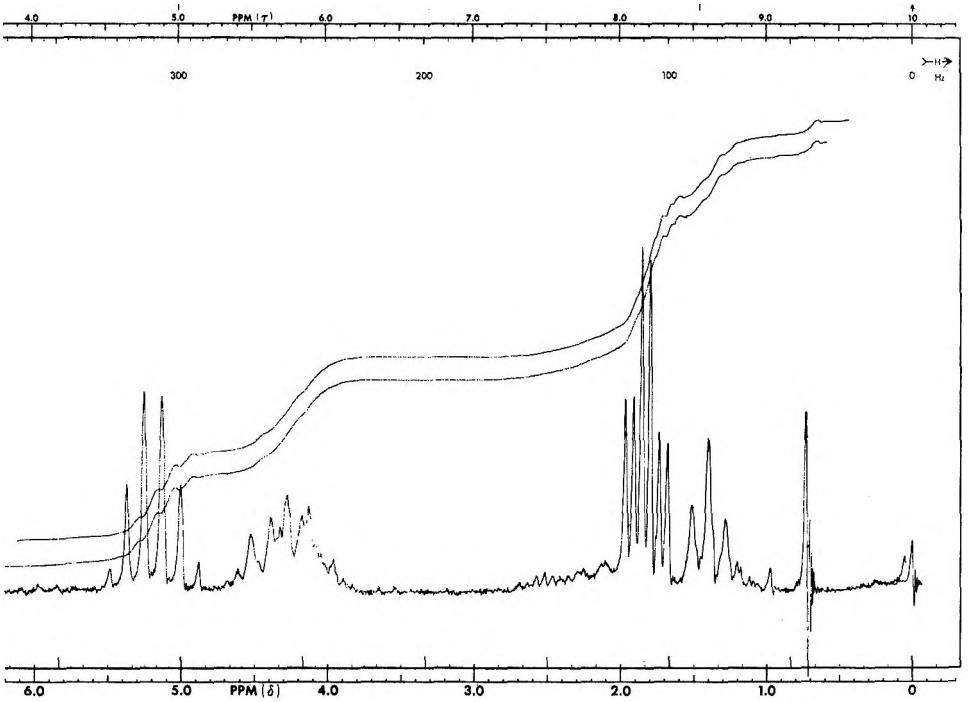
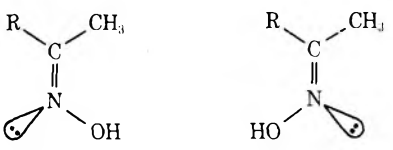


Figure 3.—60-MHz spectrum of diethyl 2-aziridinylphosphonate (0.0005 mol) in 0.4 ml of $DCCl_3$ containing 30 mg of $Eu(DPM)_3$.

of both invertomers was found to be 20 mg in a solution of 89 mg of **1** in 0.4 ml of $DCCl_3$.

One significant observation is that peaks of the invertomer B (compare Figures 1–3) did not significantly shift on addition of 20 or 30 mg of $Eu(DPM)_3$. This can be explained on the basis that there is little coordination of $Eu(DPM)_3$ with the nitrogen lone pair in the invertomer B due to steric hindrance of the bulky $O\leftarrow P(OC_2H_5)_2$ group. Similar steric interference to coordination was observed in our study of syn–anti isomerism in oximes.[13] In the syn form of the oximes studied, coordination with the lone pair was not so effective as in the anti form owing to steric hindrance from the bulky alkyl groups (R). From the ratio of the corresponding peaks for both invertomers A and B, the invertomer ratio was calculated as 3:1 (A:B).



syn anti

R = C_2H_5, $CH_3(CH_2)_2$, $CH_3(CH_2)_4$, $CH_3(CH_2)_5$, $(CH_3)_2CH$, $(CH_3)_2CHCH_2$

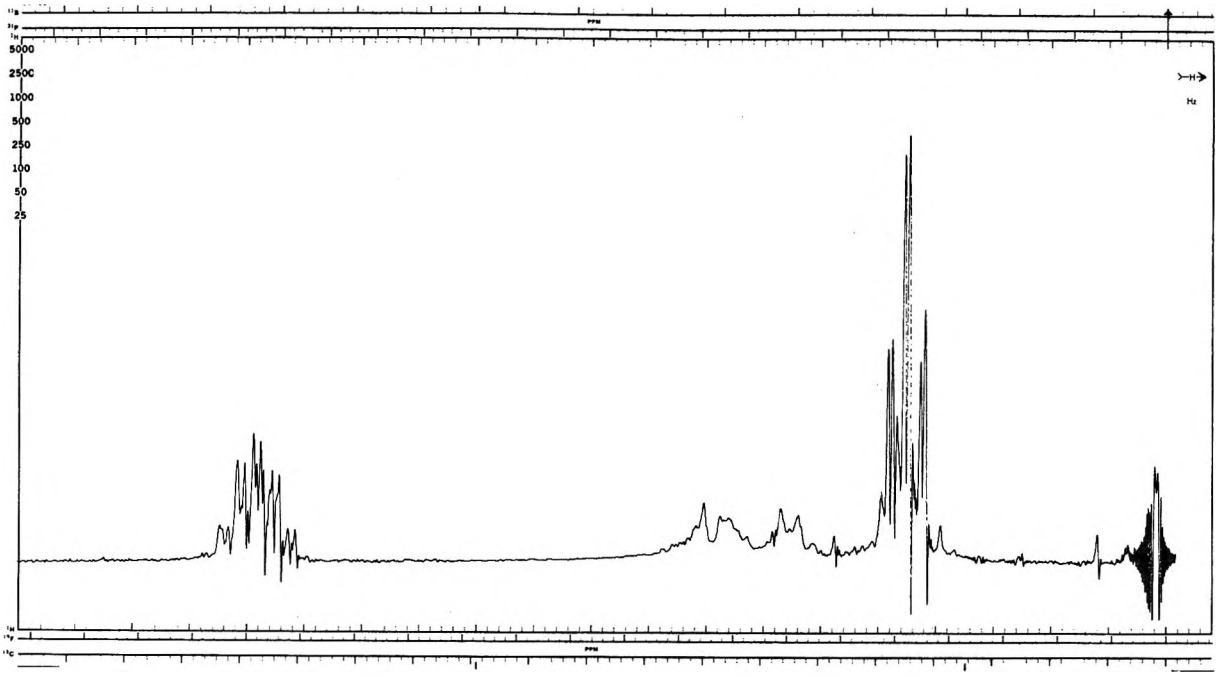


Figure 4.—100-MHz spectrum of diethyl 2-aziridinylphosphonate in benzene.

In the invertomer A the value of paramagnetic induced shift [$\Delta\delta$, $\Delta\delta$ = δ with Eu(DPM)$_3$ − δ without Eu(DPM)$_3$] decreased in the order aziridine ring protons > methylene protons of P(O)(OEt$_2$) > methyl protons of P(O)(OEt)$_2$, in all the three concentrations studied (Table I). This order suggests that the coordination of europium takes place with the nitrogen lone pair on the basis that shifts for protons close to the point of association are larger than those protons further removed.[12] A comparison of the Eu(DPM)$_3$-induced shifts for aziridines and related (but open chain) phosphonates shows that the shifts are very high in the case of aziridines (Table II). This may be attributed to the high basicity of the nitrogen lone pair in aziridines. It is known that Eu(DPM)$_3$-induced shifts are higher for amines compared to alcohols and ethers.[12c] Eu(DPM)$_3$-induced shifts for the phosphonates **6**–**10** can be explained on the basis of coordination of europium with P→O group. In the phosphonates **8**–**10**, since protons nearer to the P→O group are more shifted on addition of Eu(DPM)$_3$ than the protons nearer to the nitrogen atom, coordination of europium may occur with the P→O group. The coordination at the nitrogen lone pair in the phosphonates **8** and **10** may be less favorable owing to the probable lowered basicity of the nitrogen in view of its bonding to more electronegative elements. In **9** a steric effect around the nitrogen atom may reduce its complexing ability. The observation that europium coordinates with the P→O group in the phosphonates **6**–**10** suggests a possible bidendate arrangement of europium with the aziridine nitrogen and P→O group in **1**. This could also explain the high induced shifts in **1**.

TABLE I

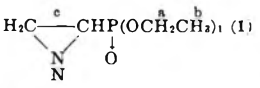
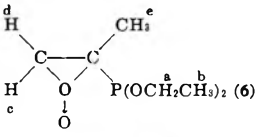
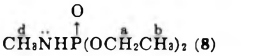
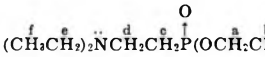
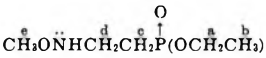
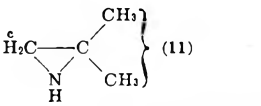
$\Delta\delta$ VALUES FOR THE INVERTOMER A

Wt of Eu(DPM)$_3$,[a] mg	$\Delta\delta_{CH_3}$	$\Delta\delta_{CH_2}$	$\Delta\delta$ ring protons
10	0.16	0.35	0.78
20	0.34	0.70	1.55
30	0.5	1.05	2.3

[a] In a solution of 89 mg of aziridine **1** in 0.4 ml of $DCCl_3$.

TABLE II

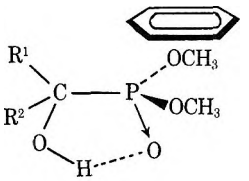
PARAMAGNETIC SHIFTS[a]

Substrate	$\Delta\nu^a$	$\Delta\nu^b$	$\Delta\nu^c$	$\Delta\nu$ (other protons)
 (1)	42	20	~90	
 (6)	19	7	21	9 (d), 12.5 (e)
 (7)	26	11	25	14 (d)
 (8)	25	12		13 (d)
 (9)	24	9	~20	~13 (d), 3.5 (e), 2 (f)
 (10)	24.5	9.5	22	27 (d), 4 (e)
 (11)			73	55 (e)

[a] $\Delta\nu$ (Hz), observed with 20 mg of Eu(DMP)$_3$ in a solution of 0.005 mol of substrate in 0.4 ml of $DCCl_3$.

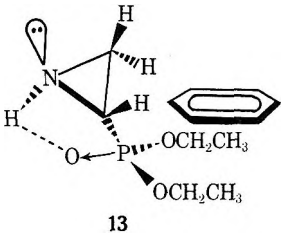
The pmr spectrum of **1** in benzene (10% solution w/v) (Figure 4, 100 MHz spectrum) showed an interesting solvent effect. For example, in $DCCl_3$ the CH_3 of P(O)(OCH$_2$CH$_3$)$_2$ gave a triplet centered at δ 1.35 corresponding to the invertomer A and a smaller triplet at 1.33 corresponding to the invertomer B. However, in benzene as solvent an upfield shift of both the triplets occurs. In addition doubling of the triplet corresponding to the invertomer A was also observed (Figure 4).

The solvent shifts in an anisotropic solvent like benzene for different type of compounds have been explained on the basis of equilibrium formation of collision complexes between the benzene molecule and a polar functional group in the solute.[14] Benzene-induced shifts for two slowly inverting aziridines have been suggested in the literature.[15] It was observed that the upfield shift is more sensitive to the protons trans to the oriented nitrogen lone pair than to those which are cis oriented. Thus a model for the collision complex was proposed in which the benzene-solvent molecule occupies a position as far away as possible at the opposite side of the nitrogen lone pair.[15] In the present case, the benzene-induced shifts (going from $DCCl_3$ to C_6H_6, $\Delta = \delta_{DCCl_3} - \delta_{C_6H_6}$) for the methyl group in invertomer A and B are 0.27 (measured from the center of the two triplet for invertomer A at δ 1.09 and 1.075) and 0.21 ppm, respectively. The higher shift in invertomer A can be explained because of the trans arrangement of the nitrogen lone pair and the $P(O)(OCH_2CH_3)_2$ group. In the invertomer B, the arrangement is cis. The doubling of the triplet in invertomer A occurs because of the presence of an asymmetric center in the molecule and restricted rotation around the C–P bond owing to internal hydrogen bonding. Benzene-induced upfield shifts have also been reported in the case of several dimethyl alkylphosphonates.[16] In these phosphonates, where the $P(O)(OCH_3)_2$ group is attached to an asymmetric center, a different solvent shift was noted for the two methyl groups resulting in a peak doubling. A model for the benzene substrate complex as shown in **12** has been proposed where a benzene molecule occupies a position perpendicular to the P→O group and as far away from the negative end of the P→O dipole.



12

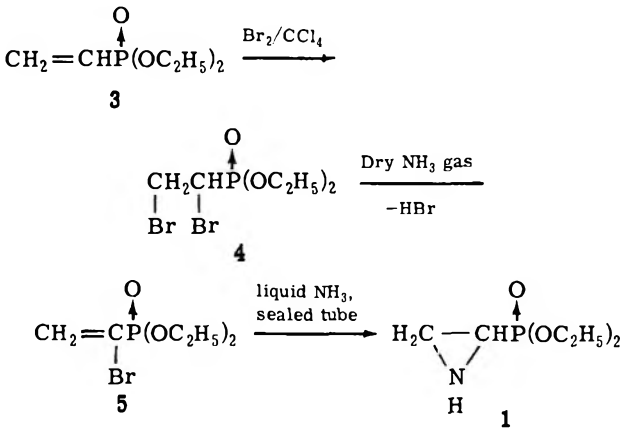
In the present system **1**, we propose a model for the complex in which the benzene molecule occupies a similar position as in **12** but as far away from the nitrogen lone pair as shown in **13** (representation for invertomer A). This model explains the higher upfield shift (0.27 ppm) for invertomer A due to the trans stereochemistry of the nitrogen lone pair and the $P(O)(OCH_2CH_3)_2$ group, compared to the invertomer B (0.21 ppm) where the stereochemistry is cis.



13

To observe the effect of heating on the invertomer ratio of aziridine **1**, variable high temperature nmr spectra was recorded up to 110° with neat sample of **1**, where only a slight increase in the amount of invertomer B was observed.

The synthesis of aziridine **1** was carried out according to the following scheme. While the synthesis was in progress in our laboratories, a patent[17] on the



synthesis of **1** appeared in the literature. Bromination of diethyl vinylphosphonate (**3**) using bromine in CCl_4 gave the crude dibromo compound **4** in theoretical yield. The crude product was at least 95% pure as shown by nmr. However, distillation of **5** results in partial decomposition. It was found convenient to purify the vinyl bromide **5**, which was obtained by passing dry ammonia gas through the dibromo compound **4**. The yield of pure vinyl bromide from crude **4** was 86–88% depending upon the purity of **4**. Reaction of vinyl bromide **5** with liquid ammonia in a sealed tube at room temperature gave the aziridine **1** in varying yields of 56–62%. In the case of aziridine **1** also partial polymerization was observed upon distillation. However, preliminary purification of the crude aziridine **1** by chromatography over neutral alumina before distillation reduced the degree of polymerization.

Owing to the difference in the hydrogen bonding in the two invertomers A and B, some solubility difference in solvents might be expected for the two forms. Thus, repeated extraction of aziridine **1** with hexane gave a hexane-soluble portion which contained more of invertomer B (ratio of A:B decreased from 3:1 to 3:2) compared to the starting mixture (Figure 5; *cf.* with Figure 2). However, a complete separation of the two forms could not be affected by all standard techniques attempted. Although invertomers A and B behave like rather special geometric isomers, the similarity in adsorption ability on substrates for chromatography and in solubility undoubtedly contributes to the separation problem. Work is continuing in the area.

Experimental Section

General and Spectra.—Infrared spectra of thin films were recorded on a Beckman IR-5A. Dilution studies to detect intramolecular hydrogen bonding in **1** were carried out in CCl_4 solutions using a Beckman IR-7 instrument. Nmr spectra were

(14) N. S. Blacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, Chapter 7.

(15) T. Yonezawa, I. Morishima, and K. Fukuta, *Bull. Chem. Soc. Jap.*, **41**, 2297 (1968).

(16) C. Benezra and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2270 (1966).

(17) Merck and Co., Inc., German Patent 2,011,092 (Sept 17, 1970); *Chem. Abstr.*, **74**, 42491u (1971).

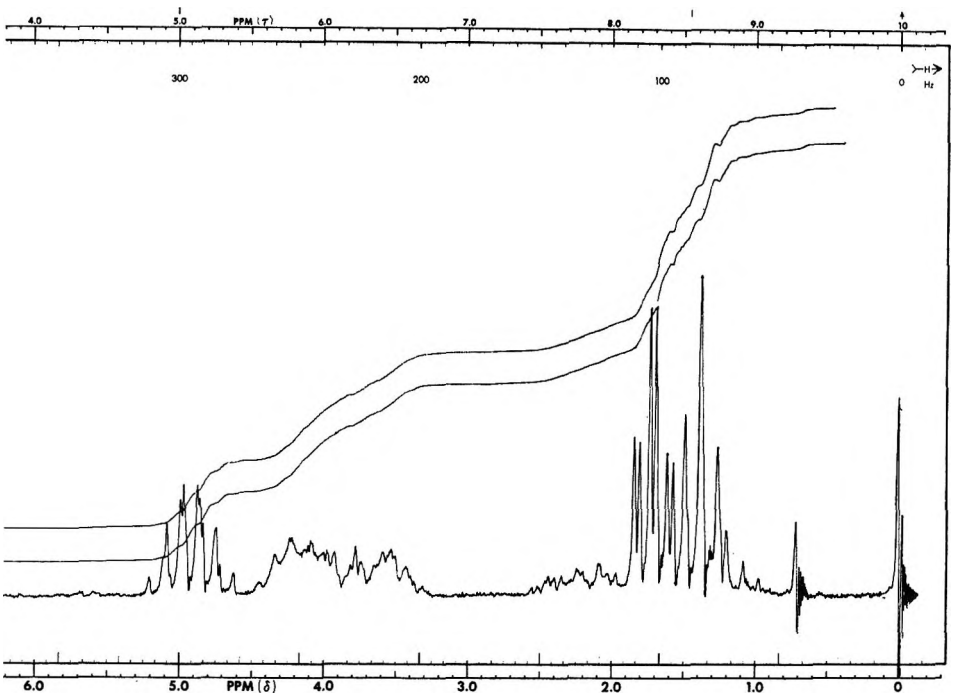


Figure 5.—60-MHz spectrum of diethyl 2-aziridinylphosphonate (hexane-soluble portion) (0.0005 mol) in 0.4 ml of $DCCl_3$ containing 20 mg of $Eu(DPM)_3$.

obtained on a Varian A-60 spectrometer, with TMS as internal standard while 100-MHz spectra were run on a Varian XL-100 spectrometer with TMS as internal standard. The shift reagent tris(dipivalomethanato)europium(III) was purchased from Norell Chemical Co., Inc. Diethyl vinylphosphonate (**3**) and diethyl 2-diethylaminoethylphosphonate (**9**) were prepared by the method of Kosolapoff.[18] 2,2-Dimethylaziridine (**11**) was prepared according to the known procedure.[19]

Diethyl 1,2-Dibromoethylphosphonate (**4**).—To a solution of diethyl vinylphosphonate (**3**, 16.4 g, 0.1 mol) in dry carbon tetrachloride (100 ml), dry bromine (19.2 g, 0.12 mol) in CCl_4 (100 ml) was added at 50° in the course of 90 min. After the addition was over, the reaction mixture was maintained at 60° for 8 hr. Evaporation of CCl_4 gave 32.3 g (theoretical) of **4**. The nmr spectrum of crude **4** did not show any impurities. An analytical sample was prepared by distillation under vacuum: bp 128–129° (2 mm); $n^{29}D$ 1.4861 [lit.[20] bp 123–125° (3 mm), $n^{20}D$ 1.4943]; ir (film) 1260 cm^{-1} (P→O); nmr (CCl_4) δ 1.35 (t, 6, J = 7 Hz, CH_3) and 4.17 [m, $P(O)OCH_2$] and the multiplets of C-1, C-2 hydrogens appeared as overlapping peaks with the $P(O)OCH_2$ methylene hydrogen. The area under these multiplets corresponded to seven hydrogens.

Diethyl 1-Bromovinylphosphonate (**5**).—A slow stream of dry ammonia gas was passed through **4** (32.4 g, 0.1 mol) with cooling in ice water until no more ammonium bromide precipitated out (about 45 min). The ammonium bromide was filtered off, and it was washed with 300 ml of benzene. The filtrate and washings were rinsed and washed with water and dried ($MgSO_4$). Evaporation of benzene gave 24 g of crude **6**, which was distilled under reduced pressure to give a single fraction of pure **5** (21.4 g, 88%): bp 65–66° (0.1 mm); $n^{28}D$ 1.4579 [lit.[19] bp 88–90° (3 mm); $n^{20}D$ 1.4681]; ir (film) 1585 (C=C), 1257 cm^{-1} (P→O); nmr (neat) δ 1.32 (t, J = 7 Hz, CH_3), 4.08 [m, $P(O)CH_2$], 6.45 [2 m, 1, J_{PH} = 37 Hz, vinyl proton trans to $P(O)(C_2H_5)_2$ group], and 6.8 [2 m, 1, J_{PH} = 14 Hz, vinyl proton cis to $P(O)(C_2H_5)_2$ group].

Diethyl 2-Aziridinylphosphonate (**1**).—A mixture of diethyl 1-bromovinylphosphonate (**5**, 12.15 g 0.05 mol) and 15 ml of liquid ammonia was allowed to react at room temperature in a sealed tube for 18 hr. The sealed tube was opened and the ammonia was evaporated off. The aziridine **1** was then dissolved in 100 ml of chloroform and the ammonium bromide filtered off. The chloroform solution, on evaporation, gave 8.84 g of crude reaction product. Extensive polymerization took place if distillation was attempted. Initial purification by passing the crude aziridine **1** (8.84 g) in chloroform through a column of neutral alumina (200 g, activity I) gave 6.8 g of aziridine **1**, which was further purified by vacuum distillation: bp 72° (0.15 mm); yield 5.55 g (62%); $n^{28}D$ 1.4451; ir (film) 3450 (NH free), 3240 (intramolecularly hydrogen bonded NH), and 1240 cm^{-1} (P→O); nmr ($DCCl_3$) δ 1.35 (t, 6, J = 7 Hz, CH_3), unresolved multiplets between δ ~1.5 and 2.3 (4, aziridine ring protons), and 4.12 [m, 4, J = 7 Hz, $P(O)OCH_2$].

Anal. Calcd for $C_6H_{14}O_3PN$: N, 7.82; P, 17.32. Found: N, 7.68; P, 17.12.

Diethyl 1-Methylepoxyethylphosphonate (**6**).—A solution of diethyl phosphite (27.6 g; 0.2 mol) in 50 ml of dry dimethylformamide was added very slowly to avoid frothing to a suspension of sodium hydride (5.3 g; 0.22 mol) in 300 ml of dimethylformamide with mechanical stirring and cooling in ice cold water under N_2. After the addition was completed, the mixture was heated at a water bath for 30 min when the evolution of hydrogen stopped. To this sodium salt of diethyl phosphite, α-chloroacetone (18.5 g; 0.2 mol) was added in the course of 45 min with mechanical stirring. After the addition, the reaction mixture was heated on a water bath for 3 hr. About 200 ml of DMF was removed under aspirator and the residue was diluted with 1.2 l. of water. The water solution was extracted with chloroform (1.5 l.) and the $HCCl_3$ extract was washed with water and dried ($MgSO_4$). Evaporation of $HCCl_3$ gave 31 g of crude reaction product, which upon distillation (using a 10 in. Vigreux column), gave **6**: bp 69–70° (0.1 mm) (19.5 g, 50%); $n^{23}D$ 1.4306; ir (film) 1260 (P→O), 850 cm^{-1} (oxirane ring); nmr (neat) δ 1.28 (t, 6, J = 7 Hz, CH_3CH_2O), 4.07 (m, 4, J = 7 Hz, CH_3CH_2O), 1.4 (d, 3, J = 10.5 Hz, CH_3 on the epoxide ring).

Anal. Calcd for $C_7H_{15}O_4P$: C, 43.30; H, 7.73. Found: C, 42.99; H, 7.57.

Diethyl 2-Aminomethoxyethylphosphonate (**10**).—To an alcoholic solution of methoxyamine [generated by treating methoxyamine hydrochloride (5.01 g; 0.06 mol) with alcoholic KOH (3.65 g, 0.065 mol in 25 ml of C_2H_5OH) and filtering off the KCl], diethyl vinylphosphonate (**3**, 3.28 g, 0.02 mol) was added, and the mixture was heated at 50–60° for 4 days. Alcohol was removed under aspirator vacuum and the residue was diluted with 100 ml of water. The aqueous solution was then extracted with $HCCl_3$ (3 × 50 ml) and the $HCCl_3$ extract was washed (H_2O) and dried ($MgSO_4$). Evaporation of solvent gave crude **10**, which was

(18) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **70**, 1971 (1948).

(19) K. N. Campbell, A. H. Sommers, and B. K. Campbell, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 148.

(20) M. I. Kabachnik and T. Ya Medred, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2142 (1959); *cf. Chem. Abstr.*, **54**, 10834*f* (1960).

distilled to give a single fraction: bp 79° (0.05 mm) (2.11 g, 50%); $n^{23}D$ 1.4361; ir (film) 3220 and 3450 (NH), and 1240 cm^{-1} (P→O); nmr ($DCCl_3$) δ 1.32 (OCH_2CH_3), two triplets at 1.85 and 2.15 (CH_2 adjacent to P→O, J_{HH} = 7 Hz and J_{PCH} = 18 Hz), two triplets at 3.04 and 3.13 (CH_2 adjacent to NH, J_{HH} = 7 Hz and J_{PCCH} = 13 Hz), 3.47 (s, $NHOCH_3$), and 4.08 (m, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_7H_{18}NO_4P$: P, 14.70; N, 6.63. Found: P, 14.61; N, 6.46.

Registry No.—**1**, 35212-68-1; **6**, 1445-84-7; **7**, 5324-30-1; **8**, 6326-73-4; **9**, 3958-23-4; **10**, 35212-72-7; **11**, 2658-24-4; tris(dipivalomethanato)europium(III), 15522-71-1.

Anisyl Neighboring-Group Participation in Carbonium Ion Formation in Antimony Pentafluoride and Sulfur Dioxide

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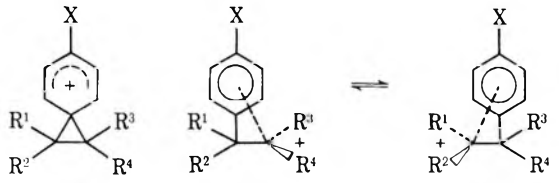
Received January 7, 1972[4]

A study by nmr spectroscopy of the carbonium ions formed in $SbF_5 \cdot SO_2$ at −60° from p-$CH_3OC_6H_4CR_2CR_2X$, p-$CH_3OC_6H_4CR_2(CH_2)_3X$, and o-$CH_3OC_6H_4CH_2CH_2X$ was carried out where each R was varied systematically from H to methyl and X was halogen, mesylate, or OH. Except for p-$CH_3OC_6H_4CH_2CH_2X$, only benzylic ion formation was observed. Where X left from a primary carbon at −60° anisyl migration occurred prior to benzylic ion formation. Where OH_2^+ (or $^+OHSbF_5^-$) leaves from a secondary carbon, D or CD_3 labeling established that less than 60% of the product ion formed could be derived from β-anisyl migration from a secondary or tertiary origin. It was suggested that β-anisylcarbonium ions formed without specific solvation at the carbonium ion center or anisyl participation probably rearrange to benzylic ions much faster than anisyl migration occurs. The activation energy (6 kcal/mol) for equilibration of all alkyl methyl groups in p-$CH_3OC_6H_4CMeCMe_3^+$ was determined. The o-anisylethyl chloride forms the corresponding oxonium ion in $SbF_5 \cdot SO_2$ rather than an ortho anisonium or benzylic ion. There is no evidence of anisyl participation in the formation of benzylic ions from p-$CH_3OC_6H_4(CH_2)_4X$ or p-$CH_3OC_6H_4CMe_2(CH_2)_3X$ in $SbF_5 \cdot SO_2$ at −60°.

Because of our previous success[5] in generating and studying simple alkoxycarbonium ions in strong acid solutions, we became interested in another group of alkoxy-stabilized carbonium ions more commonly known as anisonium ions, or methoxy-stabilized phenonium ions, **1** (X = OCH_3). Phenonium ions have been



regarded[6] by many, though not all, as being intermediates in the normal solvolysis reactions of β-arylalkyl primary and secondary halides, tosylates, etc. The well-established[5,7] thermodynamic stability of alkoxycarbonium ions and ability of the p-anisyl group to enhance the solvolysis rates[6b,8] even in systems where anchimeric assistance by other β-aryl groups was contended, seemed when this work was initiated to make the anisyl system ideal for observing phenonium ions directly by spectroscopic means.

Further, it has been demonstrated[9] that apparent discrepancies between observed product ratios and titrimetric rates in β-arylalkyl solvolysis reactions disappear if the reaction rate is treated as a sum of the rates of a neighboring aryl-assisted reaction proceeding through a phenonium ion intermediate (rate constant k_Δ) and either a solvent-assisted rate (k_s) or alternatively[9d] simply unassisted ionization in secondary derivatives as originally proposed by Winstein. The observed rate constants then are k_Δ, corrected by a factor (F) for internal return, plus k_s, *i.e.*, $k_{tit} = Fk_\Delta + k_s$. The success of this treatment does not necessarily mean that k_Δ leads to a phenonium ion intermediate or transition state; a π complex ion (transition state), or ion pair, can yield the same rate expression.

Schleyer[10] argues that in the solvolysis of secondary alkyl tosylates, etc., participation by solvent in the ionization must be very strong and there is no "leakage" or conversion between phenonium ion and the solvent-complexed classical ion. This mechanism accounts for the much larger rate enhancements by β-aryl groups of solvolysis reactions in trifluoroacetic acid, a relatively weak nucleophilic solvent. *Extrapolating this solvent effect model to $SbF_5 \cdot SO_2$ would lead to the expectation that the process characterized by k_Δ would be the only significant ionization process in this solvent system.* Further, in $SbF_5 \cdot SO_2$ we can expect carbonium

(1) Department of Chemistry, California State University, San Francisco, Calif. 94132.

(2) Supported in part by the National Institute of Mental Health.

(3) (a) Taken in part from the Ph.D. theses of James A. Cook, Jr., and James A. Manner. (b) PPG Industries Fellows.

(4) Manuscript originally received by *J. Amer. Chem. Soc.*, Aug 1970.

(5) B. G. Ramsey and R. W. Taft, *J. Amer. Chem. Soc.*, **88**, 3058 (1966).

(6) (a) H. C. Brown, K. J. Morgan, and F. J. Chloupek, *ibid.*, **87**, 2137 (1965). (b) H. C. Brown and C. J. Kim, *ibid.*, **90**, 2082 (1968), suggested replacing phenonium ions in most cases by rapidly equilibrating π-bridged β-arylalkyl cations, or more recently ion pairs. (c) H. C. Brown and C. J. Kim, *ibid.*, **93**, 5765 (1971). (d) D. J. Cram, *ibid.*, **86**, 3767 (1964), summarizes the evidence for phenonium ions up to 1964. Numerous papers have appeared since. (e) C. J. Collins has shown that products observed from 3-phenyl-2-butyl tosylate are not inconsistent with rapidly equilibrating open carbonium ions: "Carbonium Ions," Vol. I, Wiley, New York, N. Y., 1968.

(7) H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlid, *Justus Liebigs Ann. Chem.*, **632**, 38 (1960).

(8) H. C. Brown, R. Bernheimer, C. J. Kim, and S. E. Scheppele, *J. Amer. Chem. Soc.*, **89**, 370 (1967).

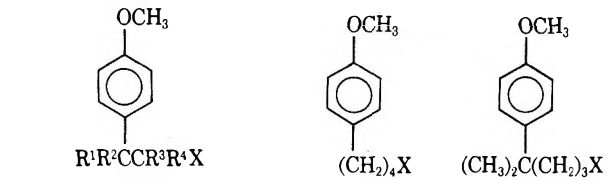
(9) (a) M. G. Jones and J. L. Coke, *ibid.*, **91**, 4284 (1969); (b) C. J. Lancelot and P. v. R. Schleyer, *ibid.*, **91**, 4291, 4296 (1969); (c) C. J. Lancelot, J. J. Harper, and P. v. R. Schleyer, *ibid.*, **91**, 4294 (1969); (d) A. F. Diaz and S. Winstein, *ibid.*, **91**, 4302 (1969), and leading references.

(10) P. v. R. Schleyer and C. J. Lancelot, *ibid.*, **91**, 4297, 4300 (1969).

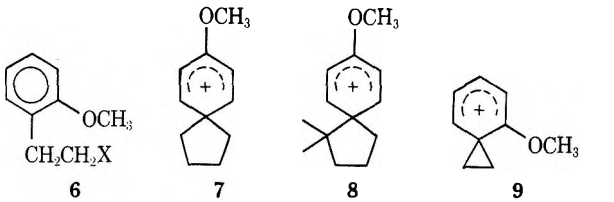
ion behavior to more closely approximate that of "free" unsolvated carbonium ions than that found for carbonium ions, or intimate ion pairs, in more normal solvents such as CH_3OH, acetic acid, etc.

The choice of β-anisylalkyl derivatives as carbonium ion precursors is also made attractive by the considerable amount of work previously reported[6b,8,11] by others on the solvolysis reactions of these systems.

We, therefore, examined the ions produced in $SbF_5 \cdot SO_2$ in the temperature range −60 to −20° from the β-anisyl precursors **3a–g** below, where X is a suitable leaving group such as OH, halogen or mesylate. The formation and nmr spectrum of the parent anisonium ion[12] **1** (X = OCH_3, $R^1 = R^2 = R^3 = R^4 = H$) has already been reported and its structure as a static ion firmly[13] established by ^{13}C nmr. The ionization of **3h** (X = Cl) in $SbF_5 \cdot SO_2$ at −60° to give the 1-anisyl-1-propyl cation has also been published.[12] We wish to report here the results obtained for the remaining members of the series **3b–g**, and for **4**, **5**, and **6**, since ions **7**, **8**, and **9** have been postulated as intermediates[14] in the solvolysis of derivatives of **4**, **5**, and **6**.



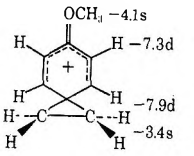
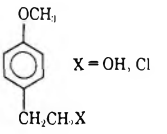
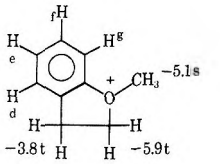
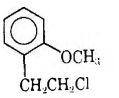
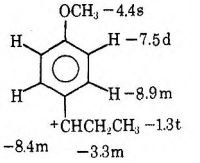
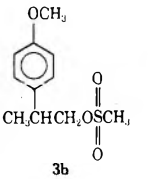
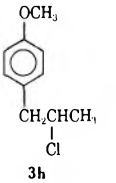
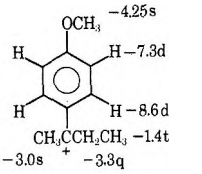
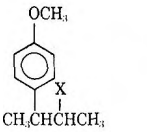
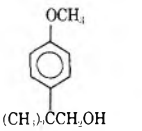
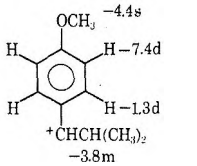
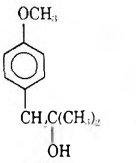
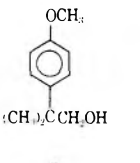
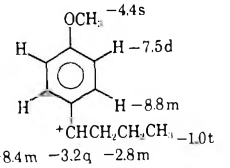
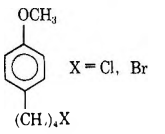
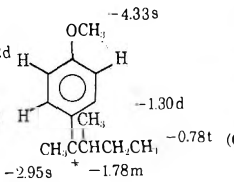
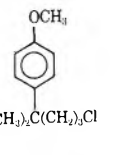
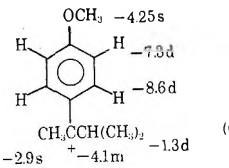
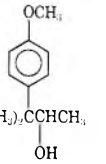
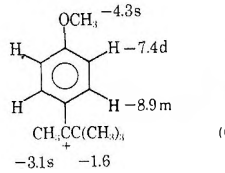
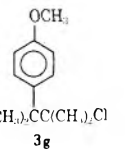
3a, $R^1 = R^2 = R^3 = R^4 = H$
b, $R^1 = Me$; $R^2 = R^3 = R^4 = H$
c, $R^1 = R^2 = Me$; $R^3 = R^4 = H$
d, $R^1 = R^3 = H$; $R^2 = R^4 = Me$
e, $R^1 = R^2 = R^4 = Me$; $R^3 = H$
f, $R^1 = R^2 = H$; $R^3 = R^4 = Me$
g, $R^1 = R^2 = R^3 = R^4 = Me$
h, $R^1 = R^2 = R^3 = H$; $R^4 = Me$



Results and Discussion

Some of the spectra presented here are of ions generated from β-anisylalkyl alcohols. Spectra obtained in this way are less clean than those obtained from ionization of corresponding halides or benzylic precursors. We have chosen, however, to present the spectra exactly as obtained rather than "cleaning" them up in any way by deleting peaks of side products. Where there could be any doubt about the presence or identity of any benzylic ion, that ion was also generated from benzylic halides or alcohols to obtain a better spectrum, and a criteria of exact correspondence between both spectra of the ions firmly established the identity of the benzylic ion produced. Chemical shifts, given in Table I, are taken from the best spectrum of the

TABLE I
CATION NMR CHEMICAL SHIFTS (δ) AND β-ANISYL PRECURSORS

Registry no.	Cation	Precursors in $SbF_5 \cdot SO_2$
12312-28-6		 **3a**
35144-41-3		
18207-34-6		 **3b**  **3h**
35144-43-5		 **3d**, X = Cl, OH  **3c** at −20°
35144-44-6		 **3f**  **3c**
23002-63-3		
35144-46-8		
35144-47-9		 **3e**
22666-69-9		 **3g**

(11) C. J. Kim and H. C. Brown, *J. Amer. Chem. Soc.*, **91**, 4289 (1969).
(12) G. A. Olah, E. Namanworth, M. B. Comisarow, and B. Ramsey, *ibid.*, **89**, 711 (1967); **89**, 5259 (1967).
(13) G. A. Olah and A. M. White, *ibid.*, **91**, 5801 (1969).
(14) (a) S. Winstein, C. R. Lindegren, H. Marshall, and L. L. Ingraham, *ibid.*, **75**, 147 (1953).

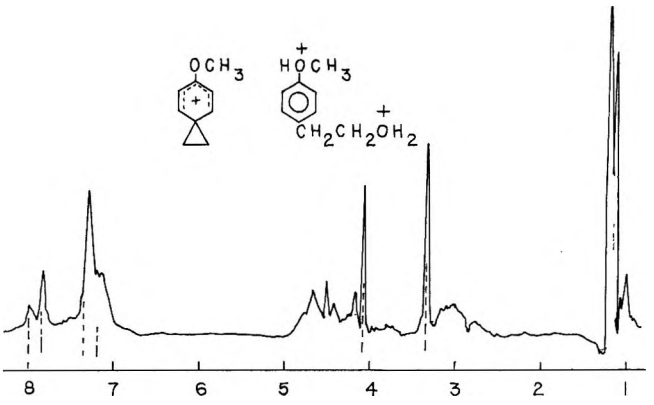


Figure 1.—Nmr spectrum of the reaction mixture from reacting 2-(4-methoxyphenyl)ethanol; chemical shifts for anisonium ion generated from 2-anisyl-1-chloroethane (- - -) with SbF_5 in SO_2 at −70°.

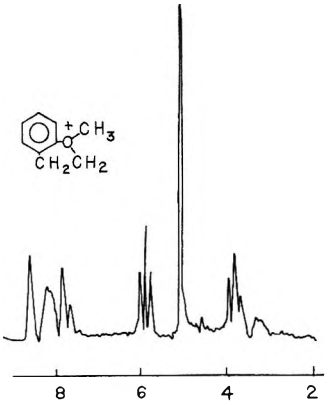


Figure 2.—Nmr spectrum of the reaction mixture of 2-(2-methoxyphenyl)-1-chloroethane and SbF_5 in SO_2. Ionization at −70°, spectrum recorded at −10°.

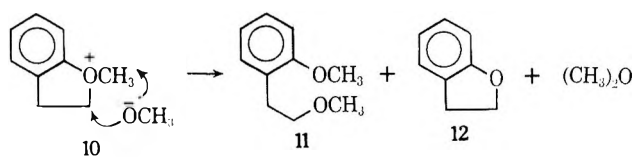
ion available. We will now present the results for each system individually.

The 2-*p*-Anisylethyl System (3a).—The formation of the *p*-anisonium ion from 2-*p*-anisyl-1-chloroethane in $SbF_5 \cdot SO_2$ at −70° has already been reported.[12] We also find, however, that the *p*-anisonium ion can be generated under the same conditions from the alcohol (**3a**, X = OH) with some minor formation of what appears to be the diprotonated ion[12] (Figure 1). This result is important with regard to the study of other systems such as 2-*p*-anisyl-2-methylpropanol, where we were unable to prepare unrearranged derivatives of the alcohol and therefore used the alcohol directly to generate the ions. The "diprotonated ion" itself is stable at −70° and does not convert at any appreciable rate to anisonium ion.

The spectrum of the anisonium ion generated from the alcohol (Figure 1) is certainly not as clean as that previously reported[12] in which the anisonium ion is generated from the chloride, but the simple expedient of overlaying a clean spectrum of the anisonium ion generated from 2-*p*-anisylethyl chloride over the spectrum of Figure 1 is sufficient to remove doubts over the identity of the anisonium ion. Quenching results confirm this conclusion. Figure 1 is provided to enable the reader to compare the kind of spectra which may be obtained from alcohols with those of the same ion generated from alkyl chlorides and also that reported elsewhere.[12]

The 2-(2-Methoxyphenyl)-1-ethyl System (6).—The nmr spectrum of the ion generated from 2-(2-methoxyphenyl)-1-chloroethane in $SbF_5 \cdot SO_2$ (Figure 2) is stable over the temperature range −70 to −10° and is most consistent with the formation of the oxonium ion **10** (Scheme I). The chemical shift (δ 5.1) of the CH_3O group is in good agreement with that observed for other methyloxonium ions such as O-protonated anisylethanol (δ 5.0). The appearance of two triplets, one of which, at δ 5.9, is at lower field than the CH_3O resonance, is also in good agreement with the structure assigned.

SCHEME I



The nmr spectra of quenching products of **10** indicated the major product to be 2-(2-methoxyphenyl)-1-ethyl methyl ether (**11**); however, a 5% yield, based on starting material (20% based on recovered neutral product), of dihydrobenzofuran (**12**) was also obtained. The formation of **12** would appear to require ion **10** as a logical precursor. The products are presumed to have formed in the reactions indicated in Scheme I. Oxonium ions are known[5] to be excellent alkylating agents.

On the basis of similar solvolysis rates and activation parameters, Winstein originally concluded[14a] that both 2-(2-methoxyphenyl)- and 2-(*p*-anisyl)ethyl tosylates solvolyze by a similar mechanism involving formation of a phenonium ion. No product study was made by Winstein in this case. Later, however, Winstein[15] found substantial amounts of furans from the solvolysis of 2-(2-methoxyphenyl)-2-methylpropyl tosylate and proposed an intermediate oxonium ion analogous to cation **10**. Probably, therefore, ion **10** does correspond to the intermediate in the solvolysis reactions. However, the formation of **10** may also be the result of a very low activation energy in $SbF_5 \cdot SO_2$ such that ground-state geometry is the controlling factor over ring or methoxyl participation.

The 2-(*p*-Anisyl)-1-propyl System (3b).—Because considerable difficulty was met in attempts to prepare 2-(4-methoxyphenyl)-1-propyl halides from the alcohol without rearrangement, the mesylate **13** was ionized in $SbF_5 \cdot SO_2$ to give the ion **15**, whose nmr spectrum[12] has previously been published. Phenyl followed by hydride migration (Scheme II) as the route to ion **15** rather than methyl migration was established by nmr observation of the ion **16** from 2-(4-methoxyphenyl)-*2-d*-propyl methanesulfonate. The aliphatic methyl group of **16** appears as a doublet centered at δ 1.34.

The 1-(*p*-anisyl)-*1-d*-propyl cation **17** was obtained from the corresponding carbinol in $SbF_5 \cdot SO_2$. After periods at −60° of 20 min and at −40° of 20 min, the spectrum gave no sign of extensive exchange of D. This rules out ion **17** as a precursor to **16** under the conditions of the experiment. After 45 min at −20°, however, equilibration between D and CH_2 hydrogens

(15) R. Heck, E. Corse, E. Greenwald, and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 3278 (1957).

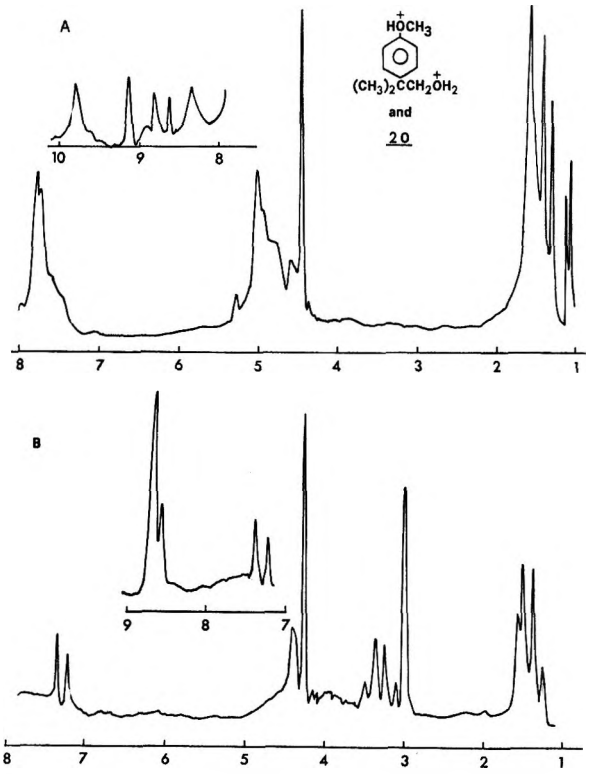
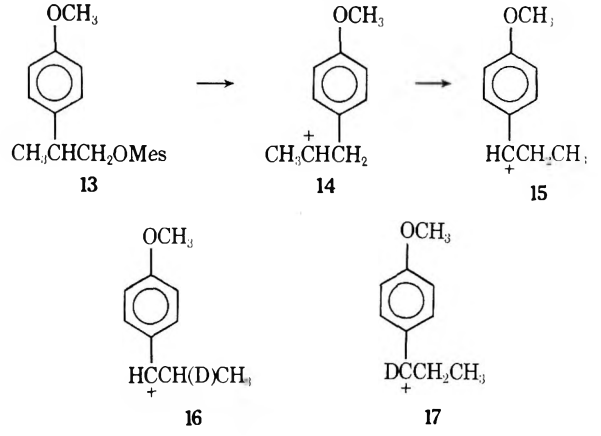


Figure 3.—(A) Nmr spectrum of the reaction mixture of 2-(4-methoxyphenyl)-2-methylpropanol and SbF_5 in SO_2. Ionization at −70°. (B) At −20°.

SCHEME II



was complete. The ortho protons of **17** remain nonequivalent ($\Delta\delta$ 0.4 ppm) even at −20°, demonstrating significant restriction of anisyl ring rotation about the carbonium ion σ bond.

The 2-(*p*-Anisyl)-2-methyl-1-propyl System (3c).—Because we were unable to prepare a pure unrearranged halide or mesylate derivative, 2-(*p*-anisyl)-2-methyl-1-propanol was allowed to react with $SbF_5 \cdot SO_2$ under those conditions previously found to be successful in generating the anisonium ion from *p*-anisylethanol. At −70° the expected product of anisyl migration, 1-(*p*-anisyl)-2-methyl-1-propyl cation **20**, is clearly observed by careful comparison of the spectrum of Figure 3a with that of the ion **20** generated from 1-(*p*-anisyl)-2-methyl-2-propanol (Figure 4). The major species present appears to be the diprotonated alcohol **18**. (It is also possible that OH and OCH_3 may be complexed with SbF_5 rather than H^+.) When the

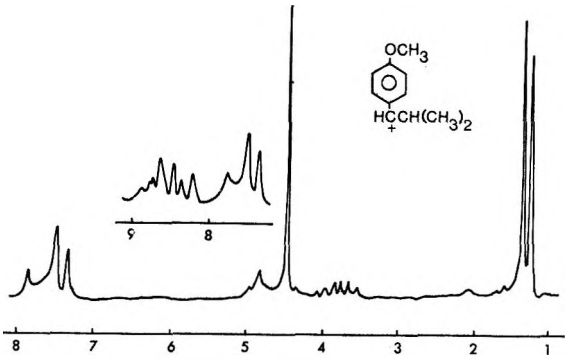


Figure 4.—Nmr spectrum of the reaction mixture of 1-(4-methoxyphenyl)-2-methyl-2-propanol and SbF_5 in SO_2. Spectrum recorded at −40°.

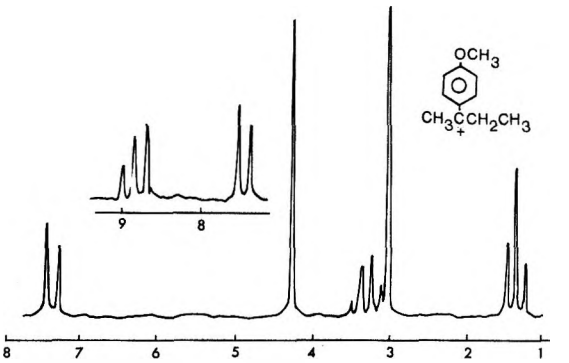
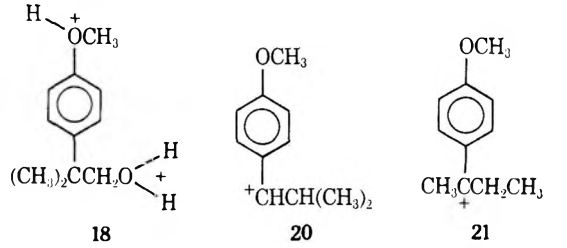


Figure 5.—Nmr spectrum of the reaction mixture of 2-(4-methoxyphenyl)-2-butanol and SbF_5 in SO_2. Spectrum recorded at −20°.

solution is warmed to −20°, species **18** disappears and the principal ion obtained is the 2-*p*-anisyl-2-butyl cation **21**, as determined from careful comparison of Figure 3b with the nmr spectrum of 2-(*p*-anisyl)-2-butanol (**19**) in $SbF_5 \cdot SO_2$ (Figure 5). Since an $SbF_5 \cdot SO_2$ solution of the 1-(*p*-anisyl)-2-methyl-1-propyl cation **20** can be held at −20° for over 1 hr without detectable appearance in its nmr spectrum of ion **21**, the ion **21** must be formed from acid-complexed [OH_2^+ or $^+O(H)SbF_5^-$] *p*-methoxyneophyl alcohol directly at −20°, not through rearrangement of ion **20**, and by methyl rather than anisyl migration. If one assumes initial formation at −20° of a very reactive primary carbonium ion (or ion pair), there are several possible explanations for subsequent preferred methyl over anisyl migration. Statistically, methyl migration is preferred over anisyl migration. Furthermore, a migrating anisyl ring must assume a sterically unfavorable geometry, because of the adjacent methyl groups in which the ring is perpendicular to the plane of the incipient phenonium ion three-membered ring. The stability of **18** (or analogous SbF_5 complex) at −70° also suggests deactivation of the anisyl ring toward



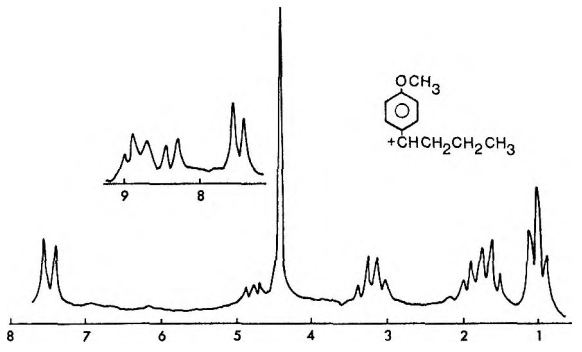


Figure 6.—Nmr spectrum of the reaction mixture of 4-(4-methoxyphenyl)-1-chlorobutane and SbF_5 in SO_2 at −70°.

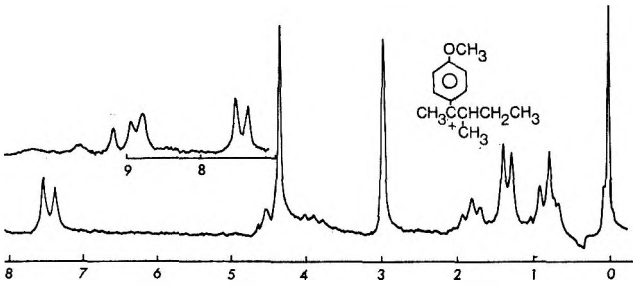


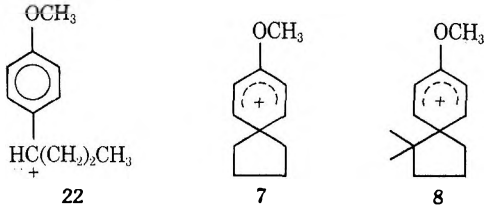
Figure 7.—Nmr spectrum of the 2-*p*-anisyl-3-methyl-2-pentyl cation in $SbF_5 \cdot SO_2$ at −70°.

neighboring group participation and a resultant decreased migration aptitude at −20°.

A scheme in which a primary carbonium ion pair at −20° is in rapid preequilibrium with the anisyl-*tert*-butyl cation (anisonium ion optional) may be ruled out by the absence of the formation of ion **21** from ionization of 1-(4-methoxyphenyl)-2-methyl-2-propanol, which yields ion **20** exclusively.

The 4-(*p*-Anisyl)-1-butyl Halides (4) and 4-(*p*-Anisyl)-4-methyl-1-chloropentane (5).—Since observation of the simple anisonium ion, but not phenonium ions, with alkyl substitution of the cyclopropyl ring, could be explained by the presence of the strained three-membered ring, and because of the ease with which this cyclopropyl ring could open to secondary or tertiary carbonium ions, it was hoped that ions **7** and **8**, where one or both of these factors were absent, might be observed by nmr.

The 4-(*p*-anisyl)-1-butyl halides in $SbF_5 \cdot SO_2$ at −60°, however, did not give the desired phenonium ion **7**. The chloride (and bromide only by using 7 molar excess of SbF_5) could be ionized to the 1-(*p*-anisyl)-1-butyl cation **22**, whose nmr spectrum (Figure 6) was

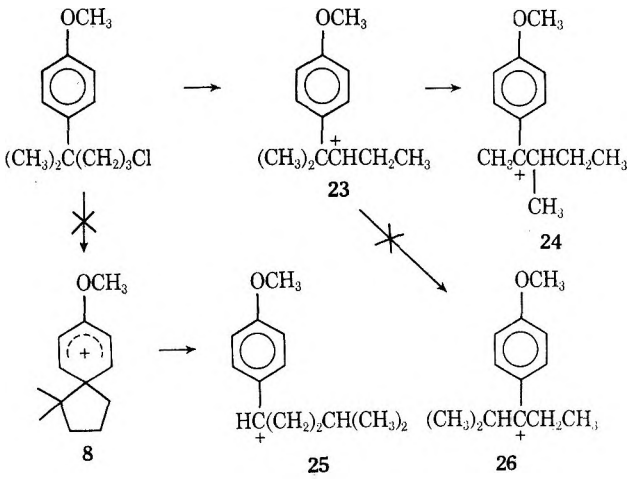


confirmed by generating the ion from the corresponding benzylic methyl ether in $SbF_5 \cdot SO_2$. Although the *tert*-butyl cation is easily generated[3] even from *n*-butyl iodide, all attempts to generate **22** from 4-anisylbutyl iodide (or the alcohol) failed. The anisyl group appears to deactivate the *n*-butyl halide, perhaps by an electron-withdrawing inductive effect of a benzyl group on the initial formation of a protonated cyclopropyl cation intermediate.

The failure to observe ion **7** from the 4-*p*-anisylbutyl halides in $SbF_5 \cdot SO_2$ does not rule out the intervention of ion **7** in the route to **22**, but, in view of previous success with the parent anisonium ion and the expected stability of **7**, had it been formed, it should have been easily detected at −70°. Opening the ion **7** requires at best formation of a π-complexed primary ion, and this should require prohibitive activation energy.

These conclusions are greatly strengthened by the formation of ion **24** from 4-(*p*-anisyl)-4-methyl-1-chloropentane in $SbF_5 \cdot SO_2$ at −70° (Scheme III).

SCHEME III

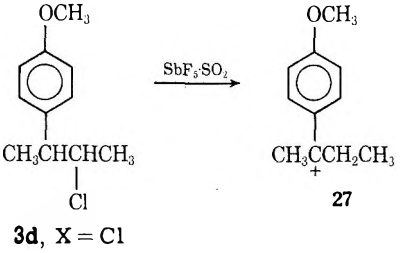


The spectrum of ion **24** (Figure 7) was also obtained from 2-*p*-anisyl-2-methoxy-3-methylpentane in $SbF_5 \cdot SO_2$. There was in the nmr spectrum (Figure 7) no evidence of **8**, **25**, or other ions which would be expected products of anisyl participation in the ionization.

The observed product ion **24** can be arrived at from ion **8** only if we postulate either a long series of hydride and methyl shifts which *must* at some time require the formation of a *primary* carbonium ion, or, even less likely, the preferential opening of **8** to a primary ion. We, therefore, conclude that the formation of ion **24** took place without participation by the anisyl group.

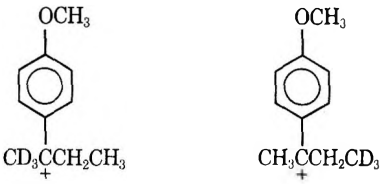
If we make the reasonable assumption that the formation of **24** proceeds through ion **23**, whose presence was not, however, experimentally observed, the absence of ion **26** becomes significant. The implication is that in $SbF_5 \cdot SO_2$ migration of methyl groups from a tertiary center to a "preformed" secondary carbonium ion center is much more rapid than anisyl migration.

The 3-(*p*-Anisyl)-2-butyl System (3d).—The 2-(*p*-anisyl)-2-butyl cation **27** is obtained from ionization



of either 3-(*p*-anisyl)-2-chlorobutane or 2-(*p*-anisyl)-2-butanol (Figure 5). The structure of the ion is established by the appearance of a typical ethyl group triplet (δ 1.3) and quartet (δ 3.3), a singlet methyl adjacent to a positive charge (δ 3.0), and the large downfield shift of the ortho and meta ring protons. There is no change in the spectrum over the temperature range −60 to −20°.

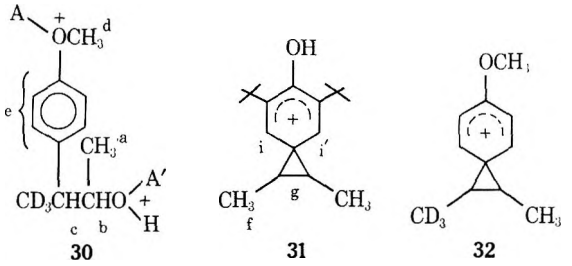
The nmr spectra of 4,4,4-trideuterio-3-(*p*-anisyl)-2-butanol in $SbF_5 \cdot SO_2$ at −60° and after warming to −20° are given in Figures 8A and 8B. At −20° the spectrum is unchanged after 1.5 hr. The relative amounts of ions **28** and **29** were determined by integra-



28 **29**

tion of the singlet at δ 3.05 for CH_3C^+, and the methyl triplet at δ 1.31 for CH_2CH_3. At −60°, the ratio of ion **28** to **29** is greater than 10:1. Thus, at −60° neither prior equilibrium with an anisonium ion nor rapidly equilibrating β-anisylcarbonium ion pairs can be of significant importance, and hydride ion migration must be about ten times faster than net anisyl migration to a carbonium ion center. The resonances at δ 1.55–1.80, 4.75, 4.95, and 7.7 present at −60° disappear on warming to −20°, and integration of the spectrum (Figure 8B) then gives 80% of cation **28** from net hydrogen migration and 20% of cation **29** from net anisyl migration.

If the intermediate present at −60° which disappears at −20° is assumed to be the acid-complexed alcohol **30**, where A is H or SbF_5, the following assign-



30 **31** **32**

ments can be made: δ 1.55–1.80 (a and c), 4.75 (b), 4.95 (d), and 7.7 (e). These assignments are in good agreement with resonances observed for corresponding hydrogens of protonated alcohols, 2-(*p*-anisyl)-2-methyl-1-propanol and 2-*p*-anisylethanol. It is not obvious, however, why at −20° ion **30** should give **29**, whereas the comparable ion **18** did *not* give the anisyl migration product **20** under similar conditions. It may be that the primary protonated alcohol **18** is in rapid equilibrium at −20° with the SbF_5 complex, which in turn ionizes at −20° without the anisyl assistance which it required at −60°. The ion **30** (A′ = H), on the other hand, may ionize with anisyl participation at some temperature between −60 and −20°, since it yields the more easily formed secondary ion.

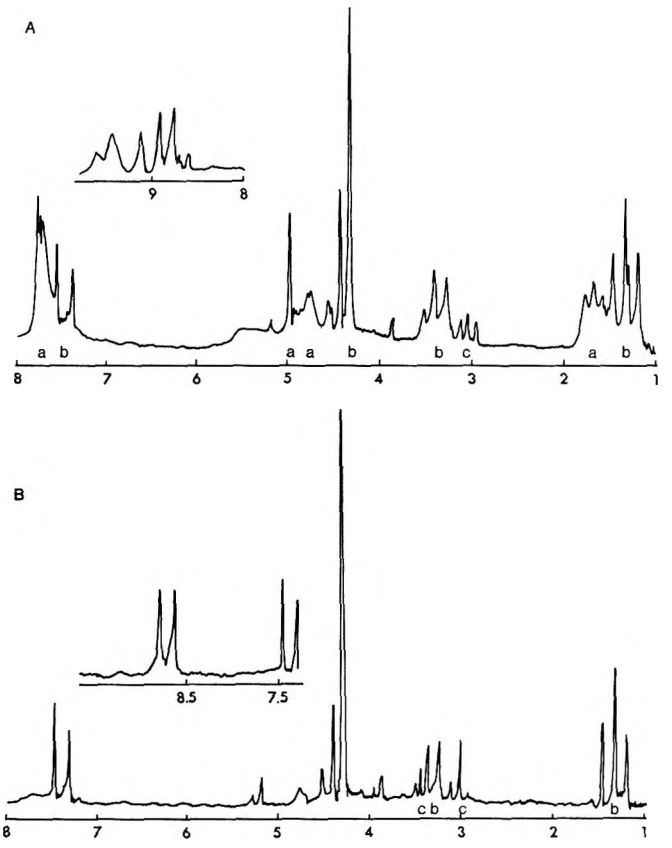
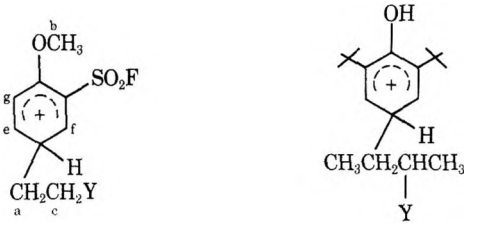


Figure 8.—Nmr spectra of p-$CH_3OC_6H_4CH(CD_3)CH(OH)CH_3$ in $SbF_5 \cdot SO_2$, A at −60° and B at −20°. Peaks indicated by a are assigned to the dioxygen-protonated or complexed ion. Peaks indicated by b are assigned to ^+p-$CH_3OC_6H_4C(CD_3)CH_2CH_3$, and those indicated by c to ^+p-$CH_3OC_6H_4C(CH_3)CH_2CD_3$.

Chamot and Pirkle[16] have reported the nmr spectra of what they believe to be the cis and trans isomers of ion **31** from 1,2-dimethyl-5,7-di-*tert*-butylspiro[2.5]-octa-4,7-dien-6-one in FSO_3H at −60°. However, in the spectrum[16] assigned to **31**, the cyclopropyl hydrogens are more than 1 ppm further downfield than their position (δ 3.5) in the anisonium ion. In fact, the chemical shifts reported for **31** seem quite close to those observed[17] by us for *p*-anisylethanol in fluorosulfonic or sulfuric acid at −60°, and eventually assigned to a species such as **33**, with resonances at δ 3.10 (a), 3.90



Y = $^+OH_2$, OSO_3H, OSO_2F Y = $^+OH_2$, OSO_3H, OSO_2F

33 **34**

(b), 4.71 (c), 7.19 (g), and 7.75 (e,f). An analogous ion from the dienone might be an ion such as **34**. Moreover, since we can find no nmr evidence of ions analogous to **32** or **30** from 2-(*p*-anisyl)-3-chlorobutane in $SbF_5 \cdot SO_2$ at −70°, in spite of repeated attempts, we prefer at this time to interpret the nmr of the 3-(*p*-anisyl)-2-butyl alcohols in $SbF_5 \cdot SO_2$ in terms of ions

(16) D. Chamot and W. H. Pirkle, *J. Amer. Chem. Soc.*, **91**, 1570 (1969).
(17) B. Ramsey, unpublished results.

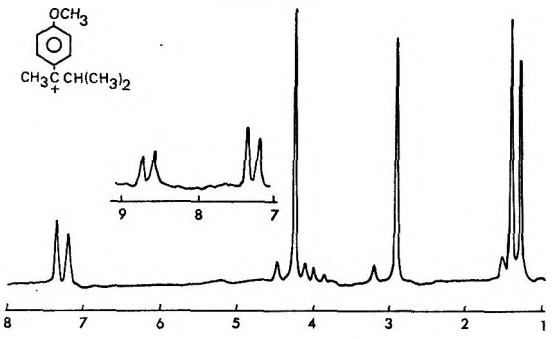
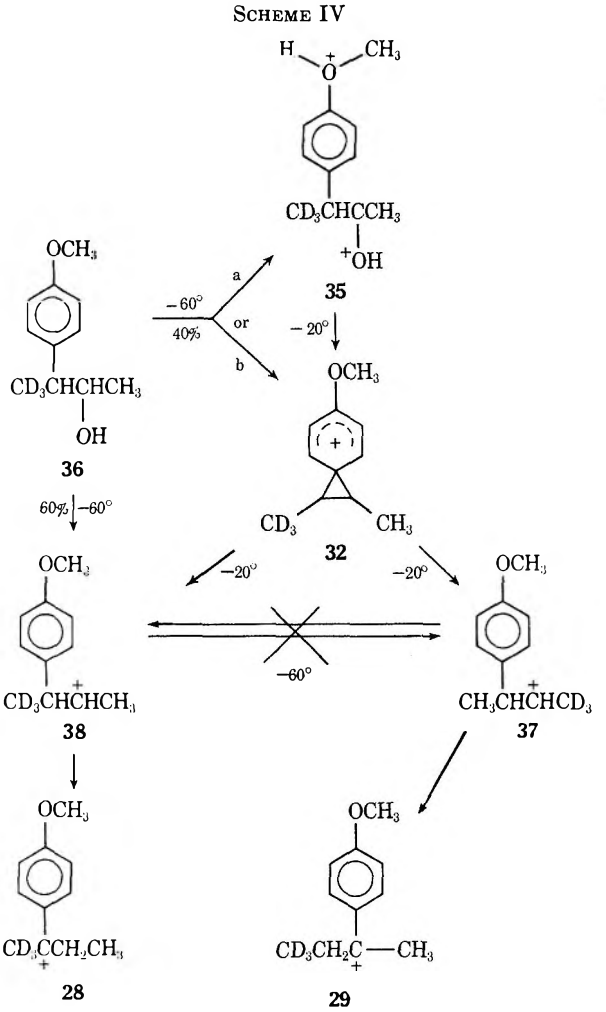


Figure 9.—Nmr spectrum of the reaction mixture of 2-(4-methoxyphenyl)-2-methyl-3-butanol and SbF_5 in SO_2 at −60°.

27, **28**, **29**, **30**, or **35** rather than an anisonium ion **32**, *in which case hydride migration is at least ten times faster than either net anisyl migration or anisonium ion formation at −60°.*

Scheme IV is suggested for an ionization in $SbF_5 \cdot SO_2$ of **36** which proceeds through intermediates[18] **38**, **32**, and **35**. (A final choice between alternatives a and b at −60° awaits a more detailed report of Chamot and Pirkle on proposed ion **31**.)

SCHEME IV



(18) Formation of **28** without intervention of **38** requires that an assisted ionization of the alcohol with simultaneous migration of the neighboring groups is more important for the hydride than the anisyl. This is contrary to previous experience.

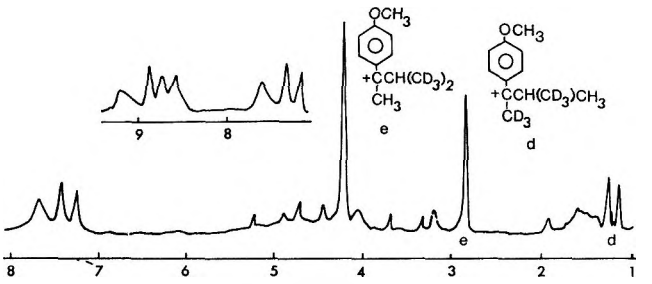
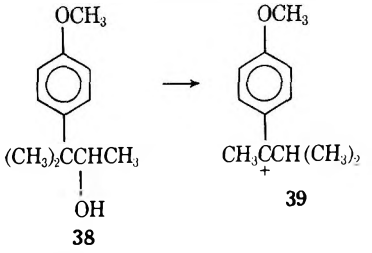


Figure 10.—Nmr spectrum of p-$CH_3OC_6H_4C(CD_3)_2CH(OH)CH_3$ in $SbF_5 \cdot SO_2$ at −60°.

Rapid equilibration between **37** and **38**, clearly absent at −60°, can probably also be ruled out at −20° since $\Delta S^{\pm}$ for anisyl migration is more negative than for hydride migration, and an increase in temperature should favor benzylic ion formation. Provided that the *relative* migration aptitudes of anisyl and CH_3 groups are not reduced by H^+ or SbF_5 coordination to the methoxy group, the absence of an equilibration between ions **37** and **38**, which is faster than benzylic



ion formation in $SbF_5 \cdot SO_2$, suggests that similar rapidly equilibrating β-anisyl ions are not important intermediates in the solvolysis of 2-anisyl-3-butyl derivatives in more normal solvents such as acetic acid, formic acid, etc., where benzylic products are not found. It may also be significant that the deaminative acetolysis of 3-phenyl-2-butylamine (which would not proceed through an ion pair intermediate) yields a substantial amount of benzylic products,[19] whereas solvolysis of the tosylate[20] does not.

The 3-(*p*-Anisyl)-3-methyl-2-butyl System (3e).—Ionization of 3-(*p*-anisyl)-3-methyl-2-butanol in $SbF_5 \cdot SO_2$ at −60° gave the ion **39**, whose nmr spectrum (Figure 9) is characterized by the doublet of the isopropyl-methyl group at δ 1.3 and the large downfield shift of the ortho (δ 8.6) and meta (δ 7.3) ring protons. The spectrum of the ion shows no change on warming to −20°.

As expected on the basis of relief of steric strain, anisyl migration is more important from a tertiary carbon than from a secondary carbon. When 4,4,-4-trideuterio-3-trideuteriomethyl-3-(*p*-anisyl)-2-butanol is ionized at −60° in $SbF_5 \cdot SO_2$, a mixture of ions **43** (42%) and **41** (58%) is obtained (based on the integration of the nmr spectrum in Figure 10). After 15 min at −20°, the ratio changes to 46:54 and, after 70 min reaches a ratio 60:40, which corresponds to K_H/K_D = 1.3.

Ions **41** and **43** do not interconvert at −60° at an appreciable rate; therefore they must be formed in competing processes (Scheme Va or b). Since opening of the anisonium ion to **40**, a tertiary ion, should be much more rapid than opening to **42**, a secondary ion,

(19) D. J. Cram and J. F. McCarty, *J. Amer. Chem. Soc.*, **79**, 2866 (1957).
(20) S. Winstein and R. Baker, *ibid.*, **86**, 2091 (1964).

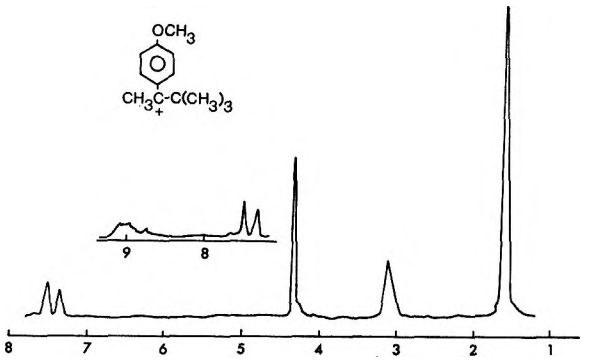
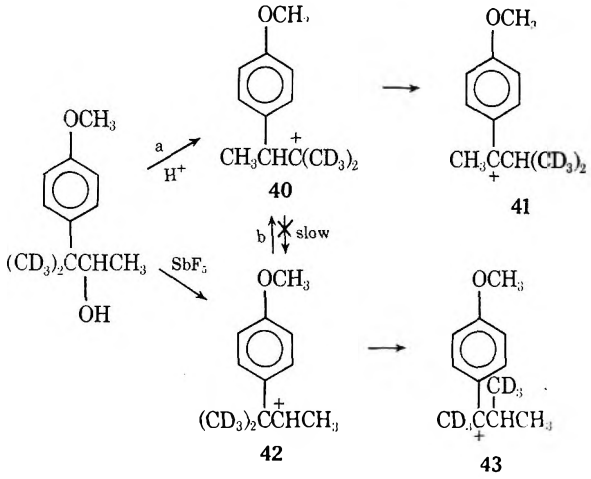


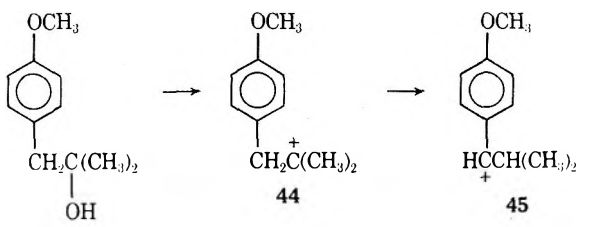
Figure 11.—Nmr spectrum of 2-(4-methoxyphenyl)-2,3-dimethyl-3-butanol in $SbF_5 \cdot SO_2$ at −70°.

SCHEME V



either a common anisonium ion intermediate or migration of the anisyl group concurrent with ionization to form **40** should lead to ion **41** as the exclusive product. Ion **43** must then arise directly from methyl migration to the secondary carbonium ion center of **42**. Formation of **41** by way of **42** (Scheme Vb) cannot be ruled out, but the apparent absence of similar anisyl migrations in ion **23** from the ionization of 4-anisyl-4-methyl-1-chloropentane, and in ion **38** of Scheme IV, suggest that an alternative interpretation such as Scheme Va should be found. This alternative is simply based on the postulate that in secondary alcohols $-OH_2^+$ ionization may take place provided aryl assistance is available, but $-OSbF_5^+$ ionization proceeds without aryl assistance.

The 3-(4-Methoxyphenyl)-2-methyl-2-propyl System (3f).—The ionization of 1-(4-methoxyphenyl)-2-methyl-2-propanol gave only the anisyl isopropylcarbonium ion **45** (Figure 4). It seems safe to assume that the reaction below proceeds without anisyl migration. No



change in the spectrum was observed between −70 and −15°.

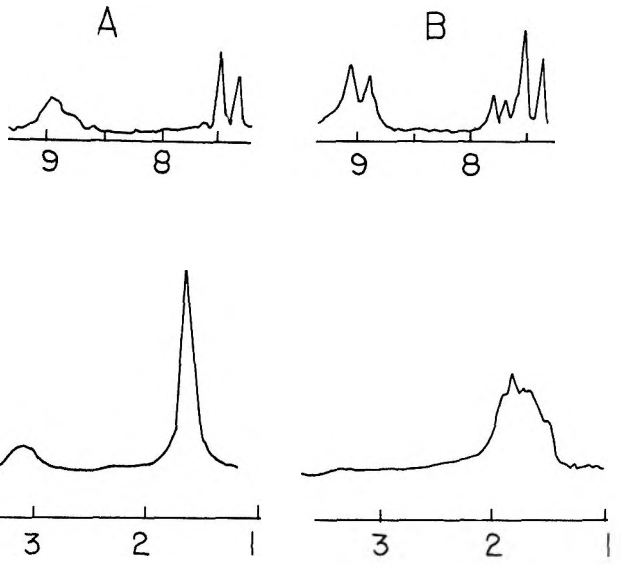
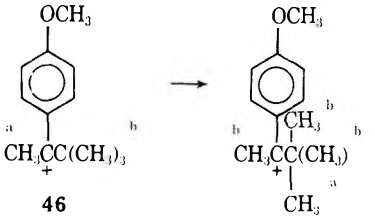


Figure 12.—Nmr spectrum of 2-(4-methoxyphenyl)-2,3-dimethyl-3-butanol in $SbF_5 \cdot SO_2$, A at −50°, B at −20°.

The 3-(4-Methoxyphenyl)-2,3-dimethyl-2-butyl System (3g).—The nmr spectrum (Figure 11) of 3-(4-methoxyphenyl)-2,3-dimethyl-2-butanol in $SbF_5 \cdot SO_2$ at −70° is clearly that of the *p*-anisyl *tert*-butyl methyl carbonium ion **46**. Complete scrambling of methyl groups is found when the methyl-deuterated analog of ion **47** is generated at −70° from 1,1,1-trideuterio-2-trideuteriomethyl-3-(*p*-anisyl)-3-methyl-2-butanol. At −50° the broadening of the methyl resonances is quite pronounced, and the collapse of the methyl resonances is observed at −20° (Figure 12). If the exchange process is written according to eq 1, and P_{ab}



(1)

$$P_{ab} = \frac{3\pi\sqrt{\delta^2 - \Delta\nu^2}}{4\sqrt{2}} \quad (2)$$

is the transition probability for the benzylic methyl group a, eq 2 may be derived as the relation between P_{ab}, $\Delta\nu$ (the chemical shift difference between methyl a and b and δ (the methyl a and b limiting chemical shift difference) in hertz. The value of δ was obtained as 91 cps at −70°. Chemical shift differences ($\Delta\nu$) were obtained at −60° (90 Hz), −50° (88 Hz), and −30° (83 Hz).

An Arrhenius activation energy (E_a = 6.5 kcal/mol) was obtained from a plot of log P_{ab} as calculated from eq 2 *vs.* $1/T$. The enthalpy and entropy of activation are $\Delta H^{\pm}$ = 6.1 kcal/mol and $\Delta S^{\pm}$ = −12 eu. If the rate determined from the collapse temperature, which is the least accurate measurement, is omitted, an activation energy of only 5.0 kcal/mol is obtained. (The Varian variable-temperature probe used is reliable only to ±1°. In addition there are also temperature gradients within the sample tube. This leads to estimated errors of as much as ±3 kcal/mol in E_a and ±12

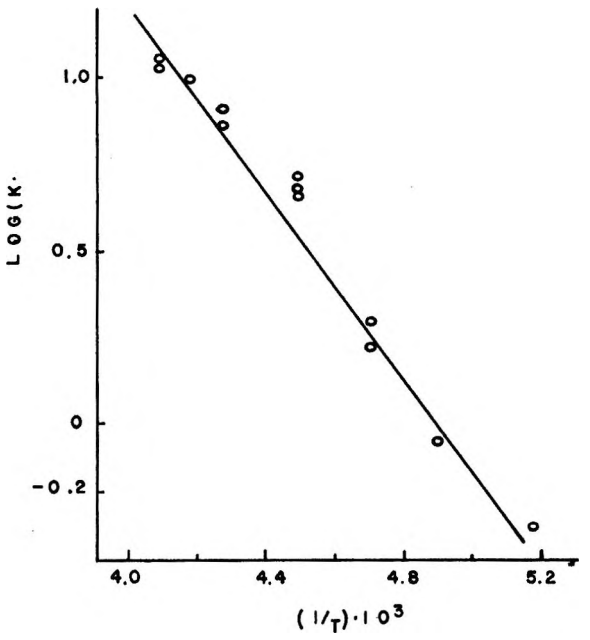
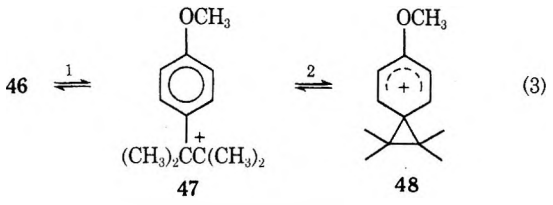


Figure 13.—Log k (based on excess line broadening) for CH_3 exchanging of ^{+}p-$CH_3OC_6H_4CH(CH_3)C(CH_3)_3$ *vs.* $1/T$.

eu in $\Delta S^{\pm}$, which are probably more realistic than standard deviations commonly reported.)

The exchange rate as a function of temperature was also obtained by measuring the exchange line broadening of the $(CH_3)_3C$ methyl peak and using the line width of the CH_3O peak at each temperature to approximate the natural line width of $(CH_3)_3C$ in the absence of exchange. As may be seen from Figure 13, the results of plotting log k *vs.* $1/T$ are reasonably good and the calculated E_a (6.0 kcal/mol), $\Delta H^{\pm}$ (5.6 kcal/mol), and $\Delta S^{\pm}$ (−27 eu) are in agreement with those previously calculated from chemical shift differences by eq 2, within experimental error.

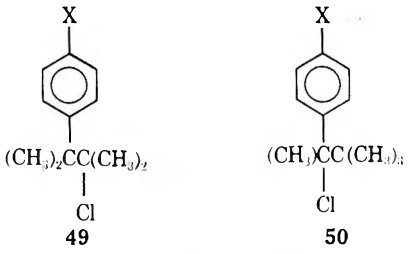
In view of the zero to slightly positive entropy of activation found for the rate-determining methide shift in equilibration of the *tert*-amyl cation methyl groups[21] and also for the rate-determining hydride shift[22] in the isopropyl cation, we would like to modify an earlier conclusion[23] and suggest that a negative (−12 to −27 eu) activation entropy for methyl of equilibration of ion **46** is best explained by a transition state leading to a phenonium ion; *i.e.*, step 2 of eq 3 may be rate determining.



(3)

Brown and Kim[6b] reported the results of CD_3-labeled scrambling of the compounds p-$RC_6H_4C(CH_3)_2C(CD_3)_2X$ (R is H or OCH_3) in a variety of reactions normally regarded as proceeding by carbonium ion, SN1, mechanisms. Based on the small rate enhancement caused by the anisyl relative to phenyl, and the observed 100% CD_3 scrambling in the reactions of p-$CH_3OC_6H_4C(CH_3)_2C(CD_3)_2X$ (*except* dehydration of the alcohol over alumina and reaction of the sodium alkoxide with bromoform), Brown and Kim concluded that carbonium ion reactions of p-$CH_3OC_6H_4C(CH_3)_2C(CH_3)_2OH$ derivatives proceeded through rapidly equilibrating 3-anisyl-2,3-dimethyl-2-butyl cations. Benzylic ion products were less than 5%. It is very difficult to reconcile Brown's model with our results, since we have concluded (eq 3) that in $SbF_5 \cdot SO_2$ benzylic ion formation is not only competitive with but faster than anisyl migration. The difference may lie either in the ability of SbF_5 to complex the anisyl methoxyl group, or, if the equilibrating 2-butyl cations are in fact ion pairs in more normal solvents, the absence of the closely associated anion in $SbF_5 \cdot SO_2$ may result in faster benzylic ion formation. There is after all no *a priori* reason why relative free energies or rates of interconversion of carbonium ion ion pairs (or highly solvated ions) should parallel those of the dissociated "nonsolvated" cations expected in $SbF_5 \cdot SO_2$.

The activation energy and entropy determined for the equilibration of methyl groups in the p-anisyl methyl *tert*-butyl carbonium ion has some bearing on conclusions reached by Olah, *et al.*,[24a] on the identity of the carbonium ions present when **49** or **50** are dissolved in $SbF_5 \cdot SO_2$. Where X = CH_3, the spectrum was assigned to equilibrating benzylic (**51**) and phenonium ions (**53**), for X = H, to **53**, the phenonium ion, and to **52** where X = CF_3. Considerations outlined below, however, suggest an alternative interpretation of these data for X = CH_3 and H.



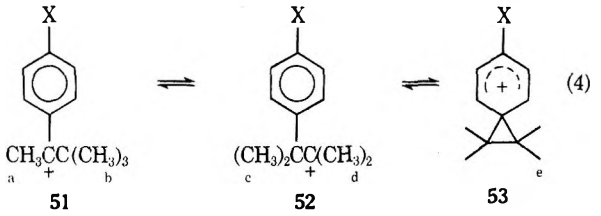
X = H, CH_3, or OCH_3

The relative free energies of formation, $\delta\Delta G$, for the di- and triaryl carbonium ions $(p\text{-}XC_6H_4)_{3-n}C^{+}H_n$ (n = 0, 1) in sulfuric acid have been reported.[25] The p-methyl and methoxyl ions are about 4 and 10 kcal/mol, respectively, more stable than the unsubstituted aryl carbonium ions. The gas-phase relative ionization potentials[26] of the benzyl, p-methyl-, and p-methoxyl benzyl radicals (0.0, −7, and −18.7 kcal/mol, respectively) may be used to estimate an upper limit on the ability of these para substituents to stabilize a benzylic cation, since electron demands on the substituent would be much smaller in solution.

Clearly, the activation energy (6 kcal/mol) for the exchange of methyl groups in ion **46** is very close to that expected for the relative difference in energies of the p-methyl- and p-methoxy-substituted ions and of the same order of magnitude as the unsubstituted phenyl methyl *tert*-butyl carbonium ion. Since the energies

(21) M. Saunders and E. L. Hagen, *J. Amer. Chem. Soc.*, **90**, 2436 (1968).
(22) M. Saunders and E. L. Hagen, *ibid.*, **90**, 6881 (1968).
(23) B. G. Ramsey and J. Cook, *Tetrahedron Lett.*, 535 (1969).
(24) (a) G. Olah, M. B. Comisarow, and C. J. Kim, *J. Amer. Chem. Soc.*, **91**, 1458 (1969); (b) G. Olah and R. Porter, *ibid.*, **93**, 6877 (1971).
(25) N. C. Deno and A. Schriesheim, *ibid.*, **77**, 3051 (1955).
(26) J. L. Franklin, "Carbonium Ions," Vol. 1, Wiley, New York N. Y., 1968, p 105.

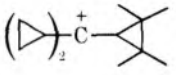
of the tertiary carbonium ions **52** should be relatively insensitive to substituent X, the energies of the benzylic ion **51** and tertiary ion **52** may be expected on the basis of the above relative energies to be very similar (within 1 kcal) where X is CH_3 (eq 4) and comparable even



51 **52** **53** (4)

where X is H. This may be more easily realized graphically from Figure 14, which indicates estimated ΔG substitution and experimental $\Delta G^{\ddagger}$ for exchange for the benzylic and alkyl cations. Certainly where X is CH_3 and possibly where X is H, the activation energy for the equilibration of ions **51** and **52** or even all three ions **51**, **52**, and **53** may be less than 3 or 4 kcal/mol, and the absence of line broadening in the nmr spectra of these systems even at $-120°$ should not be regarded[24a] as conclusive evidence for the presence of only a single major species.

Fundamental to Olah's assignment[24a] *of the proton nmr spectrum of the parent phenonium ion* ($X = H$) *is assigning a chemical shift of* δ *2.3 to methyl groups of phenonium ion* **53** ($X = H$). This may be too far downfield in view of the methyl chemical shifts of δ 1.25 obtained by Deno[27] for ion **54** or even δ 1.9 for ion **31**, which is itself suspected.



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If perhaps a more reasonable choice of δ 1.6 is made for the chemical shift of methyls c, and if the remaining methyl chemical shifts are estimated [for methyls a, δ 3.2 on the assumption that the benzylic methyl chemical shift differences between p-$CH_3C_6H_4C(CH_3)_2^+$ (δ 3.45) and p-$CH_3C_6H_4CCH_3C(CH_3)_3^+$ (estimated $\Delta\delta$ 0.21 ppm) should be slightly greater than the difference of 0.16 observed[24] for the corresponding p-CH_3O substituted ions because of an expected smaller para substituent effect in the *tert*-butyl substituted benzylic ions, resulting from *tert*-butyl steric hindrance to phenyl ring stabilization of the positive charge [for methyls b δ 1.5 from ion **46** (X = CH_3O); the average of methyls c and d δ 2.8 from ion **52** (X = CF_3)]; these chemical shifts will satisfy both observed alkyl methyl nmr chemical shifts within 0.1 ppm and drowning product ratios provided the ratios of the concentrations of ions **51**, **52**, and **53** are taken as 4:3:3 where X is methyl or 1:5:4 where X is H. The 4:3:3 ratio of ions **51**, **52**, and **53** (X = CH_3) also satisfactorily predicts the chemical shift of the p-CH_3 if the chemical shifts are taken as δ 2.8 (**51**), 2.3 (**52**), and 2.4–2.5 (**53**). Qualitatively it is easily seen that ring proton chemical shifts and the ortho–meta chemical shift differences may be accounted for by equilibrating ions **51**, **52**, and **53**. Chemical shifts of ring protons will be much more sensitive to the nature of X and the amount of ring to carbonium ion π bonding in ion **52**; therefore, adequate

(27) N. C. Deno, H. G. Richey, Jr., J. S. Liu, D. Lincoln, and J. O. Turner, *J. Amer. Chem. Soc.*, **87**, 4533 (1965).

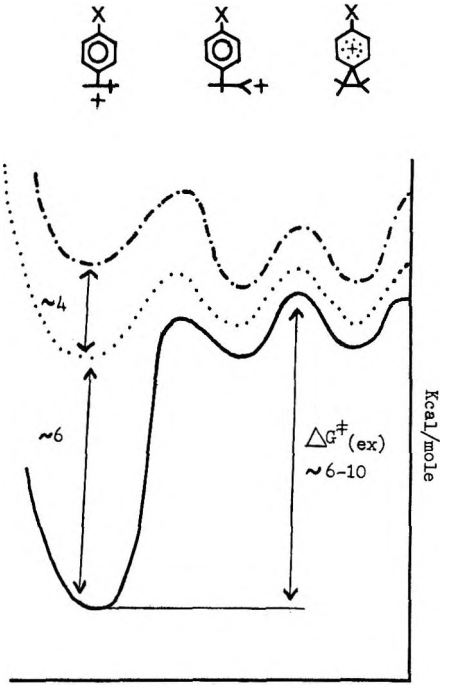

Figure 14.—A suggested qualitative free energy surface for the relative free energies of ^+p-$XC_6H_4CMeCMe_3$, ^+p-$XC_6H_4CMe_2CMe_2$, and p-X-phenonium ion; X = CH_3O (——), CH_3 (· · · · ·), H (—·—·).

models for these protons are not available. Still, the above-suggested approximate ratios of ions also predict the average ring proton chemical shifts within 0.2 ppm, where the average ring ortho and meta hydrogen chemical shifts of contributing ions are taken from anisonium ion, **51**, X = OCH_3, and **52**, X = CF_3.

We have not in any way tried to optimize all of the parameters, and better agreement could undoubtedly be obtained by slightly different equilibrium ion concentrations, allowing for increased downfield shift in a through d in ions **51** and **52** as one proceeds from CH_3O to CH_3 to H, *and by recognizing that ratios of drowning products may themselves only reflect approximate equilibrium ratios of ions.*

If the interpretation of a negative and apparently large activation entropy in equilibration of CH_3 groups in the p-$CH_3OC_6H_4C(CH_3)C(CH_3)_3^+$ ion is correct in its conclusion that the highest energy transition state is that for step 2, eq 3, anisonium ion **48** must be very nearly equal to if not higher in energy than the β-anisyl alkyl cation **47**, and replacement of CH_3O by CH_3 or H should not lead to a system in which the anisonium ion is the most stable ion present.

Figure 14 represents our interpretation of the relative free energies of benzylic p-$XC_6H_4CMe_2CMe_2^+$ and phenonium ions as a function of X. *The only systems where phenonium ions are firmly established as the only major species present in strong acid remain those in which the phenonium ion cyclopropyl ring does not possess substituents capable of stablizing positive charge.*

In the time interval since the original submission of this manuscript in substantially its present content,[4] Olah and coworkers[24b] have published conclusions in general agreement with those arrived at here, although it is still maintained by Olah and coworkers on the basis of ^{13}C nmr that the major species is benzylic ion **51** when X is CH_3 and phenonium ion **53** when X is H.

Summary of Conclusions.—The carbonium ions and their precursors reported in this paper are summarized in Table I with their proton chemical shifts.

There are at least two acids present in $SbF_5 \cdot SO_2$ solutions, SbF_5 itself and unavoidable small amounts of HF, and this tends to complicate the results obtained in ionization of alcohols. In terms of the theory of hard and soft acids we would expect the OH group to lie somewhere between Cl and F in its effectiveness as a leaving group when attacked by $SbF_5(Sb_2F_{10})$. At $-60°$ our results with the primary alcohols agree well with the idea that ^+p-$CH_3OC_6H_4CH(CH_3)CH_2OH$-$SbF_5^-$ and ^+p-$CH_3OC_6H_4C(CH_3)_2CH_2OHSbF_5^-$ ionizations proceed with anisyl participation *via* phenonium ions, but that the alkyl OH_2^+ does not leave from a primary carbon at any appreciable rate at $-60°$. The β-anisylethanol does not form the anisonium ion in $FSO_3H \cdot SbF_5$, a H^+ superacid, at $-60°$.

It is pertinent to this point that we have confirmed[3] that, although *n*-propyl fluoride gives an isopropyl ion in $SbF_5 \cdot SO_2$, the chlorides and bromides do not. Apparently, ionization of primary halides other than fluoride requires at least some anchimeric assistance, if only from neighboring alkyl groups. Products at $-60°$ are then determined by competition between $SbF_5 \cdot SO_2$ and $HF \cdot SbF_5$ for the alkyl OH group. This appears to carry over also to secondary alcohols but with a new twist.

Ionization of OH from a secondary carbon when attacked by SbF_5 seems to proceed by a mechanism in which the β-anisylalkyl cation is formed without assistance from the anisyl group, or presumably neighboring alkyl, hydride, or solvent. Strong evidence, we believe, indicates that at $-60°$ hydride migration is at least ten times faster than anisyl migration for the ion ^+p-$CH_3OC_6H_4CH(CH_3)CHCH_3$, and methyl migration is at least nearly as fast as anisyl migration in the ion ^+p-$CH_3OC_6H_4C(CH_3)_2CHCH_3$ at $-60°$. An additional term, k_E, the overall rate constant for eq 5, could be introduced into a generalized formulation for the observed solvolytic rate as in eq 6. In eq 6 k_Δ and k_s represent nucleophilic participation by neighboring groups and solvent, respectively, but k_E is a rate constant for what is essentially electrophilic substitution on X. The $(AXR)^n$ is either a transition state or intermediate which ionizes without aryl assistance.

$$A^{n+} + XR \xrightarrow{\text{slow}} (AXR)^{n+} \xrightarrow{\text{fast}} (AX)^{n-1} + R^+ \quad (5)$$

$$k_{obsd} = Fk_\Delta + k_s + k_E \quad (6)$$

The fate of the protonated secondary alcohol apparently reflects the increased ease with which a secondary carbonium ion may be formed over a primary one, since during the process of warming to -20 from $-60°$ disappearance of the protonated alcohol *p*-$CH_3OC_6H_4CH(CH_3)CH(CH_3)OH_2^+$ is accompanied by the appearance of product ions of anisyl group migration or anisonium ion formation. Our results seem at least consistent with the idea that protonated secondary alcohols will ionize in $SbF_5 \cdot SO_2$ at temperatures between -60 and $-20°$ *with* anisyl participation. To reconcile this with the behavior of *p*-$CH_3OC_6H_4C(CH_3)_2CH_2OH_2^+$ at $-20°$, we suggest that this ion may convert rapidly to the $OH \cdot SbF_5$ complex, which at $-20°$ then ionizes without anisyl participation to a primary ion or ion pair precursor of **21**.

The consequences of the previous arguments are apparent in Scheme V, for example, with the assumption that the reaction represented by eq 5 is important where A is SbF_5 but not where A is HF, $HFSb_2F_{10}$, etc.

In the ionization of secondary alcohols in $SbF_5 \cdot SO_2$, we have observed an unexpected decrease in migratory aptitude of anisyl groups toward a carbonium ion center relative to CH_3 or H migration. The unique properties of the $SbF_5 \cdot SO_2$ solvent system offer at least two basically different explanations for this result.

First of all, rapid initial coordination of the anisyl CH_3O group by SbF_5 may destroy the ability of the anisyl group to provide anchimeric assistance to ionization, or, even if such assistance is not required, the migration aptitude of the anisyl group toward a preformed carbonium ion center is reduced to such an extent that CH_3 or H migration rates are comparable to or greater than that of anisyl. The first step in the reaction schemes presented previously would be formation of $^+CH_3O(A)C_6H_5CR_2CR'X$ (A is SbF_5 or H^+), and all anisyl alkyl cations such as **23**, **38**, **40**, etc., in Schemes III–V should be written with complexed methoxy groups $[CH_3O^+(A)-]$. We have some objections to this mechanism, however, in that we have recently[17] found that prior coordination of CH_3O to BF_3 in the case of $(CH_3O)_2C_6H_5CH_2CH_2X$ followed by addition of SbF_5 produces the *o,o*-2,6-dimethoxyphenonium ion, not the oxonium ion analog of **10**. This in turn implies that under the conditions reported here the oxonium ion **10** was formed from uncomplexed *o*-$CH_3OC_6H_5CH_2CH_2Cl$ precursor in $SbF_5 \cdot SO_2$. It also demonstrates that Lewis acid coordination of anisyl CH_3O group will not necessarily prevent anisonium ion formation.

A variation of the above mechanism assumes competitive formation of two intermediates, ^+p-$CH_3O(A)C_6H_5CR_2CH(CH_3)OH$ and either the anisonium ion or p-$CH_3OC_6H_5CR_2CHCH_3^+$. The first of these gives only products of R migration, whereas the latter two produce products of anisyl migration (or anisonium ion formation). This mechanism seems most satisfactory to us for the case of initial formation of anisonium ion rather than p-$CH_3OC_6H_5CR_2CHCH_3^+$, since it more readily accounts for the greater anisyl migration where R_2 is CH_3, CH_3 than where R_2 is CH_3, H. In this case in Scheme V, for example, ion **42** should be written with $^+CH_3O(A)-$, ion **40** should be left as is or replaced with an anisonium ion, and the methoxyls of **38** (Scheme IV) and **23** (Scheme III) indicated as SbF_5 complexed. We are not satisfied with this mechanism, however, since it requires fortuitiously comparable rates for SbF_5 coordination to CH_3O and for anisonium ion formation.

At this time we prefer the following alternative explanation for our results in the secondary alcohol series. Very recently Brown and Kim[6c] and Ramsey and Das,[28] have independently suggested that the solvolysis of secondary alkylaryl derivatives in solvents such as acetic and formic acid proceeded through intimate ion pair intermediates. Brown and Kim reached this conclusion from a general consideration of solvolysis rates and activation parameters; Ramsey and Das based their conclusion on correlation of the logarithm of titrimetric rate constants with aryl group

(28) B. G. Ramsey and N. K. Das, *J. Amer. Chem. Soc.*, in press.

ionization potential. We suggest here then that the essential difference between the $SbF_5 \cdot SO_2$ solvent system and acetic acid, formic acid solvent systems, etc., is the combined absence of the intimate ion pair in $SbF_5 \cdot SO_2$ and significant solvent stabilization of the cation center. In other words, we suggest that in a "free" poorly solvated β-arylalkyl carbonium ion alkyl or hydride shift to form a benzylic ion may be faster than phenonium ion formation or net aryl migration. Some brief speculations as to why this might be the case are given below.

In an intimate ion pair ($R^+ \cdots XS_n^-$) the leaving group X, which it is reasonable to assume is at least partially solvated, should have a greater effect in stabilization of the β-anisylalkyl cation ($^+AnCR_2CR'_2X\bar{S}_n$) than the benzylic ion ($^+AnCRCRR'_2X\bar{S}_n$), in which the positive charge is largely delocalized into the anisyl ring. There are steric considerations also, for in the free β-anisyl cation migration of R to form the benzylic ion may take place from either side of the plane of the carbonium ion. In the ion pair, however, R migration would be expected only from the more restricted geometry in which the migrating R (H or CH_3) is coplanar with and on the opposite side of the anion of the ion pair. This geometry would also introduce significant steric interactions between the anisyl group and the partially solvated leaving group XS_n^-. We would not, therefore, be surprised to find that conversion of β-arylalkyl carbonium ion ion pairs to benzylic ions (or ion pairs) is slower than the rate of formation of benzylic ions from the "free" alkyl cation. Dissociation of intimate ion pairs may be faster in $SbF_5 \cdot SO_2$ than other solvents because SbF_5 is polymeric and an anion transport mechanism similar to that for H^+ and OH^- ions in water is available. Further, since coordination of CH_3O by SbF_5 should reduce not only the ease of phenonium ion formation, but also benzylic ion formation, *relative* competitive rates of anisyl (or anisonium ion formation) and alkyl or hydride migration may be insensitive to whether the CH_3O group is acid complexed or not in $SbF_5 \cdot SO_2$.

Experimental Section

All compounds had nmr and infrared spectra consistent with the assigned structure. Physical properties agreed with those reported in the literature.

2-(o-Anisyl)-1-chloroethane.—Lithium aluminum hydride reduction of *o*-anisylacetic acid gave the alcohol, which was converted to the chloride in 66% yield by reaction with excess thionyl chloride in pyridine. The chloride was purified by distillation at 67–68° (0.4 mm), $n^{28}D$ 1.5321.

Anal. Calcd for $C_9H_{11}OCl$: C, 63.34; H, 6.50. Found: C, 63.18; H, 6.46.

2,3-Dihydrobenzofuran.—Atmospheric hydrogenation of benzofuran in ethanol using 5% Pd on C gave dihydrobenzofuran.

4-(p-Anisyl)-1-chlorobutane.—Reaction of 4-(*p*-anisyl)-1-butanol, obtained from lithium aluminum hydride reduction of the acid, with excess thionylchloride in pyridine gave the title compound in 76% yield after distillation, $n^{27}D$ 1.5215. Gas chromatography on Carbowax 20M indicated a purity of ≥99%.

Anal. Calcd for $C_{11}H_{15}OCl$: C, 66.48; H, 7.61. Found: C, 66.63; H, 7.80.

4-(p-Anisyl)-1-bromobutane.—The bromide was obtained from reaction of the corresponding alcohol with thionyl bromide. Distillation at 0.07 mm (bp 112°) gave a product which was 75% bromide, 11% chloride, and 12% alcohol (by gas chromatography).

1-(p-Anisyl)-1-methoxybutane.—The benzylic alcohol was prepared in 92% yield by adding 4-methoxybenzaldehyde to *n*-propylmagnesium bromide in ether. The crude alcohol was treated with a mixture of excess sodium hydride in dimethyl sulfoxide followed by addition of methyl iodide. The reaction was hydrolyzed by cautious addition of water, and the mixture was poured into a large volume of water and extracted with pentane. The pentane solution was washed with water, dried, and evaporated to give a quantitative yield of the crude ether. Distillation at 0.09 mm (bp 65°) yielded the product.

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.29; H, 9.30.

4-(p-Anisyl)-4-methyl-1-chloropentane.—The Grignard reaction of methylmagnesium iodide with butyrolactone gave 2-methyl-2,5-pentanediol in 43% yield after distillation, bp 74–79° (0.15 mm). Reaction of the diol with 3 equiv of anhydrous aluminum chloride and 0.5 equiv of anisole in CS_2 under typical Friedel–Crafts conditions gave, after work-up and vacuum distillation, the alcohol 4-(*p*-anisyl)-4-methylpentanol, bp 113–115° (0.3 mm). The alcohol was converted in 50% yield to 4-(*p*-anisyl)-4-methyl-1-chloropentane by refluxing in carbon tetrachloride with an equimolar amount of triphenylphosphine, according to the method of Lee and Downie.[29] The 4-(*p*-anisyl)-4-methylpentyl chloride was obtained as a 70:30 mixture of the ortho and para isomers by distillation (bp 88–94°) at 0.2 mm. A second distillation provided a product whose nmr spectrum in the region of δ 7.0 indicated only para substitution.

2-(p-Anisyl)-2-methoxy-3-methylpentane.—The Grignard reaction of *p*-anisylmagnesium bromide with 3-methyl-2-pentanone gave 2-(*p*-anisyl)-3-methylpentan-2-ol. The crude alcohol was allowed to react first with a 2 molar excess of sodium hydride in dimethyl sulfoxide followed by 4 equiv of methyl iodide. Hydrolysis with water followed by petroleum ether (bp 30–60°) extraction and vacuum distillation at 0.2 mm (bp 84–90°) gave the title compound (86%) contaminated with 11% of 2-(*p*-anisyl)-3-methyl-2-pentene (structure based on positive Br_2 and permanganate tests for olefin, absence of vinyl hydrogens in nmr, and analysis.)

2-(p-Anisyl)-1-propyl Methanesulfonate.—Crude 2-(*p*-anisyl)-propionic acid was prepared in 100% yield by analogy to the method of Hauser,[30] from *p*-anisylacetic acid, potassium amide in liquid ammonia, and methyl iodide. Lithium aluminum hydride reduction of the acid gave the propanol, which was converted by excess methanesulfonyl chloride in pyridine to 2-(*p*-anisyl)-1-propyl methanesulfonate mp 48–49°.

Anal. Calcd for $C_{11}H_{16}O_4S$: C, 54.08; H, 6.60. Found: C, 53.85; H, 6.52.

2-(p-Anisyl)-2-*d*-1-propyl Methanesulfonate.—An ether solution of the 2-*p*-anisylpropionic acid dicarbanion, prepared from reaction of the acid with 2 equiv of KNH_2 in liquid ammonia, was drowned in D_2O. The resultant 2-deuterated acid was reduced to the alcohol with lithium aluminum hydride, and the title mesylate was prepared as above for the nondeuterated compound. Only 55% deuteration was achieved; however, the nmr spectrum of the nondeuterated ion was easily subtracted from the spectrum of the mixture in $SbF_5 \cdot SO_2$.

2-(p-Anisyl)-2-methylpropanol.—The methylation of 2-(*p*-anisyl)propionic acid was carried out first by reaction with 2 equiv of $NaNH_2$ in liquid ammonia and then addition of methyl iodide. Work-up and recrystallization from hexane gave 2-*p*-anisyl-2-methylpropionic acid (67% yield), mp 82–83.5°, which was reduced to the desired propanol in 92% yield with lithium aluminum hydride.

3-(p-Anisyl)-2-chlorobutane.—Treatment of 1-(*p*-anisyl)-2-propanone with $NaNH_2$ in liquid ammonia, followed by addition of methyl iodide, gave 2-(*p*-anisyl)-3-butanone in 60% yield after distillation, bp 72–75° (0.1 mm). A mixture of erythro and threo isomers was obtained after lithium aluminum hydride reduction of the ketone to the alcohol, bp 66° (0.05 mm). Reaction of 3-*p*-anisyl-2-butanol with thionyl chloride in pyridine followed by short-path distillation at 86° (0.1 mm) gave a liquid, $n^{19.5}D$ 1.5273, which was a mixture of *erythro*- and *threo*-3-*p*-anisyl-2-chlorobutanes.

Anal. Calcd for $C_{11}H_{15}OCl$: C, 66.45; H, 7.61. Found: 66.53; H, 7.60.

4,4,4-Trideuterio-3-(p-anisyl)-2-butanol.—The title compound was prepared as above from 1-*p*-anisyl-2-propanone, $NaNH_2$,

(29) J. B. Lee and I. M. Downie, *Tetrahedron*, **23**, 359 (1967).

(30) C. R. Hauser and W. J. Chambers, *J. Amer. Chem. Soc.*, **78**, 4942 (1967).

and CD_3I followed by reduction of the methylated ketone with $LiAlH_4$ to the alcohol. The nmr spectra indicated greater than 98% deuteration in the desired compound; overall glc purity was 95%.

2-(*p*-Anisyl)-2-methyl-3-butanol.—The corresponding ketone was prepared by successive methylation of 1-(*p*-anisyl)-2-propanone with methyl iodide and sodium amide in liquid ammonia. Lithium aluminum hydride reduction of the ketone gave the desired alcohol in 87% yield, bp 83° (0.03 mm).

Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.17; H, 9.34. Found: C, 74.31; H, 9.33.

4,4,4-Trideuterio-3-tridueteriomethyl-3-(*p*-anisyl)-2-butanol.—The title compound was prepared as above for 2-(*p*-anisyl)-2-methyl-3-butanol, using CD_3I in methylation of 1-(*p*-anisyl)-2-propanone. Within experimental error integration of nmr spectra of the title compound indicated greater than 98% theoretical deuteration in the desired position.

1-(*p*-Anisyl)-2-methyl-2-propanol.—The Grignard reaction of methyl iodide and ethyl *p*-anisylacetate gave the title compound in 94% yield.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.59; H, 8.94.

2-(*p*-Anisyl)-2,3-dimethyl-3-butanol.—The ethyl ester of 2-(*p*-anisyl)-2-methylpropionic acid was converted to the title alcohol by reaction for 15 hr at room temperature with methylmagnesium iodide in ether. Work-up followed by distillation (0.08 mm) gave the alcohol, bp 85–90°, in 50% yield.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.10; H, 9.66.

1,1,1-Trideuterio-2-tridueteriomethyl-3-(*p*-anisyl)-3-methyl-2-butanol.—The Grignard reaction of methyl-d_3-magnesium iodide in ether with the ethyl ester of 2-(*p*-anisyl)-2-methylpropionic acid gave the desired title alcohol after work-up in the usual fashion. Nmr spectra indicated greater than 98% deuteration in the desired position.

Preparations of Ions.—The ions were prepared by adding the substrate (0.02 mol) dropwise from a syringe equipped with a 25-gauge needle to a rapidly stirred solution of distilled SbF_5 (0.07 mol) in excess SO_2 (5–7 ml), following the general procedure of Olah.[31]

In general, a 3:1 molar ratio of SbF_5 to substrate was found necessary to obtain complete ionization of the substrate. The reactions were run under dry nitrogen.

The nmr spectra was taken on a Varian Associates Model A-60 spectrometer equipped with a variable-temperature probe and improved to give a signal-to-noise ratio of 15:1. The spectra were obtained using internal capillary reference tetramethylsilane (TMS) which was calibrated against tetramethylammonium ion (chloride in $SbF_5 \cdot SO_2$ solution, δ 2.95 ppm). Chemical shifts are reported as parts per million downfield from TMS. The chemical shifts for all ions reported here are computed in Table I.

Quenching of Ions.—Quenching of the ions was accomplished by pouring the ion solution into dry methanol or methanol and sodium methoxide at −70°. After stirring for 1 hr, the mixture was evaporated to dryness on a rotary evaporator, and the residue was taken up in water and pentane. The aqueous phase was extracted with fresh pentane and the pentane solution was dried ($MgSO_4$) and evaporated. Identification of the products was by glc analysis, by comparison, and by retention times and peak enhancement. Sometimes products were also trapped as they were eluted from the glc and were identified by comparing their infrared or nmr spectra to those of authentic materials.

Quenched $SbF_5 \cdot SO_2$ solutions of 2-*p*-anisylethanol yielded 45% 2-(*p*-anisyl)-1-methoxyethane and 41% of the starting alcohol.

Quenched solutions of 2-(*o*-anisyl)-1-chloroethane, after extraction of pentane with aqueous Na_2SO_3, gave 20% 1,2-dihydrobenzofuran (per cent yield of neutral product).

The 4-(*p*-anisyl)-1-chlorobutane $SbF_5 \cdot SO_2$ solutions after quenching gave a crude product whose nmr spectrum agreed with that of authentic 1-(*p*-anisyl)-1-methoxybutane.

Registry No.—2-(*o*-Anisyl)-1-chloroethane, 35144-25-3; 4-(*p*-anisyl)-1-chlorobutane, 23002-61-1; 4-(*p*-anisyl)-1-bromobutane, 35191-43-6; 1-(*p*-anisyl)-1-methoxybutane, 35144-27-5; 4-(*p*-anisyl)-4-methyl-1-chloropentane, 35144-28-6; 4-(*o*-anisyl)-4-methyl-1-chloropentane, 35144-29-7; 4-(*p*-anisyl)-4-methylpentanol, 26315-95-7; 2-(*p*-anisyl)-2-methoxy-3-methylpentane, 35144-31-1; 2-(*p*-anisyl)-1-propyl methanesulfonate, 35144-32-2; 2-(*p*-anisyl)-3-methylpropionic acid, 2955-46-6; 2-(*p*-anisyl)-3-butanone (erythro), 35144-34-4; 2-(*p*-anisyl)-3-butanone (threo), 35144-35-5; 3-(*p*-anisyl)-2-chlorobutane (erythro), 26348-35-6; 3-(*p*-anisyl)-2-chlorobutane (threo), 26348-36-7; 2-(*p*-anisyl)-2-methyl-3-butanol, 14614-79-0; 1-(*p*-anisyl)-2-methyl-2-propanol, 35144-39-9; 2-(*p*-anisyl)-2,3-dimethyl-3-butanol, 23002-62-2.

(31) G. A. Olah, *et al.*, *J. Amer. Chem. Soc.*, **86**, 1360 (1964).

Alkylation of Benzene with Straight-Chain Olefins. IV. Effect of the Counterion on the Isomerization of Secondary Carbonium Ions

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1-Dodecene and *trans*-6-dodecene alkylate benzene in the presence of anhydrous hydrogen fluoride at 0 and 55° to give different isomer distributions of phenyldodecanes. Lower olefins, C_{10} and C_8, behave in a similar manner, but 1-hexene and *trans*-3-hexene afford similar amounts of 2- and 3-phenylhexanes at 0°. Addition of BF_3 to HF alters the isomer distribution significantly and raises the amount of the 2 isomer at the expense of the internal ones. At 35° or higher alkylation in the presence of HF-BF_3 is accompanied by isomerization of the products to a certain equilibrium distribution that results in the same isomer distribution regardless of the position of the double bond in the starting olefin. This product isomerization is suppressed at 0° and the isomer distribution of the products depends on the position of the double bond in the olefin. Experimental evidence is presented which shows that the change in the isomer distribution due to the addition of BF_3 at 0°, *i.e.*, in the absence of product isomerization, is due to the introduction of BF_4^- ions in the ion pairs rather than to the rise in the acidity of the system.

Alkylation of benzene with a long-chain olefin in the presence of strong Friedel–Crafts catalysts such aluminum chloride affords all the isomeric phenylalkanes except the 1 isomer.[1] Friedel–Crafts alkylations have long been known to be accompanied by isomerization, disproportionation, and transalkylation.[2-5] The phenylalkanes initially formed undergo extensive isomerization to a certain equilibrium distribution that is different from the isomer distribution obtained in the absence of product isomerization. The reaction in the presence of product isomerization is thermodynamically controlled and the isomer distribution of the product is the same regardless of the position of the double bond in the starting olefin.[6,7] Consequently both 1-dodecene and *trans*-6-dodecene afford nearly identical isomer distributions including about 32% 2-phenyldodecane and 31% 5 and 6 isomers. We define this as a distribution ratio of 32:31. Product isomerization which accompanies the alkylation reaction can be suppressed by carrying out the reaction at 0° or by using a weaker catalyst such as aluminum chloride–nitromethane. Under these conditions the isomer distribution of the product is kinetically controlled[7] and depends on the position of the double bond in the olefin.[6] Thus 1-dodecene shows a significantly higher distribution ratio, 44:20, while the internal olefin is very much lower, 18:53.

Alkylation in the presence of anhydrous hydrogen fluoride is not accompanied by product isomerization even at 55°. It is similar to the reaction with aluminum chloride at 0° in that terminal and internal olefins afford different isomer distributions.[8] However, the isomer distribution of the product from the reaction with HF is significantly different from that with $AlCl_3$ even though both are carried out under conditions which do not permit product isomerization. Thus at 0–5° 1-dodecene affords the ratio 18.5:47.7 in the presence of HF and 44.0:19.7 in the presence of $AlCl_3$.

From the point of view of their catalytic activity in these reactions the most important differences between HF and $AlCl_3 \cdot HCl$ are (a) the difference in their acidity, and (b) the difference in the mobility of F^- and $AlCl_4^-$ ions. The Hammett acidity function, H_0, for anhydrous HF is -10.8 and that for $AlCl_3 \cdot HCl$ is about -16 which makes the latter a much stronger acid. The acidity of hydrogen fluoride, however, can be varied over a very wide range (six powers of 10) by addition of certain Lewis acids (coacids) such as BF_3, NbF_5, or SbF_5 which raise the acidity of the solvent by setting up the equilibrium[9]

$$BF_3 + 2HF \rightleftharpoons H_2F^+ + BF_4^-$$

Since the ionic product of anhydrous hydrofluoric acid is only 2×10^{-10} and the equilibrium constant for the reaction

$$BF_4^- \rightleftharpoons BF_3 + F^-$$

is between 5×10^{-3} and 2.5×10^{-7} addition of BF_3 to HF converts fluoride ions into tetrafluoroborate ions.[10-12] This makes the system HF–BF_3 particularly useful for this study since both the acidity and the counterion, or gegenion, of the ion pair can be varied over a wide range and the experimental conditions can be controlled such that alkylation occurs in the absence of product isomerization.

Results

Alkylation of benzene with 1-dodecene in the presence of anhydrous hydrogen fluoride at 0° affords a product with a distribution ratio of 18.5:47.7. Addition of gaseous BF_3 to the reaction mixture results in a substantial rise in the amount of the 2-phenyldodecane and a corresponding decrease in the internal isomers. Thus a 5% solution of BF_3 in HF at the same temperature raises the distribution ratio to 41.0:26.8. This effect appears to be a function of the amount of BF_3

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in HF as can be seen from Table I. The same type of effect is also observed with the internal olefin, *trans*-6-

TABLE I

ALKYLATION OF BENZENE WITH OLEFINS IN THE PRESENCE OF HF–BF_3 AT 0–5°

Olefin	% BF_3 in HF	% 2-Phenyl	% 3-Phenyl	% 4-Phenyl	% 5- + 6-Phenyl
1-Dodecene	0	18.5	15.5	18.3	47.7
	1.0	22.5	16.7	16.0	44.8
	2.5	35.0	19.4	14.7	30.9
	4.0	39.7	20.3	13.8	26.2
	5.0	41.0	18.4	13.8	26.8
		100.0[a]			
b	5.0	33.5	17.8	16.2	32.5
		37.8[a]	25.3	17.4	19.5
c	2.1 (NaF)	21.6	17.2	16.3	44.9
d	6.3 (KBF_4)	22.5	17.0	16.9	43.6
6-Dodecene	0	10.6	12.7	17.9	58.6
	5.0	24.7	15.8	15.9	43.6
1-Decene	0	22.6	21.8	23.4	32.2
	5	41.7	22.1	16.4	19.8
5-Decene	0	16.2	19.3	25.5	39.0
	5.0	29.1	20.7	20.3	29.9
1-Octene	0	32.1	32.4	35.5	
	5.0	47.3	28.3	24.4	
4 Octene	0	28.5	32.4	39.1	
	0	40.0	29.2	30.8	
1-Hexene	0	57.3	42.7		
	5	63.5	36.5		
e	0	62.6	37.4		
3-Hexene	0	57.0	43.0		
	5	61.0	39.0		
e	0	59.8	40.2		

[a] Analysis of the added 2-phenyldecane to detect product isomerization. [b] Reaction was carried out at 35–40°. [c] Sodium fluoride instead of BF_3 was used in this experiment and it amounts to 0.5 *M*. [d] Potassium tetrafluoroborate was used instead of BF_3 and it amounts to 0.5 *M*. [e] Reaction was carried out at 155°.

dodecene, where addition of 5% BF_3 raises the distribution ratio from 10.6:58.6 to 24.7:43.6. A sample of 2-phenyldecane added along with the olefin to detect any product isomerization showed no isomerization to the internal phenyldecanes indicating the absence of any product isomerization as well. At 35°, however, the 2-phenyldecane tracer showed extensive isomerization to the internal isomers and the distribution ratio of the product, phenyldodecane, fell to 33.5:32.5, which is similar to that obtained with $AlCl_3 \cdot HCl$ at the same temperature.[7] Alkylation in the presence of a 0.5 *M* solution of KBF_4 in HF raises the 2-phenyl content of the product by a small but measurable amount (from 18.5 to 22.5%) as does also alkylation in the presence of KF (Table I).

Alkylation of benzene with C_{10} or C_8 olefins in the presence of anhydrous hydrogen fluoride is similar to that with the dodecenes in that the position of the double bond is a factor in the isomer distribution of the product. Table I shows that the amount of the 2-phenylalkane is greater for the terminal olefins than for the internal ones. Also addition of BF_3 to HF results in a substantial change in the isomer distribution of the products from both types of olefins in favor of greater formation of the 2-phenylalkane isomer at the expense of the internal ones.

Both 1-hexene and *trans*-3-hexene alkylate benzene in the presence of HF at 0° to afford, within the experimental error, similar amounts of 2- and 3-phenylhexanes. This indicates that in contrast to the higher olefins the position of the double bond is not a factor in the isomer distribution of the product. However, at 55° a slight difference between the two olefins appears with the α olefin producing slightly greater amounts of the 2 isomer. A similar result was obtained with HF–BF_3 or recycled aluminum chloride (Table II).

TABLE II

ALKYLATION OF BENZENE WITH 1- AND 3-HEXENES IN THE PRESENCE OF RECYCLED $AlCl_3$[a]

Olefin	Temp, °C	% 2-Phenyl	% 3-Phenyl
1-Hexene	5	67.2	32.8
3-Hexene	5	62.5	37.5
1-Hexene	35–40	68.7	31.3
3-Hexene	35–40	65.9	34.1

[a] Recycled aluminum chloride was used to prevent product isomerization.[6]

In the presence of HF alone the yields of the monoalkylbenzenes were ~90%. Only the hexenes gave a small amount (2%) of dialkylbenzene. Addition of BF_3 resulted in a rise in the amount of dialkylbenzene which increased with decreasing chain length and amounted to 25% of the yield in the case of the hexenes. Under these conditions the yield of phenylhexanes dropped to 62%.

Discussion

The generally accepted mechanism for Friedel–Crafts alkylations involves interaction of the olefin with the catalyst to form a carbonium ion, the corresponding ion pair, or a polarized complex. This undergoes rapid isomerization in varying degrees and finally attacks benzene in what is considered to be the rate-determining step, to form the products.[13] In the alkylation of benzene with a long-chain olefin such as 1-dodecene the alkylation step is too fast to permit the intermediate secondary carbonium ions to come to equilibrium prior to their attack on benzene.[6,8] The present data indicate that shortening the alkyl chain to C_{10} or C_8 is not sufficient to bring about the equilibrium condition among the carbonium ions before the alkylation step of the reaction sequence. Consequently, the α olefins 1-decene and 1-octene afford different isomer distributions from the corresponding internal ones, *trans*-5-decene and *trans*-4-octene. With the hexenes, however, the secondary carbonium ions apparently do come to equilibrium at 0° and the isomerization reaction

$$C\text{-}C\text{-}C\text{-}C\text{-}\overset{+}{C}\text{-}C \rightleftharpoons C\text{-}C\text{-}C\text{-}\overset{+}{C}\text{-}C\text{-}C$$

is, therefore fast compared with the alkylation step itself. Consequently both 1-hexene and *trans*-3-hexene afford similar isomer distributions. This condition of equilibrium among the hexyl carbonium ions appears to be only barely reached since at 55° the two isomeric olefins no longer afford the same isomer distribution. The difference between them, though small, is real and

(13) S. H. Patinkin and B. S. Friedman in ref 3, Chapter 14, p 3.

reproducible.[14] It is also obtained with recycled aluminum chloride both at 5 and 35° (Table II).

Addition of BF_3 to HF at 0° alters the isomer distributions of all of the products and results in a substantial rise in the amount of the 2 isomer at the expense of the internal ones. Boron trifluoride increases the acidity of the system by shifting the equilibrium toward the formation of H_2F^+. The present data indicate that the rise in acidity is not responsible for the change in the isomerization across the chain or the substantial increase in the 2-phenyl content of the product, for, if this were so, then a decrease in acidity should be expected to have the opposite effect. Alkali metal fluorides behave as bases in HF and are completely ionic.[16] A 0.5 *M* solution of NaF in HF decreases the Hammett acidity function, H_0, from -10.8 to -8.6.[12] Alkylation of benzene with 1-dodecene in the presence of a 0.5 *M* NaF in HF resulted in an increase in the 2-phenyl content of the product from 18.5 to 21.6%. Therefore, decreasing the acidity of the catalyst did not result in a corresponding decrease in the 2-phenyl content of the product as would be expected had the original change in the isomer distribution been due to the increase in the acidity of the system brought about by addition of BF_3 to HF.

The absence of any effect for the acidity on the isomerization of the intermediate carbonium ions was also demonstrated for aluminum chloride alkylations. It is well known that in $AlCl_3$, H_2SO_4, and other acid-catalyzed alkylations, strong bases are produced which gradually destroy the catalyst.[17,18] Repeated alkylations of benzene with 1-dodecene in the presence of the same $AlCl_3$ catalyst phase were carried out at 0–5° until the catalyst became too weak to bring about complete alkylation and large amounts of the α olefin appeared in the product (seven alkylations). The isomer distributions of all the products from all of these reactions remained essentially the same with a distribution ratio of 43:20. Since 0.5 *M* NaF in HF, which has H_0 -8.6, is an effective alkylation catalyst the acidity of the last recycled $AlCl_3$ must have fallen below this level. Therefore, in this series of experiments the acidity was gradually decreased from H_0 -16 to below -8.6 without any visible effect on the isomer distribution of the product. The same result was also obtained in the presence of NaCl which acts as a base toward $AlCl_3$.[19] Thus alkylation with a catalyst that contained a mixture of recycled $AlCl_3$ plus NaCl and the same recycled catalyst plus fresh $AlCl_3$ afforded the same isomer distribution in spite of the large difference in the acidity of the two catalyst systems.

As was mentioned above, addition of BF_3 to HF increases the amount of the 2 isomer at the expense of the internal ones. This is more readily seen for the α olefins where the proton enters the alkylating agent near the end of the chain. Thus 1-decene affords the ratio 22.6:32.2 in the presence of HF and the ratio 41.7:19.8 in the presence of HF–BF_3. In other words, there is a tendency for the positive charge of the ion pair to remain near the end of the chain. This is also true of the other olefins and indicates that addition of BF_3 slows down the isomerization reaction of the intermediate carbonium ions relative to their rates of alkylation of benzene. This can also be seen from the fact that 1-dodecene affords 18.5% 2 isomer in the presence of HF and 41.0% in the presence of HF–BF_3. The slowing of the isomerization across the chain causes the intermediate ions to be farther away from the equilibrium position in the presence of HF–BF_3 than in the presence of HF alone.[20]

Studies on the reaction

$$BF_4^- \rightleftharpoons F^- + BF_3$$

in HF show that the equilibrium is largely toward the formation of the tetrafluoroborate ion.[11,12] The present data is in accord with the suggestion that the slowing of the isomerization reaction along the chain of an α olefin is due to the replacement of fluoride ions by tetrafluoroborate ions. The great mobility of F^- in HF solution is well known and Kilpatrick and Luborsky have demonstrated that addition of BF_3 to the potassium fluoride solution in HF results in a drop in conductivity owing to the replacement of solvated fluoride ions by the less mobile tetrafluoroborate ions.[11,21] Since the ions exist as ion pairs the negative ion must move along with the positive charge as it moves across the chain. This is in agreement with the behavior of KBF_4 which has been shown to be completely ionic in HF. As would be expected, however, its effect on the isomer distribution is not so large as that of BF_3 since in the latter case the fluoride ion is replaced by the tetrafluoroborate ion while addition of KBF_4 leaves the concentration of the fluoride ion essentially the same. A much larger effect was obtained by alkylation in the presence of HF–BF_3–KBF_4 where the distribution ratio from 1-dodecene rose to 39.0:27.8. Since KBF_4 acts as a base toward HBF_4[22] it was possible to alkylate with it at 55° without interference from product isomerization.

Finally, examination of Table I reveals that addition of BF_3 results in an increase in the amount of the 2 isomer from both types of olefins at the expense of the internal ones. In other words, there is a shift in the distribution of the intermediate carbonium ions toward greater formation of the 2 ion. Thus 5-decene affords the ratio 16.2:39.0 in the presence of HF and the ratio 29.1:29.9 in the presence of HF–BF_3. This can also

(14) *Cf.* F. Asinger, B. Fell, H. Verbeek, and J. Fernandez-Bustillo, *Erdöl Kohle Chem.*, **11**, 786 (1967). These authors report that, in the alkylation of benzene with isomeric *n*-heptenes in the presence of HF or H_2SO_4, they obtained the same isomer distribution regardless of the position of the double bond in the starting olefin, concentration of the acid, mode of addition of the reactants, or temperature of the reaction. However, they were working between 0 and $-30°$. On the other hand, Kelly and Lee obtained results in hydride transfer reactions with 4-methyl-2-pentene and 4-methyl-1-pentene which led them to suggest that an appreciable time is required for a series of hydride shifts leading to the formation of the *tert*-carbonium ion structure.[15]

(15) J. T. Kelly and R. J. Lee, *Ind. Eng. Chem.*, **47**, 757 (1955).

(16) K. Fredenhagen, *Z. Anorg. Chem.*, **242**, 23 (1939); K. Fredenhagen and G. Cadenbach, *Z. Physik. Chem.*, **146**, 245 (1930).

(17) G. A. Olah and M. W. Meyer in "Friedel-Crafts and Related Reactions," Vol. I, George Olah, Ed., Interscience, New York, N. Y., 1963, p 736.

(18) N. C. Deno in "Progress in "Physical Organic Chemistry," Vol. 2, S. G. Cohen, A. Streitwieser, Jr., R. W. Taft, Ed., Interscience, New York, N. Y., 1964, p 141.

(19) F. H. Blunk and D. R. Carmody, *Ind. Eng. Chem.*, **40**, 2072 (1948).

(20) Although the isomer distribution of the phenylalkanes is not expected to correspond exactly to the actual concentration of the intermediate carbonium ions owing to differences in the rates of their alkylation of benzene, nevertheless, it is reasonable to assume that differences in the isomer distributions reflect differences in the concentrations of the intermediate ions. When the same isomer distribution is obtained regardless of the position of the double bond in the chain then the intermediate ions must have attained the equilibrium condition.[8]

(21) M. Kilpatrick and F. E. Luborsky, *J. Amer. Chem. Soc.*, **75**, 577 (1953).

(22) H. H. Perkampus, *Advan. Phys. Org. Chem.*, **4**, 235 (1966).

be readily explained by the effect of replacing the F^- ions by the larger BF_4^- ions in the ion pairs. In the 2-alkyl carbonium ions the positive charge is located near the end of the chain which permits more efficient solvation by the catalyst and a closer approach by the BF_4^- ions. As the charge enters the middle of the chain, the ion is more efficiently shielded from the BF_4^- ions by its two alkyl groups. This results in slightly greater stability for the 2-alkyl carbonium ions. In addition, evidence has previously been obtained which suggests that the 2-carbonium ion reacts faster with benzene than the internal ones.[6] Since the proton enters the alkylating agent at the center of the chain, which is only two carbon atoms away from the 2 position, this effect combines with the first one to raise the amount of the 2 isomer.

Experimental Section

Materials and Apparatus.—All of the 1-alkenes were obtained from the Aldrich Chemical Co. and the internal olefins were obtained from Farchan Research Laboratories, Cleveland, Ohio. Benzene was dried by azeotropic distillation and anhydrous aluminum chloride was Allied Chemical reagent grade. Anhydrous hydrogen fluoride and gaseous boron trifluoride were obtained from the Matheson Co. and used as received. 2-Phenyldecane was synthesized from acetophenone and *n*-octylmagnesium bromide (Grignard reaction). The tertiary alcohol was dehydrated over potassium bisulfate, and the olefin was hydrogenated to the phenyldecane with palladium on charcoal (5%). The product was about 97% pure as established by glc analysis.

The alkylation reactions were carried out in a 2-l. stainless steel reactor equipped with agitator, thermocouple, cooling coil, pressure gage, and various inlet ports for introducing catalyst and olefin, sampling the reaction mixture, venting the apparatus, and withdrawing the products. All the inlets were provided with stainless steel valves. Strict safety precautions were followed to avoid any contact with liquid or gaseous HF or BF_3.

General Procedure of Alkylation.—Anhydrous benzene (3.9 mol) was charged to the reactor and cooled to 5 to 7° with ice water circulated through the cooling coil. Anhydrous hydrogen fluoride (4 mol), cooled to about −30° with Dry Ice, was then added. All the valves were then closed except the venting valve which was connected through a Tygon tube to a BF_3 lecture bottle which rested on a balance. The calculated amount of BF_3 was then introduced, the valve was closed, and agitation was started. (For alkylations with HF only the BF_3 step was eliminated.) When the temperature reached 0–5°, 0.4 mol of the α olefin in 1 mol of benzene was pumped into the reactor over a 10-min period, using a microbellows pump (Research Appliance Co.). The reaction mixture was aged for 10 min at the same temperature, after which time it was settled for 1 hr to allow separation of the two phases. The catalyst was then drained onto crushed ice, neutralized, and discarded. The alkylate layer was quenched with ice and most of the benzene was removed under suction. The crude alkylbenzene was examined by glc using a Varian Aerograph Model 1800 equipped with an Infotronics electronic integrator. The stainless steel column was 150 ft. × 0.01 in. and was coated with silicon OV7. The crude products were then distilled and the material boiling in the range of the arylalkane was collected. In the presence of HF alone the yields were 87–91% of the theoretical amount. With HF–BF_3 they were 62, 70, and 77% for the C_6, C_8, and C_{10} alkylbenzenes, respectively. After removal of the phenylhexanes, distillation of the residue continued and a fraction boiling at 113–126° (2 mm) was collected (25%). This is close to the boiling point of dodecylbenzene.[8] Its ir spectrum showed it to be primarily dialkylbenzene (12.1 and 12.65 μ). The residues from the alkylations of the higher olefins also showed these bands indicating dialkylation of benzene as a side reaction.

The same procedure was followed for the alkylation of benzene with the internal olefins but the scale of the experiments was only half that of the α olefins.

Registry No.—Benzene, 71-43-2; 1-dodecene, 112-41-4; *trans*-6-dodecene, 7206-13-5; 1-decene, 872-05-9; *trans*-5-decene, 7433-56-9; 1-octene, 111-66-0; *trans*-4-octene, 14850238; 1-hexene, 592-41-6; *trans*-3-hexene, 13269-52-8.

Radical Reactions of Tetrafluorohydrazine. Preparation of Bis(difluoramino)alkanols and Nitrates[1]

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The synthesis of difluoramino-substituted alkanols has been accomplished by the addition of tetrafluorohydrazine to alkenols or to alkenyl esters followed by hydrolysis. The latter method proved satisfactory in giving the alkanols in good yields and purity. It was demonstrated that the alkanols could be nitrated to yield the difluoramino-containing nitrate esters.

Bis(difluoramines) containing reactive functional groups are of considerable interest and importance in the development of NF chemistry. Petry and Freeman[2] have reported the most comprehensive study of the tetrafluorohydrazine (N_2F_4) olefin addition reaction yielding vicinal bis(difluoramines). Olefins examined were composed of two groups: (a) the simple aliphatic olefins and (b) olefins containing various functional groups such as halo, alkoxy, acetoxy, carbonyl, and aryl. The bis(difluoramines) containing acetoxy, alkoxy, and halo substituents were stable, even when attached to carbon atoms bonded to difluoramino groups, while products containing carbonyl, imino, and hydroxyl groups attached in the α position were prone to decompose with loss of hydrogen fluoride or difluoramine.[3,4] The study of bis(difluoramines) containing various functional groups was expanded to include the preparation of a series of bis(difluoramino)alkanols and their corresponding nitrate esters.

Bis(difluoramino)alkanols.—The preparation of bis(difluoramino)alkanols was accomplished by the direct addition of tetrafluorohydrazine (N_2F_4) to alkenols, or by a more preferred method, the addition of N_2F_4 to a suitable ester derivative of the alkenol followed by hydrolysis or methanolysis to give the alcohol adduct.

(1) This work was carried out under the sponsorship of the U. S. Army Missile Command, Redstone Arsenal, Ala., under Contract DA-01-021 ORD-11909 (Z).

(2) R. C. Petry and J. P. Freeman, *J. Org. Chem.*, **32**, 4034 (1967).

(3) S. F. Reed, *ibid.*, **32**, 2893 (1967).

(4) J. P. Freeman, W. H. Graham, and C. O. Parker, *J. Amer. Chem. Soc.*, **90**, 121 (1968).

In most instances the addition reactions were conducted in inert chlorinated solvents at temperatures of 50–100° in both subatmospheric and elevated pressure reactors. Adducts were isolated by distillation and characterized by their infrared spectra and elemental analyses.

The reactions were carried out initially with the alkenols, as depicted below for allyl alcohol. Al-

$$CH_2{=}CHCH_2OH + N_2F_4 \longrightarrow F_2NCH_2CH(NF_2)CH_2OH$$

though the adducts were obtained in satisfactory yields (60–80%), they contained small quantities of impurities which were difficult to remove during purification. The chief impurity in both the crude and distilled products was shown by infrared to be a material containing the carbonyl group. Absorption in the 1750–1690-cm^{-1} range indicated a keto or aldehyde group.

A plausible explanation for the appearance of the carbonyl-containing impurity results from a reaction involving the abstraction of hydrogen from the α position of the alcohol by the difluoramino radical. A variety of radicals are known[5] to abstract hydrogen from

$$RCH_2OH + NF_2 \longrightarrow \dot{R}CHOH + HNF_2$$

alcohols in a similar manner. The nature of the R group, whether alkenyl or bis(difluoramino)alkyl, would be of little importance in this hydrogen abstraction reaction. Subsequent coupling of the α-hydroxylalkyl radical with the difluoramino radical would give the α-(difluoramino)alkanol which, at the reaction temperatures, would probably decompose readily with loss of difluoramine and formation of an aldehyde.[4]

$$\dot{R}CHOH + NF_2 \longrightarrow RCH(NF_2)OH$$

$$RCH(NF_2)OH \longrightarrow RCHO + HNF_2$$

Difluoramine was, in fact, observed as a component of the excess gas fraction from these reactions. It accounted for 6–16% of the excess condensable gas fraction, which indicated conversions of N_2F_4 to difluoramine of approximately 1%, although in isolated instances conversions as high as 3% were noted. The vpc analyses showed 1–5% of impurities in the crude alcohol adducts and usually less than 1% in the distilled products. Unfortunately, the distilled samples of the adducts from the allylic alcohols continued to slowly decompose over a period of days with notable discoloration. This behavior of the adducts is attributed to the unstable nature of the carbonyl-containing impurity. Decomposition of the impurity with loss of hydrogen fluoride, followed by further acid-catalyzed decomposition, is thought to account for the observations noted.

$$F_2NCH_2CH(NF_2)CHO \longrightarrow F_2NCH_2C(=NF)CHO$$

The simple aliphatic alkenols usually were converted to their adducts in good yields, but several other types of unsaturated alcohols did not give the desired adducts. Furfuryl alcohol underwent polymerization prior to the addition of a significant quantity of N_2F_4, and 2-butene-1,4-diol reacted with N_2F_4 mainly by hydrogen abstraction to give a mixture of difluoramines and carbonyl-containing products which were not examined in detail. When divinyl carbinol was treated with N_2F_4, a bis(difluoramine) containing a considerable amount of impurities was obtained in moderate yield (40–55%), along with a high boiling viscous residue which remained after distillation of the bis(difluoramine). The structure of the bis(difluoramine) was never ascertained because of difficulty in removing impurities, and the high-impact sensitive residue was not characterized, although it probably contained some of the desired tetrakis(difluoramine).

To eliminate the difficulties encountered in obtaining bis(difluoramino)alkanols directly from the alkenols, the latter were first converted to suitable ester derivatives, the adduct of the ester was prepared, and the alcohol adducts were generated from the ester adducts *via* hydrolysis or methanolysis reactions. These studies have demonstrated that conversion of the alkenols to their formate or trifluoroacetate derivatives followed by the sequence of reactions shown below is a general method for the synthesis of bis(difluoramino)alkanols. The trifluoroacetates and formates were selected as protective groups because of their ease of preparation and subsequent hydrolysis or methanolysis.

$$CH_2{=}CHCH_2OC(=O)R + N_2F_4 \longrightarrow F_2NCH_2CH(NF_2)CH_2OC(=O)R$$

R = H or CF_3

$$F_2NCH_2CH(NF_2)CH_2OC(=O)R \xrightarrow[\text{methanolysis}]{\text{hydrolysis or}} F_2NCH_2CH(NF_2)CH_2OH + RC(=O)OH \text{ or } RC(=O)OCH_3$$

Alkenyl trifluoroacetates were prepared by treating the appropriate alkenols with trifluoroacetic anhydride in the presence of triethylamine or pyridine.[6] A reaction of formic acid with the alcohol in refluxing benzene with azeotropic removal of water gave the formates in yields of 55–70%. Adducts of the esters were prepared by heating the neat esters with N_2F_4 at 80–100° in stainless steel cylinders or in solution under pressure. Characterization data for the ester adducts are presented in Table I. The infrared spectra showed a strong carbonyl absorption near 1785 cm^{-1} (trifluoroacetates) and 1722 cm^{-1} (formates), and NF absorption at 800–1000 cm^{-1}. The presence of by-products arising *via* hydrogen abstraction reactions was not detected in any instance.

In addition to the simple alkenyl esters employed in this study, other esters examined were those prepared from the dienols: divinyl carbinol, 2,4-pentadien-1-ol, and 2,5-hexadien-1-ol. When divinyl carbinol, as its trifluoroacetate, was treated with N_2F_4 under normal reaction conditions, the monoadduct, 3-[1,2-bis(difluoramino)-4-pentenyl] trifluoroacetate, was the major product. Attempts to conduct the reaction under more vigorous conditions led to decomposition of the mixture. The alternate route *via* the formate ester was not possible because of the rearrangement of the ester to 2,4-pentadienyl formate in the preparative reaction. It was later found that, when divinylcarbinyl acetate was treated with N_2F_4, the reaction could be controlled to give either 3-[1,2-bis(difluoramino)-4-pentenyl] acetate or 3-[1,2,4,5-tetrakis(difluoramino)pentyl] acetate as the major products. No suitable techniques were

(5) R. S. Davidson, *Quart. Rev., Chem. Soc.*, **21**, 249 (1967), and references cited therein.

(6) R. S. Yost and R. D. Shoults, U. S. Patent 3,023,238 (1964).

TABLE I

ALKENYL TRIFLUOROACETATE AND FORMATE ADDUCTS WITH N_2F_4

Adduct of	Registry no.	Yield, %	Bp, °C (mm)	$n^{20}D$
$CF_3C(=O)OCH=CH_2$	24414-89-9	67	41–42 (20)	1.3195
$CF_3C(=O)OCH_2CH=CH_2$	16531-90-1	83	58 (16)	1.3540
$CF_3C(=O)OCH_2C(CH_3)=CH_2$	35209-93-9	59	52 (8)	1.3578
$CF_3C(=O)OCH_2C(CH_2CH_3)=CH_2$	35209-94-0	74	74 (2)	1.3613
$CF_3C(=O)O(CH_2)_4CH=CH_2$	35209-95-1	67	69 (0.3)	1.3762
$CF_3C(=O)OCH_2CH=CHCH_3$	35209-96-2	44	55 (2.5)	1.3612
$CF_3C(=O)OCH(CH=CH_2)_2$[a]	35209-97-3	67	70–71 (2)	
$HC(=O)OCH=CH_2$	30947-80-9	61	40–42 (24)	
$HC(=O)OCH_2CH=CH_2$	21416-97-7	80	36 (1.7)	1.3852
$HC(=O)OCH_2CH=CHCH=CH_2$[b]	35210-00-5[c]	41	80–82 (0.8)	
	35210-01-6[d]			
$HC(=O)OCH_2CH=CHCH_2CH=CH_2$[b]	35210-02-7[e]	70	88–89 (0.6)	
	35210-03-8[f]			

[a] Bis(difluoramine). [b] Mixture of bis(difluoramines). [c] 3-Pentenyl adduct. [d] 2-Pentenyl adduct. [e] 2-Hexenyl adduct. [f] Tetrakis adduct.

found for the hydrolysis of either acetate ester adduct to the alcohol.

The reaction of N_2F_4 with 2,4-pentadienyl formate gave only a mixture of bis(difluoramino)alkenyl formates arising from the addition of 1 mol of N_2F_4 to the conjugated double bond system of the ester through either 1,2 or 1,4 addition. Further addition of a

$$CH_2{=}CHCH{=}CHCH_2OOCH + N_2F_4 \longrightarrow F_2NCH_2CH{=}CHCH(NF_2)CH_2OOCH + F_2NCH_2CH(NF_2)CH{=}CHCH_2OOCH$$

second mole of N_2F_4 was not realized under the experimental conditions.[7] In contrast, when 2,5-hexadienyl formate was treated with N_2F_4, both the 5,6-bis(difluoramino)-2-hexenyl formate and the 2,3,5,6-tetrakis(difluoramino)hexyl formate could be obtained as major products by controlling the experimental conditions. These two reactions demonstrate the difference in relative ease of N_2F_4 addition to nonconjugated dienes over the conjugated dienes. The difficulty in obtaining completely saturated products from the conjugated dienes has been attributed to the reversible nature of the reaction.[2]

It is important also to point out that isolation and purification of the mixed adducts obtained from the N_2F_4–diene reactions were extremely difficult because of their similarity of properties (bis adducts) and the unusual high boiling points and ultrasensitivity of the tetrakis adducts. While totally pure individual adducts were not realized in these instances, all the analytical evidence available, including vpc data, is indicative of the presence of the designated products.

Treatment of the ester adducts with anhydrous methanol at 50 to 70° with or without an acid catalyst such as *p*-toluenesulfonic acid or Amberlyst 15[8] gave the alcohol adducts in 70–90% yield after distillation. Catalysts were beneficial in increasing the rate of methanolysis of the esters. The alcohols (Table II) were shown to be of high purity by vpc analyses and displayed no tendency to decompose on storage. Characteristic absorption bands at 3400–3500 cm^{-1} and 800–1000 cm^{-1} were noted in their infrared spectra.

(7) In reactions conducted at temperatures of 150–200° and pressures exceeding 300 psi, the tetrakis(difluoramino)pentyl formate was obtained in excellent yield. Studies conducted by Dr. K. E. Johnson of Rohm and Haas Co., Redstone Research Laboratories, Huntsville, Ala.

(8) Ion exchange resin, trademark of the Rohm and Haas Co., Philadelphia, Pa.

TABLE II

DIFLUORAMINOALKANOLS

Alkanol	Registry no.	Yield, %	Bp, °C (mm)	$n^{20}D$
1,2-Bis(difluoramino)-ethanol	13084-47-4	87	40–42 (18)	1.3948
2,3-Bis(difluoramino)-propanol	16531-91-2	89	44 (3)	1.3967
2-Methyl-2,3-bis(difluoramino)propanol	21678-71-7	73	43 (1)	1.3952
2,3-Bis(difluoramino)-butanol	24403-11-0	78	58 (1)	1.3990
1,2-Bis(difluoramino)-pentan-3-ol	24403-12-1	90	85–87 (1)	
5,6-Bis(difluoramino)-hexan-1-ol[a]	24403-13-2	79		
1,2,4,5-Tetrakis(difluoramino)pentan-3-ol[a]	21828-55-7	65		
4,5-Bis(difluoramino)-2-penten-1-ol[a,b]	35210-11-8			
2,4-Bis(difluoramino)-3-penten-1-ol	35210-12-9	77		
2,3,5,6-Tetrakis(difluoramino)hexan-1-ol[a]	35210-13-0	69		
2-Difluoramino-2-difluoraminomethylpropane-1,3-diol[a]	35210-14-1	71		

[a] Decomposed on attempted distillation. [b] A mixture of bis adducts.

An alternate method of effecting the generation of the alcohol adducts was to hydrolyze the esters in a mixture of methanol and dilute (5%) mineral acid (HCl or H_2SO_4). In most instances the hydrolysis reactions were satisfactory, giving slightly lower yields than the methanolysis reactions; however, some decomposition of the adducts occurred in isolated instances, as evidenced by low fluorine and high nitrogen analyses of the alcohols. It was further shown that the use of concentrated hydrochloric acid–methanol mixtures resulted in hydrolysis and partial conversion of the alcohols to the corresponding chlorides, as evidenced by the unusually high chlorine content (7–9%) of the hydrolysis products. This side reaction was not apparent when dilute acid was used. These factors, along with the usually lower yields of the alcohol adducts (50–85%) obtained from the acid hydrolysis,

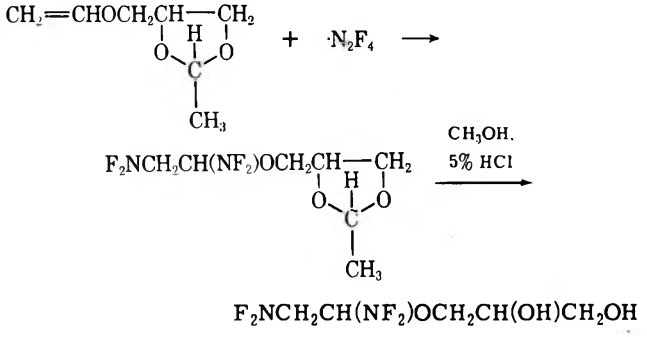
TABLE III

BIS(DIFLUORAMINO)ALKYL NITRATES

Nitrate	Registry no.	Yield, %	Bp, °C (mm)	$n^{20}D$
$F_2NCH_2CH(NF_2)CH_2ONO_2$	18804-80-3	85.5	45–46 (2)	1.3996
$F_2NCH_2C(CH_3)(NF_2)CH_2ONO_2$	35210-16-3	97	40–41 (1)	1.4055
$F_2NCH_2C(CH_2ONO_2)(NF_2)CH_2ONO_2$	35210-17-4	96.5		1.4380
$F_2NCH_2CH(NF_2)OCH_2CH(ONO_2)CH_2ONO_2$	35210-18-5	98.7		1.4303

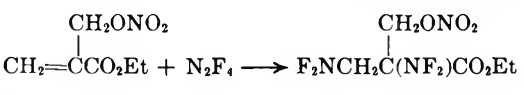
made the methanolysis technique the preferred method for generating the alcohol adducts.

Another example of employing protective groups in the alkenol–N_2F_4 reactions was demonstrated with the use of acetals. Treatment of 2-methyl-4-vinyloxymethyl-1,3-dioxolane with N_2F_4 gave 2-methyl-4-[1,2-bis(difluoramino)ethoxymethyl]-1,3-dioxolane in excellent yields (85–90%). Hydrolysis of this adduct in methanol–5% HCl gave 3-[1,2-bis(difluoroamino)-ethoxy]-1,2-propanediol (86%).



Similarly, when methyl divinylcarbinylformal was treated with N_2F_4, the products isolated were methyl 3-[1,2-bis(difluoramino)-4-pentenyl]formal and methyl 3-[1,2,4,5-tetrakis(difluoramino)pentyl]formal. Both adducts were readily hydrolyzed to the corresponding alcohols with a mixture of methanol–5% HCl at room temperature.

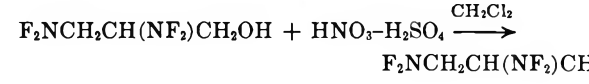
Bis(difluoramino)alkyl Nitrates.—Reactions of nitrate esters of alkenols with N_2F_4 were not considered a promising route to the mixed NF nitrates because of several factors. The thermal instability imposed by the nitrate group precludes any attempt to form the adduct in many instances. In others, unless reactions go essentially to completion and by-product formation is minimal, the purification of the product is difficult and often hazardous, since these type compounds possess high thermal and impact sensitivities. Only in isolated instances was even partial success realized in forming the adduct of unsaturated nitrates. When ethyl (α-nitratomethyl)acrylate was treated with N_2F_4 under relatively mild conditions, a crude product was obtained whose composition approximated that of the expected adduct. Attempts to distil the crude mixture resulted in decomposition. A similar reaction of



petrin methacrylate (methacrylate of pentaerythritol trinitrate) and N_2F_4 gave the adduct which analyzed satisfactorily. Presumably the ease of addition of N_2F_4 to the acrylate ester permitted mild conditions to be employed and eliminated many of the potential side reactions which occur in operating at the higher temperatures necessary for many olefin–N_2F_4 reactions.

The method of choice for preparing mixed NF_2–ONO_2 substituted compounds was to first prepare the NF_2-containing alcohols and then nitrate by suitable means. It has been demonstrated that this preparative procedure is successful in giving the desired mixed products in excellent yields and purity. The nitrate esters of bis(difluoramino)alkanols were prepared conveniently by a mixed acid nitration procedure. Nitration was carried out in methylene chloride at temperatures of 15–45° employing an excess of a 2:1 HNO_3–H_2SO_4 mixture.

The diols were treated in the same manner as the simple alcohols, except that the reaction time was extended by approximately one-half hour in the case of the diols. Although the products were isolated in a



crude state, they were usually pure, as shown by satisfactory elemental analyses and infrared spectra. Their spectra were characterized by strong NF absorption at 800 to 1000 cm^{-1} and ONO_2 absorption near 1160 and 1265 cm^{-1}. 1,2-Bis(difluoramino)ethyl nitrate, which decomposed prior to analysis, was the only unstable product. This is not surprising in view of the observations discussed earlier in this paper. Accordingly, the nitrate group may be classed with carbonyl, imino, and hydroxyl groups as α substituents in difluoramines which lead to unstable products (Table III).

This study has demonstrated that bis(difluoramino)-alkanols can be prepared in high yields and of good purity employing easily hydrolyzable esters. While alkenols can be reacted directly with N_2F_4 to give the adducts, it was shown that in these reactions hydrogen abstraction takes place to a limited extent, yielding small quantities of by-products not easily removed from the desired alkanols. Formation of mixed NF_2–ONO_2 substituted compounds was accomplished by a general nitration procedure. α-Nitrato-substituted difluoramines were found to be unstable.

Experimental Section[9]

The alkenols employed in this work were purchased from commercial sources and used as received except for divinyl carbinol, which was prepared by the method of Ramsden.[10] Tetrafluorohydrazine of greater than 95% purity and containing volatile CF compounds as impurities was used for all addition reactions. Infrared spectra were obtained on a Perkin-Elmer Infracord spectrophotometer using a sodium chloride prism. ^{19}F nmr spectra were obtained with a Varian Associates Model V-3000-B high-resolution spectrometer with a 40 Mc probe, with trifluoroacetic acid as an internal standard. All gas chromatographic work was carried out on an Aerograph Instrument

(9) All boiling points are uncorrected.

(10) H. E. Ramsden, J. R. Leebrick, S. D. Rosenberg, E. H. Miller, J. J. Walburn, A. E. Balent, and R. Cserr, *J. Org. Chem.*, **22**, 1602 (1957).

Model A-100-C using a 5′-dinonyl phthalate on Chromosorb column at 50 to 100°, unless otherwise noted.

The nature of the reaction of tetrafluorohydrazine with organic substrates implies that caution be exercised in the experimental work. It is essential that oxygen be rigorously excluded from all reaction mixtures to prevent explosions. The experimental work was conducted in remote areas, using remote-controlled equipment insofar as possible as a safety precaution to minimize personnel exposure. In addition, care in handling of products reported, particularly the mixed NF_2–ONO_2 substituted compounds, is necessary since they are impact sensitive in most instances.

In many reactions final purification of several products was not attempted. Since most of these materials analyzed satisfactorily as obtained from the reactions so that characterization was not in doubt, their final purification was not considered necessary. The main concern with these highly thermal and impact-sensitive materials was the hazardous nature of the purification operation, which required the distillation of a high boiling liquid.

Allyl Alcohol–N_2F_4.—To a 100-ml round-bottomed flask fitted with a magnetic stirrer was introduced 11.6 g (0.2 mol) of allyl alcohol and 25 ml of carbon tetrachloride. The flask was connected to a glass manifold system containing a 2-l. expansion bulb, and the total system was deaerated by passing through three freeze–thaw cycles while under vacuum. Tetrafluorohydrazine (15.0 g, 144 mmol) was charged into the system and the mixture was heated to 90° for a period of 4.3 hr. Analysis of the residual condensable gas fraction by mass spectroscopy showed that 8.68 g (83 mmol) of N_2F_4 has reacted. Also present in the condensable gas fraction was difluoramine (0.18 g, 3 mmol). After removal of the condensable gases and the introduction of air, the flask containing the mixture was placed on a rotatory evaporator to remove the solvent and unreacted alcohol. The crude residue was analyzed by its infrared spectrum: 3450 (s), 1718 (w), and 800–1000 (s) cm^{-1}. Gas chromatography showed the presence of one significant impurity (2%), along with several minor ones. Distillation of the crude material gave a water-clear distillate [bp 47–48° (4 mm), $n^{20}D$ 1.3993] in the amount of 20.2 g (81%). Infrared analysis showed a pronounced decrease in the carbonyl absorption. A second vpc analysis showed a significant decrease in the impurities. On standing overnight a slight discoloration was noted in the sample. This discoloration increased over a period of several days, along with some etching of the glass container. Redistillation of the sample effected an improvement in the stability of the product; however, over a period of several days, the discoloration was again noted.

Anal. Calcd for $C_3H_6F_4N_2O$: C, 22.22; H, 3.70; F, 46.91; N, 17.58. Found: C, 22.49; H, 3.95, F, 46.72; N, 17.51.

Allyl Trifluoroacetate–N_2F_4.—The preparation of 2,3-bis(difluoramino)propyl trifluoroacetate is typical of the N_2F_4 addition reactions of the neat alkenyl esters. To a 1-l. stainless steel evacuated reactor fitted with pressure gage, valve, and a ball joint for attachment to a vacuum line was charged 7.7 g (0.05 mol) of allyl trifluoroacetate (previously degassed) and 10.4 g (0.1 mol) of N_2F_4 while being cooled externally in a liquid nitrogen bath. After disconnection from the vacuum line, the reactor was allowed to warm to ambient temperature and then placed in an oil bath and heated to 100° for a period of 5 hr, during which time the pressure dropped from a maximum of 56 to 26 psi. On cooling, the gaseous contents of the reactor were removed under vacuum into a series of cold traps located on a vacuum manifold. The product fraction was collected in a Dry Ice–acetone cooled trap. The liquid fraction obtained from this trap was distilled to give 10.09 g (77.2%) of 2,3-bis(difluoroamino)propyl trifluoroacetate, bp 58° (16 mm), $n^{20}D$ 1.3540.

Anal. Calcd for $C_5H_5F_7N_2O_2$: C, 23.21; H, 1.94; F (hydrolyzable), 51.60; N, 10.85. Found: C, 23.05; H, 1.99; F (hydrolyzable), 51.47; N, 10.69.

Allyl Formate–N_2F_4.—Allyl formate (8.6 g, 100 mmol) previously degassed was condensed into a stainless steel reactor with N_2F_4 (14.66 g, 141 mmol) and heated to 90° for a period of 6 hr. Isolation in the usual manner gave 16.27 g of liquid residue which was distilled at reduced pressure to give 15.38 g (80%) of the adduct: bp 36° (1.7 mm); $n^{20}D$ 1.3852, d^{23}_4 1.442; ir 1723 and 800–1000 cm^{-1}.

Anal. Calcd for $C_4H_6F_4N_2O_2$: C, 26.66; H, 3.34; F, 42.22; N, 15.56. Found: C, 26.51; H, 3.41; F, 42.37; N, 15.49.

2,4-Pentadienyl Formate–N_2F_4.—Under similar experimental conditions 5.6 g (56 mmol) of 2,4-pentadienyl formate was treated with 10.4 g (100 mmol) of N_2F_4 at 100° for a period of 5 hr. After cooling and degassing the reactor, it was opened and the liquid contents were removed mechanically. Distillation at reduced pressure gave 4.69 g of a clear product, bp 80–82° (0.8 mm), shown by vpc analysis to be a mixture of two components in near equal portions. The ^{19}F nmr spectrum showed two triplets of near equal area centered at −5397 and −5257 Hz representing the $-CH_2NF_2$ groups and absorption at −4740 Hz indicative of a $-CHNF_2$ group; ir spectra showed 1722 and 800–1000 cm^{-1}. From these data the products were determined to be 4,5-bis(difluoramino)-2-pentenyl formate and 2,5-bis(difluoramino)-3-pentenyl formate arising from 1,2 and 1,4 addition of N_2F_4 to the conjugated double bond of 2,4-pentadienyl formate. There was no evidence to support the formation or presence of the tetrakis(difluoramine) in this reaction.

Anal. Calcd for $C_6H_8F_4N_2O_2$: C, 33.30; H, 3.70; F, 35.14; N, 12.97. Found: C, 33.08; H, 4.05; F, 35.43; N, 13.41.

2-Methyl-4-vinyloxymethyl-1,3-dioxolane-N_2F_4.—To a deaerated solution of 8.6 g (60 mmol) of 2-methyl-4-vinyloxymethyl-1,3-dioxolane in 25 ml of CCl_4 contained in a thick-walled glass reactor attached to a high pressure manifold system was added 10.4 g (100 mmol) of N_2F_4. The mixture was heated to 70° for 5 hr with a maximum pressure of 68 psi being obtained. On cooling, the excess N_2F_4 was removed, air was introduced into the reactor, and finally the contents were removed. The CCl_4 was removed on a rotatory evaporator and the residue was distilled through a short path column to give 14.0 g (94%) of 2-methyl-4-[1,2-bis(difluoramino)ethoxymethyl]-1,3-dioxolane [bp 55–56° (0.02 mm)] as a heavy oil.

Anal. Calcd for $C_7H_{12}F_4N_2O_3$: C, 33.87; H, 4.83; F, 30.65; N, 11.29. Found: C, 33.57; H, 4.74; F, 30.44; N, 11.49.

Methyldivinylcarbinylformal–N_2F_4.—Methyldivinylcarbinylformal (2.0 g, 15.6 mmol) in 25 ml of CCl_4 contained in a thick-walled glass reactor was treated with 5.2 g (50 mmol) of N_2F_4 at 90° for 5 hr at a maximum pressure of 101 psi. Following the usual isolation procedure, 4.2 g of a mixture of products was obtained as determined by vpc analysis. Distillation at reduced pressure gave 1.31 g of a product: bp 51° (2.2 mm); $n^{20}D$ 1.4026; vpc 98%; ir 1640 (w) and 800–1000 (s) cm^{-1}. These data, in conjunction with the elemental analysis, confirmed the identity of the product to be methyl-3-[1,2-bis(difluoramino)-4-pentenyl]formal.

Anal. Calcd for $C_7H_{12}F_4N_2O_2$: C, 36.21; H, 5.17; F, 32.75; N, 12.06. Found: C, 36.15; H, 5.30; F, 32.55; N, 12.03.

The residue [2.72 g; $n^{20}D$ 1.3967; vpc 95%; ir 800–1000 (vs) cm^{-1}] was considered to represent the compound methyl-3-[1,2,4,5-tetrakis(difluoramino)pentyl]formal, although the elemental analysis was slightly high in carbon.

Methanolysis of Bis(difluoramino)alkyl Trifluoroacetates.—A typical transesterification is described for the preparation of 2,3-bis(difluoramino)propanol. To a 100-ml round-bottomed flask fitted with magnetic stirrer and distillation assembly was introduced 5.95 g (0.21 mol) of 2,3-bis(difluoramino)propyl trifluoroacetate and 25 ml of anhydrous methanol. The flask was heated intermittently by means of 65–67° hot water bath during a period of 3 hr. A total of 26.0 g of methyl trifluoroacetate (96%) distilled from the reaction mixture. The remaining residue was distilled to give 30.5 (89%) of 2,3-bis(difluoramino)-propanol: bp 44° (3 mm); ir 3425 (s) and 800–1000 (vs) cm^{-1}.

Anal. Calcd for $C_3H_6F_4N_2O$: C, 22.22; H, 3.70; F, 46.91; N, 17.28. Found: C, 22.06; H, 3.84; F, 46.66; N, 17.58.

In a series of methanolysis reactions 2,3-bis(difluoramino)-propanol was obtained in yields of 70–89%. Experimental data on the typical methanolysis of other alkenyl trifluoroacetate adducts are presented in Table IV.

TABLE IV
METHANOLYSES OF BIS(DIFLUORAMINO)ALKYL TRIFLUOROACETATES

Alkyl group	Time, hr	Temp, °C	% methyl ester	% alcohol adduct
$F_2NCH_2CH(NF_2)$–	3	50	82	87
$F_2NCH_2C(NF_2)(CH_3)CH_2$–	2.5	50	84	73
$F_2NCH_2CH(NF_2)CH(CH_2CH_3)$–	3.5	55	89	90
$F_2NCH_2CH(NF_2)(CH_2)_4$–	3	55	81	79
$CH_3CH(NF_2)CH(NF_2)CH_2$–	3	50	85	78
$F_2NCH_2CH(NF_2)CH(CH{=}CH_2)$–	4	50	72	76

TABLE V

HYDROLYSIS OF 2,3,5,6-TETRAKIS(DIFLUORAMINO)HEXYL FORMATE

Formate	MeOH, ml	H_2O, ml	Catalyst	Time, hr	Temp, °C	Yield, %
	35	30	5 ml of HCl	3.0	27	73
	40	30	Amberlyst 15, 1 g	3.0	27	76
6.68 g (50 mmol)	40	30	*p*-TSA, 1 g	3.0	27	71.5
	40		10 ml of concd HCl	0.5	27	20
	40		10 ml of concd HCl	1.0	27	16

Hydrolysis of 2,3-Bis(difluoramino)propyl Formate.—A typical hydrolysis reaction is described. To a mixture of 100 ml of methanol, 95 ml of H_2O and 5 ml of concentrated HCl was added slowly 19.0 g (100 mmol) of 2,3-bis(difluoramino)propyl formate. There was no noticeable exotherm. After stirring at ambient temperature for 24 hr, the excess methanol was removed on a rotatory evaporator and the aqueous solution was extracted with ether. The combined ether extracts were washed with water and dried over anhydrous $MgSO_4$, and the ether was removed by evaporation. Distillation of the liquid residue gave 2,3-bis(difluoramino)propanol: 13.65 g, 84%; bp 45° (3 mm); $n^{20}D$ 1.3964.

Anal. Calcd for $C_3H_6F_4N_2O$: C, 22.22; H, 3.70; F, 46.91; N, 17.28. Found: C, 22.15; H, 3.60; F, 46.61; N, 17.43.

Hydrolysis of 2,3,5,6-Tetrakis(difluoramino)hexyl Formate.—The hydrolysis of 2,3,5,6-tetrakis(difluoramino)hexyl formate was carried out by several methods, as shown in Table V. Catalysts employed were dilute and concentrated HCl, Amberlyst 15, and *p*-toluenesulfonic acid. Only when concentrated HCl was used did the yield of the alcohol decrease. In these instances the formate ester was converted in part to the chloride, as shown by the high chlorine content (>8%) of the product mixtures. Gas chromatography showed the chloride to account for 80–85% of the product fraction, with the alcohol being present in yields of 15–20%.

Hydrolysis of 2-Methyl-4-[1,2-bis(difluoramino)ethoxymethyl]-1,3-dioxolane.—A mixture of 13.8 g (5 mmol) of 2-methyl-4-[1,2-bis(difluoramino)ethoxymethyl]-1,3-dioxolane, 100 ml of methanol, 95 ml of water, and 5 ml of concentrated HCl was stirred at room temperature for a period of 24 hr. Removal of the methanol on a rotatory evaporator followed by ether extraction of the aqueous solution gave 9.65 g (87%) of a viscous oily liquid, with an ir of 3450–3500 (s) and 800–1000 (s) cm^{-1}. The infrared spectral data and the elemental analyses confirmed the structure to be the desired diol 3-[1,2-bis(difluoramino)-ethoxy]-1,2-propanediol.

Anal. Calcd for $C_5H_{10}F_4N_2O_3$: C, 27.03; H, 4.50; F, 34.24; N, 12.63. Found: C, 27.33; H, 4.67; F, 34.03; N, 12.77.

Ethyl (α-Nitratomethyl)acrylate–N_2F_4.—A solution of 2.19 g (12.5 mmol) of ethyl (α-nitratomethyl) acrylate in 25 ml of CCl_3 contained in a thick-walled, high-pressure glass reactor was attached to a high-pressure manifold and deaerated, and 10.4 g (100 mmol) of N_2F_4 was introduced into the system. The mixture was heated to 80° for a period of 3.5 hr at a maximum pressure of 85 psi. On cooling, the excess N_2F_4 was removed, the system was opened to the atmosphere, and the reactor was removed from the manifold. Isolation in the usual manner gave 1.5 g of a viscous oily liquid showing high impact sensitivity (ir 1747, 1606, 1274, and 800–1000 cm^{-1}).

Anal. Calcd for $C_6H_9F_4N_3O_5$: C, 25.80; H, 3.23; F, 27.23; N, 15.06. Found: C, 26.80; H, 3.79; F, 26.94; N, 15.01.

Petrin Methacrylate–N_2F_4.—Petrin methacrylate (2.0 g, 6 mmol) in 25 ml of CCl_4 contained in a 100-ml flask was placed on a high-pressure manifold system, deaerated, and treated with 10.4 g (100 mmol) of N_2F_4 at ambient temperature over a period of 2 hr (maximum pressure was 78 psi). After the usual isolation procedure, 2.8 g of a clear viscous oil was obtained (ir 1754, 1608, 1271, and 800–1000 cm^{-1}).

Anal. Calcd for $C_9H_{13}F_4N_5O_{11}$: C, 24.37; H, 2.93; F, 17.12; N, 15.8. Found: C, 24.01; H, 3.06; F, 17.50; N, 16.1.

Nitration of 2,3-Bis(difluoramino)propanol.—To a 50-ml three-necked flask (appropriately shielded) fitted with a condenser (Drierite drying tube), dropping funnel, magnetic stirrer, and air sparging tube was added 14.0 g (0.2 mmol) of 90% fuming nitric acid. The acid was air sparged until it became clear (approximately 15 min), after which the tube was replaced by a thermometer, an ice water bath was placed around the flask, and (with stirring) 10.0 g (0.1 mol) of 96% sulfuric acid was added *via* the dropping funnel. Then 10 ml of methylene chloride was added, followed by the slow addition of a solution of 16.2 g (0.1 mol) of 2,3-bis(difluoramino)propanol in 25 ml of methylene chloride. The temperature of the mixture was raised to 40–43° and the mixture was refluxed for a period of 15–20 min. On cooling the mixture was transferred to a separatory funnel containing additional methylene chloride. The acid layer was separated and the methylene chloride solution was washed with cold water, cold saturated sodium bicarbonate, and again with cold water, and then was dried over anhydrous $MgSO_4$. After filtration the solvent was removed on a rotatory evaporator to give an oily residue: 18.92 g, 85.6%; bp 45–46° (2 mm); $n^{20}D$ 1.3996; d^{23}_4 1.533; ir 1610, 1270, and 800–1000 cm^{-1}.

Anal. Calcd for $C_3H_5F_4N_3O_3$: C, 17.40; H, 2.43; F, 36.70; N, 20.29. Found: C, 17.66; H, 2.66; F, 36.86; N, 20.20.

Nitration of 3-[1,2-Bis(difluoramino)ethoxy]-1,2-propanediol.—Under similar experimental conditions, 5.6 g (15 mmol) of 3-[1,2-bis(difluoramino)ethoxy]-1,2-propanediol was added to a mixture of 8.8 g (125 mmol) of 90% nitric acid and 12.3 g (67 mmol) of 96% sulfuric acid. The mixture was refluxed for a period of 45 min. A 7.7-g (98%) portion of a viscous oily residue was obtained after washing, drying, and removal of solvent. The product was identified as the dinitrate of 3-[1,2-bis(difluoramino)ethoxy]1,2-propanediol: $n^{20}D$ 1.4303; d^{23}_4 1.530; ir 1605, 1275, and 800–1000 cm^{-1}.

Anal. Calcd for $C_5H_8F_4N_4O_7$: C, 19.24; H, 2.58; F, 24.35; N, 17.95. Found: C, 19.05; H, 2.66; F, 24.53; N, 17.70.

Registry No.—2-Methyl-4-[1,2-bis(difluoroamino)-ethoxymethyl]-1,3-dioxolane, 35210-19-6; methyl-3-[1,2-bis(difluoroamino)-4-pentenyl]formal, 35210-20-9; methyl-3-[1,2,4,5-tetrakis(difluoroamino)pentyl]formal, 35210-21-0; 3-[1,2-bis(difluoroamino)ethoxy]-1,2-propanediol, 17686-77-0; ethyl (α-nitratomethyl)acrylate–N_2F_4 adduct, 35210-23-2; petrin methacrylate–N_2F_4 adduct, 35210-24-3; tetrafluorohydrazine, 10578-16-2.

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Fluoride Ion Catalyzed Formation of Perfluoro Esters

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Trifluoroacetyl fluoride dimerizes at −108° in the presence of CsF to form $CF_3CO_2C_2F_5$. With $(CF_3)_2CFO^-Cs^+$, COF_2, $CF_3C(O)F$, $C_2F_5C(O)F$, and $C_3F_7C(O)F$ react to form the heptafluoroisopropyl esters, $FCO_2CF(CF_3)_2$, $CF_3CO_2CF(CF_3)_2$, $C_2F_5CO_2CF(CF_3)_2$, and $C_3F_7CO_2CF(CF_3)_2$. Although these compounds are formed only at low temperature, when pure they are stable at 25° and above.

Although Haszeldine[2] reported the low yield preparation of perfluoro esters in the synthesis of perfluoroalkyl iodides, these were not characterized. In

$$R_fCO_2Ag + I_2 \longrightarrow R_fI + CO_2 + R_fCO_2R_f$$
$$R_f = CF_3, C_3F_7$$

the interim, with the exception of the dimerization and trimerization[3] of COF_2 to yield FCO_2CF_3 and $(CF_3O)_2CO$ and photolysis reactions by Varetti and Aymonino[4-7] little synthetic information on perfluoro esters has appeared in the literature.

$$CF_3OF + CO \xrightarrow{h\nu} FCO_2CF_3$$
$$CF_3OOCF_3 + (CF_3)_2CO \xrightarrow{h\nu} (CF_3O)_2CO$$
$$CF_3OOCF_3 + CO \xrightarrow{h\nu} CF_3OCOOCOCF_3$$
$$CF_3OCOOCOCF_3 + (CF_3)_2CO \xrightarrow{h\nu} CF_3CO_2CF_3$$

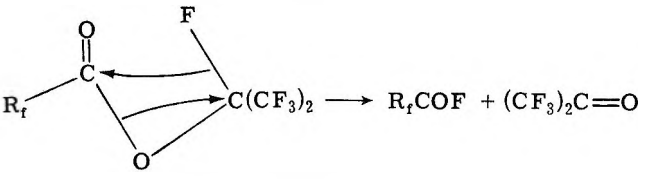
During a study of the reactions of the HNF_2–KF adduct with perfluoroacyl fluorides at −78° we isolated the ester $CF_3CO_2C(NF_2)_2CF_3$ in the case of $CF_3C(O)F$, in addition to the totally fluorinated amides,[8] $R_fC(O)NF_2$. When the reaction temperature was lowered to −105°, bis(difluoramino)trifluoroethyl trifluoroacetate was not formed but instead $CF_3CO_2C_2F_5$, the dimer of $CF_3C(O)F$, was obtained. Since the literature contains relatively few totally fluorinated esters and fewer methods of preparing them, the reactions of perfluoroacyl fluorides with alkali metal fluorides and perfluoroalkoxides was investigated.[9]

Results and Discussion

The reaction of cesium heptafluoroisopropoxide with acyl fluorides provides a convenient route to esters of the hypothetical i-C_3F_7OH. Esters of the type $R_fC(O)OC(CF_3)_2F$ have been postulated[10] as intermediates in the fluorination of $R_fC(O)Cl$ by i-C_3F_7OCs, but these esters appeared to be unstable. The bulky CF_3 groups were thought to prevent free rotation and the enhanced electrophilic nature of the ester carbonyl would facilitate fluoride ion transfer. Contrary to

$$(CF_3)_2CO + CsF \longrightarrow (CF_3)_2CFO^- + Cs^+$$
$$R_fC(O)F + (CF_3)_2CFO^- \longrightarrow R_fCO_2C(CF_3)_2F + F^- \quad (10\text{–}20\%)$$
$$R_f = F, CF_3, C_2F_5, C_3F_7$$

$$R_fC(O)Cl + i\text{-}C_3F_7OCs \longrightarrow CsCl + [R_fCOOC(CF_3)_2F]$$



$$\longrightarrow R_fCOF + (CF_3)_2C{=}O$$

this, we have found that these esters are stable and do not disproportionate once isolated. The esters are decomposed rapidly in the presence of alkali metal fluorides at −78° or above, which undoubtedly accounts for the previously reported results. The utilization of low reaction temperatures retards decomposition sufficiently to allow ester isolation but also may hamper the yield as seen in Figure 1.

Although the dimer of $CF_3C(O)F$ does form in low yield with CsF at low temperature, the dimerization occurs more efficiently when KF–HNF_2 is used. The formation of pentafluoroethyl trifluoroacetate by the latter method could at first glance be readily explained *via* the formation of the pentafluoroethoxide anion and subsequent reaction with $CF_3C(O)F$. However,

$$CF_3C(O)F + KF \longrightarrow C_2F_5O^- + K^+$$
$$CF_3C(O)F + C_2F_5O^- \longrightarrow CF_3CO_2C_2F_5 + F^-$$

when the reaction was run under identical conditions but without HNF_2, in order to confirm this pathway, none of the ester was isolated. Addition of HNF_2 to the vessel with KF and $CF_3C(O)F$ again resulted in the formation of the ester.

At −105° the extrapolated dissociation pressure of HNF_2 from the HNF_2–KF adduct is negligible[11] and therefore the HNF_2 cannot be assumed only to be forming "activated" KF *via* complexation and dissociation. To confirm this, KF was "activated" by the formation and decomposition of the hexafluoroacetone adduct but no ester was isolated with $CF_3C(O)F$. In an attempt to understand the role of the HNF_2, other reagents, such as $(CF_3)_2NOH$, which undergo complexation and substitution in an analogous manner, were used, but no ester could be isolated. Also, vacuum dried KF–HF, which would be present after HNF_2 reacted with $CF_3C(O)F$, was used without success.

Although the exact effect of the HNF_2 could not be ascertained, the above-described pathway would indicate that the low temperature reactions of perfluoroacyl fluorides with perfluoroalkoxide salts would lead to a general synthesis of totally fluorinated esters.

(1) Alfred P. Sloan Foundation Fellow, 1970–1972.
(2) R. N. Haszeldine, *Nature (London)*, **168**, 1028 (1951).
(3) B. C. Anderson, G. Crest, and G. R. Morlock, U. S. Patent 3,226,418; *Chem. Abstr.*, **64**, 9598 (1966).
(4) P. J. Aymonino, *Chem. Commun.*, 241 (1965).
(5) E. L. Varetti and P. J. Aymonino, *ibid.*, 680 (1967).
(6) E. L. Varetti and P. J. Aymonino, *An. Asoc. Quim. Argent.*, **55**, 153 (1967).
(7) E. L. Varetti and P. J. Aymonino, *ibid.*, **58**, 17 (1970).
(8) R. A. De Marco and J. M. Shreeve, *Inorg. Chem.*, **10**, 911 (1971).
(9) D. A. Couch, R. A. De Marco, and J. M. Shreeve, *Chem. Commun.*, 91 (1971).
(10) A. G. Pittman and D. J. Sharp, *J. Org. Chem.*, **31**, 2316 (1966).
(11) E. A. Lawton, D. Pilipovich, and R. D. Wilson, *Inorg. Chem.*, **4**, 118 (1965).

The infrared spectra of the new perfluoro esters are found in Table I. The carbonyl stretching frequency

TABLE I
INFRARED SPECTRA OF $R_fCO_2R_f'$

Compd	cm^{-1}
$CF_3CO_2C_2F_5$	1851 (s), 1336 (m), 1257 (s, sh), 1247 (vs), 1220 (s), 1206 (s), 1179 (s), 1110 (vs), 1092 (s), 858 (w, br), 760 (m), 740 (sh), 708 (vw), 679 (m), 529 (m)
$FCO_2C(CF_3)_2F$	1906 (s), 1881 (m), 1309 (m), 1269 (vs), 1219 (ms), 1179 (ms), 1147 (s), 1018 (ms), 948 (w), 753 (w), 726 (w), 659 (w)
$CF_3CO_2C(CF_3)_2F$	1851 (s), 1339 (s), 1305 (s), 1260 (vs), 1207 (s), 1175 (s), 1120 (vs), 1086 (s), 1010 (s), 839 (w), 758 (m), 724 (m), 677 (m), 544 (m), 525 (sh)
$C_2F_5CO_2C(CF_3)_2F$	1845 (vs), 1340 (m), 1310 (s), 1277 (vs), 1264 (vs), 1237 (vs), 1225 (s, sh), 1172 (s), 1135 (vs), 1109 (vs), 1006 (vs), 820 (w), 752 (sh), 738 (sh), 722 (m), 677 (mw), 535 (mw)
$C_3F_7CO_2C(CF_3)_2F$	1844 (s), 1360 (m), 1332 (sh), 1310 (s), 1260 (vs), 1229 (s), 1204 (s), 1176 (s), 1144 (s), 1120 (s), 1095 (sh), 1061 (m), 1010 (s), 960 (m), 921 (ms), 820 (m), 755 (m), 740 (vw), 723 (m), 680 (mw), 540 (m)

is characteristically found in the 1840–1850-cm^{-1} region for these esters and is reasonably independent of both the perfluoroacyl and perfluoroalkyl groups. In considering the trifluoroacetate esters $CF_3CO_2CF_3$, $CF_3CO_2C_2F_5$, and $CF_3CO_2C(CF_3)_2F$ the carbonyl stretching frequencies are 1852,[7] 1851, and 1851 cm^{-1}, respectively, and, for the heptafluoroisopropyl esters, $CF_3CO_2C(CF_3)_2F$, $C_2F_5CO_2C(CF_3)_2F$, and $C_3F_7CO_2C(CF_3)_2F$, the stretching frequencies are 1851, 1845, and 1844 cm^{-1}. These shifts follow the same trend as the perfluoroacyl fluorides which are found at ~1880–1895 cm^{-1} and the perfluoroacyl chlorides located at ~1800–1815 cm^{-1}. The tentative assignment of the C–O single bond stretching frequency may be accomplished by using the empirical relationship observed by Varetti and Aymonino.[12] The C–O stretching

$$\nu_{C-O} = 4112 - 1.625\nu_{C=O}$$

frequencies for $CF_3CO_2C_2F_5$, $FCO_2C(CF_3)_2F$, $CF_3CO_2C(CF_3)_2F$, $C_2F_5CO_2C(CF_3)_2F$, and $C_3F_7CO_2C(CF_3)_2F$ can then be assigned at 1110, 1018, 1120, 1109, and 1120 cm^{-1}, respectively. These values agree very well with those assigned to FCO_2CF_3 (1020 cm^{-1}) and $CF_3CO_2CF_3$ (1111 cm^{-1}) by Varetti and Aymonino.

The mass spectra are found in Table II. Although parent peaks are not observed, a small peak corresponding to M − F is seen for each derivative. For the general ester $R_fCO_2R_f'$ a consistant cracking pattern can be found with the exception of the carbonyl fluoride derivative. Fragments are observed in each ester corresponding to R_f, R_fCO, R_f', $R_f'O$, and $R_f'CO_2$ but none is found for R_fCO_2.

^{19}F nmr data for these esters are found in Table III. The CF_3 groups of the heptafluoroisopropyl esters are magnetically equivalent, even with the large C_3F_7 acyl side chain, which argues further against hindered rotation.[10] The spectra are first order and directly interpretable. Although no spin–spin coupling of the acyl CF_3 group with the isopropyl CF_3 in $CF_3CO_2C(CF_3)_2F$ occurs, because of through space coupling the CF_3 of the acyl group in $C_2F_5CO_2C(CF_3)_2F$ and $C_3F_7CO_2C(CF_3)_2F$ is split by the isopropyl CF_3.

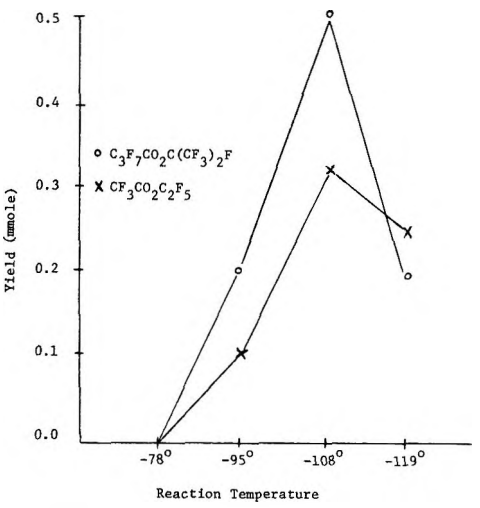


Figure 1.—Effect of temperature on perfluorinated ester yields.

TABLE II
MASS SPECTRA OF $R_fCO_2R_f'$

Compd	*m/e* (assignments, rel %)
$CF_3CO_2C_2F_5$	213 (M − F, 0.5); 180 (?, 0.3); 163 (M − CF_3, 2); 135 (C_2F_5O, 1); 119 (C_2F_5, 38); 116 (C_2F_4O, 2); 100 (C_2F_4, 1); 97 (C_2F_3O, 26); 78 (C_2F_2O, 1); 69 (CF_3, 100); 50 (CF_2, 33); 47 (CFO, 27); 43 (C_2F, 2); 31 (CF, 14)
$FCO_2C(CF_3)_2F$	213 (M − F, 0.5); 185 (C_3F_7O, 0.1); 169 (C_3F_7, 3.5); 166 (C_3F_6O, 1); 163 (M − CF_3, 7); 147 (C_3F_5O, 4); 119 (C_2F_5, 3); 100 (C_2F_4, 2); 97 (C_2F_3O, 24); 78 (C_2F_2O, 1); 69 (CF_3, 100); 66 (CF_2O, 26); 50 (CF_2, 8); 47 (CFO, 60); 31 (CF, 10)
$CF_3CO_2C(CF_3)_2F$	263 (M − F, 1); 213 (M − CF_3, 3); 169 (C_3F_7, 8); 147 (C_3F_5O, 2); 119 (C_2F_5, 3); 100 (C_2F_4, 1); 97 (C_2F_3O, 30); 78 (C_2F_2O, 1); 69 (CF_3, 100); 50 (CF_2, 10); 47 (CFO, 5); 31 (CF, 6)
$C_2F_5CO_2C(CF_3)_2F$	313 (M − F, 2); 213 (M − C_2F_5, 8); 169 (C_3F_7, 25); 147 (C_2F_5O, 25); 119 (C_2F_5, 26); 100 (C_2F_4, 8); 97 (C_2F_3O, 6); 81 (C_2F_3, 1); 78 (C_2F_2O, 2); 69 CF_3, 100); 50 (CF_2, 8); 47 (CFO, 3); 31 (CF, 13)
$C_3F_7CO_2C(CF_3)_2F$	363 (M − F, 2); 213 (M − C_3F_7, 4); 197 (C_4F_7O, 3); 169 (C_3F_7, 59); 147 (C_3F_5O 2); 119 (C_2F_5, 7); 100 (C_2F_4, 6); 97 (C_2F_3O, 5); 85 (CF_3O, 2); 78 (C_2F_2O, 2); 69 (CF_3, 100); 50 (CF_2, 4); 47 (CFO, 2); 31 (CF, 7)

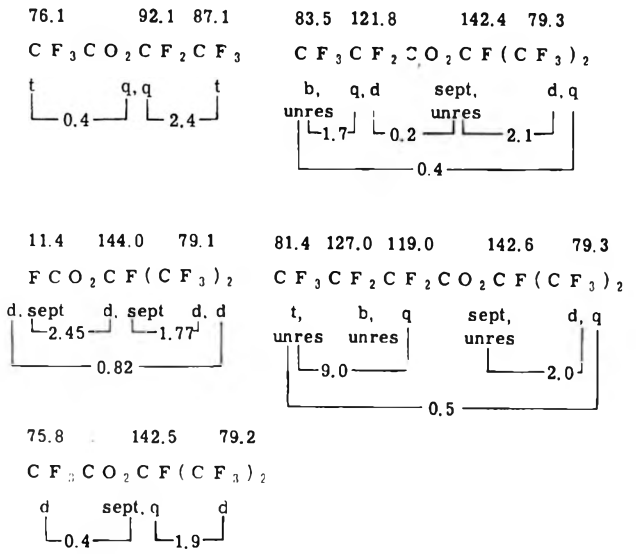
Experimental Section

Perfluoroacyl fluorides (PCR, Inc.) were purchased and used without further purification or prepared from the corresponding chloride (PCR, Inc.) and anhydrous CsF (American Potash &

(12) E. L. Varetti and P. J. Aymonino, *Spectrochim. Acta, Part A*, **27**, 183 (1971).

Table III

^{19}F Nmr Spectra[a]



[a] Upfield shifts relative to CCl_3F as internal reference.

windows. The ^{19}F nmr were obtained on a Varian Model HA-100 spectrometer operating at 94.1 MHz. The mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV. Elemental analyses were obtained from Beller Mikroanalytisches Laboratorium, Göttingen, Germany.

General Procedure.—In general, the new perfluorinated esters were prepared by preforming the $(CF_3)_2CFO^-Cs^+$ salt by condensing an excess of hexafluoroacetone on CsF[13] and allowing the mixture to warm. The unreacted hexafluoroacetone was pumped off and a measured amount of the particular perfluoroacyl fluoride was consensed onto the salt at −183°. The reaction mixture was warmed to and allowed to remain at −108° for 4 to 6 hr. After this time, any volatile materials were pumped away and the vessel was warmed slowly under dynamic vacuum to minimize the contact time between the ester and CsF. For minimum loss due to fluoride ion catalyzed decomposition, the ester should be removed from the reaction vessel below −78°. However, for the higher molecular weight esters the rate of decomposition at −78° was slow and successful isolation was possible. When pure, these esters are stable at 25° and above for long periods.

The yields of esters obtained *via* this procedure were highly variable so that two "identical" reactions may give 20 or 0% of the ester. While temperature effects are important, we feel that the state of division of the CsF is the largest single factor governing reproducibility. The experimental data are summarized in Table IV. These numbers represent average yields. These

Table IV

$R_fC(O)F$ (mmol)	$(CF_3)_2CFO^-Cs^+$, mmol	Time, ester, mmol	Trap temp,[a] °C	Mol wt[b]	C, %	F, %
$CF_3C(O)F$ (12)	CsF only	5 hr, $CF_3CO_2C_2F_5$, 0.3	−116			
COF_2 (6)	6	4 hr, $FCO_2C(CF_3)_2F$, 1.0	−96	235 (232)[c]		
$CF_3C(O)F$ (20)	3	4 hr, $CF_3CO_2C(CF_3)_2F$, 1.7	−78	284 (282)	21.7 (21.3)	68.3 (67.4)
$C_2F_5C(O)F$ (6)	6	5 hr, $C_2F_5CO_2C(CF_3)_2F$, 1.1	−96	335 (332)	21.5 (21.7)	71.0 (68.7)
$C_3F_7C(O)F$ (5)	6	4 hr, $C_3F_7CO_2C(CF_3)_2F$, 0.5	−63	382 (382)	21.9 (22.0)	68.8 (69.6)

[a] Temperature at which ester condensed under dynamic vacuum of 10^{-2}–10^{-3} Torr. [b] Vapor density determined assuming ideal gas behavior by Regnault's method. [c] Calculated value.

Chemical Corp.). Hexafluoroacetone was obtained from Allied Chemical Co. and also used without purification.

Apparatus.—Volatile liquids and gaseous materials were handled in a standard vacuum line equipped with a Heise–Bourdon tube gauge. The reactions were carried out in Pyrex glass vessels equipped with Fisher–Porter Teflon valves or in metal vessels. In general, the esters were readily separated from the slightly more volatile acid fluorides by fractional condensation (low temperature separation based on differences in volatility of components). Low temperature baths are made by cooling appropriate organic liquids to their freezing point with liquid nitrogen to give slushes.

Analysis.—Infrared spectra were taken on a Perkin–Elmer 457 spectrometer using a 10-cm Pyrex glass cell equipped with KBr

compounds exhibit moderate hydrolytic stability, *e.g.*, $CF_3CO_2C(CF_3)_2F$, is 50% recovered after 2 hr at 25° in excess water.

Registry No.—$CF_3CO_2C_2F_5$, 30952-31-9; $FCO_2C(CF_3)_2F$, 30952-33-1; $CF_3CO_2C(CF_3)_2F$, 30952-32-0; $C_2F_5CO_2C(CF_3)_2F$, 30952-34-2; $C_3F_7CO_2C(CF_3)_2F$, 30952-35-3.

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(13) C. T. Ratcliffe and J. M. Shreeve, *Chem. Commun.*, 674 (1966).

Electrophilic Substitution in Acenaphthene and Related Compounds. III.[1] Acetylation of Some Monosubstituted Acenaphthenes

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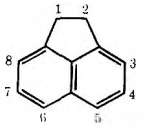
3-Acetyl-, 3-bromo-, 3-chloro-, and 3-nitroacenaphthene have been shown to acetylate exclusively in the 6 position. 3-*tert*-Butylacenaphthene also acetyles predominantly in the 6 position, in spite of preferential electronic activation of the 5 position. 5-Acetyl- and 5-acetamidoacenaphthene acetylate in position 8, while 5-*tert*-butyl- and 5-methylacenaphthene react predominantly in position 3. Reaction of 5-fluoro-, 5-chloro-, 5-bromo-, and 5-iodoacenaphthene give mixtures of the 3- and 8-acetylated products, the isomer ratio depending on the halogen (5-fluoroacenaphthene also gives 5-acetyl-6-fluoroacenaphthene). For these last compounds, partial rate factors have been obtained for substitution in the 3 and 8 positions. The halo substituents have a much smaller rate decreasing effect relative to hydrogen than in the same reaction in halobenzenes.

In part II[1] we reported on the bromination and chlorination of 3-bromo-, 3-chloro-, 5-bromo-, and 5-chloroacenaphthene as part of a detailed study of disubstitution in acenaphthene. It had previously been shown[2] that the positions para to the bridge in acenaphthene



are extremely activated to electrophilic attack. Recent detritiation studies[3] have shown that the 3(8) positions are also activated, though less so than the 5 and 6 positions. In part II it was shown that the 3-haloacenaphthenes, as expected, underwent exclusive halogenation in the 6 position. For a 5-halo substituent and attacking nucleophile with small steric requirements, the electronically activated 6 position was preferentially attacked. In the bromination of 5-bromoacenaphthene with molecular bromine, however, ir evidence indicated that approximately equal amounts of the 3,5 and 3,6 isomers were formed. This unexpected amount of the 3,5 isomer prompted us to look at acetylation of these compounds. With one exception, the bulky acetylating entity did not substitute peri to a 5 substituent, and it was possible to measure the relative amounts of 3 and 8 substitution. Many of these compounds were hitherto unknown and most have been isolated and identified. We have also included acetylation of some 3-substituted acenaphthenes. Competition experiments have also been carried out to provide information on the relative reactivities of some of the 5-substituted compounds.

As with halogenation, little was previously known about the orientation of products in acetylation of monosubstituted acenaphthenes, and the reported yields leave a significant amount of product unaccounted for. Apart from acetylation of 3-acetyl- and 5-acetylacenaphthene[4] (which gave 65 and 15%, respectively, of the 3,6 isomer), the only reported study[5] of this reaction is with 5-bromo- and 5-chloroacenaphthenes. From reaction of the former with acetyl chloride–aluminum chloride in nitrobenzene, 3-acetyl-6-bromoacenaphthene (50%) and 3-acetyl-5-bromoacenaphthene (25%) were obtained by separation of the oximes. No yields were reported from the 5-chloro compound.

Results and Discussion

The acetylations were carried out with acetic anhydride and aluminum (or zinc) chloride in dichloroethane. Product isomer proportions in a reaction mixture were determined by nmr analysis of the acetyl region of the spectrum, or by glpc, and the results are listed in Table I. Analysis of the reaction mixture from acetylation of 5-bromoacenaphthene at various times showed that the isomer ratio was not time dependent.

TABLE I

ACETYLATION OF MONOSUBSTITUTED ACENAPHTHENES[a,b]

Substituent	% overall product yield (glpc)	Disubstituted product isomer distribution, % 3,6	3,5	5,6	3,8
3-Acetyl	>95	90			
3-Bromo	~50[c]	90			
3-*tert*-Butyl	>90	60			30
3-Chloro	~65[c]	95			
3-Nitro	~50[c]	90			
5-Acetyl	~100	92			
5-Bromo	>95	56	44		
5-Chloro	>95	63	37		
5-Fluoro	>95	30	30	40	
5-Iodo	>90	35	65		
5-Methyl	~100		>90		
5-*tert*-Butyl	~80[c]	30	70		
5-Acetamido	>95	100			

[a] Using acetic anhydride under the conditions described in the text. [b] Acetylation of acenaphthene gave 80% 5-acetyl- and 20% 3-acetylacenaphthene. [c] Remainder was largely starting material.

3-Substituted Acenaphthenes.—Table I indicates that, with one exception, acetylation occurred exclusively in the 6 position. The acetyl, bromo, chloro, and nitro substituents are all electron withdrawing, and it is therefore not surprising on electronic grounds that further substitution occurs in the other ring. These results are in accord with our previous halogenation findings.[1]

Acetylation of 3-*tert*-butylacenaphthene, however, indicates that simple electronic considerations do not

(1) Part II: P. R. Constantine, L. W. Deady, and R. D. Topsom, *J. Org. Chem.*, **34**, 1113 (1969).

(2) E. Berliner, D. M. Falcione, and J. L. Riemenschneider, *ibid.*, **30**, 1812 (1965).

(3) M. C. A. Opie, G. J. Wright, and J. Vaughan, *Aust. J. Chem.*, **24**, 1205 (1971).

(4) M. Dashevskii and E. Shamis, *J. Gen. Chem. USSR*, **33**, 1534 (1963).

(5) D. Nightingale and R. Brooker, *J. Amer. Chem. Soc.*, **72**, 5539 (1950).

adequately explain the results. For this activating substituent, the predominant reaction should have occurred in the 5 position but the 3,6 isomer in fact predominated. In addition, more reaction occurred in the 8 position than in the 5 position. The 3-acetyl-8-*tert*-butylacenaphthene was identified from nmr and ir spectra. The aromatic proton region of the nmr spectrum contained an AB pattern (2 H, J = 9 Hz) and a singlet (2 H), inconsistent with the spectrum expected for 5-acetyl-3-*tert*-butylacenaphthene. The ir spectrum contained no strong peak around 770 cm^{-1}, characteristic of three adjacent hydrogens in acenaphthene compounds.

It seems clear that steric as well as electronic factors determine the product orientation in these reactions. Thus, for a 3-substituted acenaphthene, formation of the transition state for substitution in the 6 or 8 positions apparently allows greater relief of steric strain than does substitution in the 5 position.

5-Substituted Acenaphthenes.—Further substitution in 5-substituted acenaphthenes is complex, the position of substitution and proportions of products being quite dependent on the identity of the 5 substituent. Of special interest is the ratio of 3 (to give the 3,5 isomer) to 8 (3,6 isomer) substitution. The substitution pattern in each case was assigned from known[1] ir and nmr data.

In simplest terms, substitution in the 3 and 8 positions of a 5-substituted acenaphthene compared with acenaphthene should be electronically analogous to substitution in the meta position of a monosubstituted benzene relative to substitution in benzene. 5-Methyl- and 5-*tert*-butylacenaphthene were found to acetylate predominantly in the 3 position as expected for these donor substituents.

In contrast to the alkyl-substituted compounds, 5-acetamido- and 5-acetylacenaphthene underwent acetylation in the 8 position. More severe conditions were needed for complete reaction of these compounds, no doubt owing to some complexing of the acetylating entity with the substituent in each case, which results in considerable relative deactivation of the 3 position. Nitration of 5-acetamidoacenaphthene has been shown[6] to occur at the 4 position. The absence of this isomer in the acetylation reaction illustrates the greater effective bulk of the acetylating species. Results from acetylation of the 5-haloacenaphthenes are especially intriguing. Only with 5-fluoro was an appreciable amount of the 5,6 isomer produced. The small size of the fluoro atom evidently allows acetylation at the electronically activated peri position. On electronic grounds, the strongly electron-withdrawing halo groups were expected to operate like the acetyl and direct the electrophile to the 8 position. It is clear from the amount of 3,5 product produced, which increases from fluoro to iodo, that other factors are operating in these reactions. The competition experiments outlined below indicate their complexity.

An interesting side feature was an improved synthesis of 3-acetylacenaphthene, obtained by dehalogenation of the crude reaction product from acetylation of 5-bromoacenaphthene.

Competition Reactions.—Semiquantitative competition experiments were carried out by reacting suitable pairs of compounds with a deficiency of acetylating mixture under the standard conditions. From the total product yields (glpc) and the known product isomer distribution (Table I) for each compound, relative rates for substitution in the 3 and 8 positions were obtained. The data are given in Table II. While

TABLE II

RELATIVE ACETYLATION RATES OF SOME 5-SUBSTITUTED ACENAPHTHENES IN THE 3 AND 8 POSITIONS, FROM COMPETITION EXPERIMENT PRODUCT RATIOS

Competition compounds[a] A	B	Product response factor, A/B	Corrected total product ratio, A/B	k_3^A/k_3	k_8^A/k_8^B
Acenaphthene (1)	5-Cl	1.0	6.5	1.7[b]	1.1
5-F (2)	5-Cl	1.2	1.6	1.2	0.8
5-Cl (3)	5-Br	1.0	2.0	1.8	2.1
5-Br (4)	5-I (5)	0.8	1.5	1.1	2.4
Acenaphthene	5-Me	0.9	1.1	0.1	
5-Me (6)	5-*t*-Bu (7)	0.75	1.1	1.4	

[a] Registry numbers follow: 1, 83-32-9; 2, 6861-63-8; 3, 5209-33-6; 4, 2051-98-1; 5, 6861-64-9; 6, 17057-80-6; 7, 35210-35-6. [b] $6.5 \times 0.2 \times 0.5^c/1 \times 0.37$. [c] Statistical factor.

$k_{rel} \neq$ product ratio, the results indicate the order of magnitude of the relative reactivities and the order of substituent effects. Thus, for reaction at the 3 position the order Me > *t*-Bu > H > F > Cl > Br ~ I ($k_{H/I} \sim 2.5$) is obtained, and for the 8 position, H ~ Cl > F > Br > I ($k_{H/I} \sim 5$).

A number of points arise from these results.

(1) The difference between the rate of reaction of acenaphthene and of the slowest reacting halo-substituted compound is small for either position. Thus, quite marked differences in isomer distribution are produced by relatively small energy differences.

(2) The halogen order for reactivity in the 3 position (except iodo) is that commonly found for electrophilic substitution in the meta position of halobenzenes. However, the halogens have a very much reduced rate-retarding effect relative to hydrogen as compared to analogous benzenes.[7]

(3) The order Me > *t*-Bu is opposite to that found for meta reactivity in electrophilic substitution in toluene and *tert*-butylbenzene. The partial rate factors with respect to acenaphthene are of the same order of magnitude as found for alkylbenzenes.

(4) For reaction in the 8 position, the partial rate factors relative to that position in acenaphthene are F, 0.7; Cl, 1.0; Br, 0.4; I, 0.2.

With respect to the restricted range of partial rate factors observed for the halo substituents, similar results have been found in electrophilic substitution in highly activated benzenes. For example, the partial rate factors for nitration meta to the halo group in para haloanisoles compared with anisole itself have recently been shown[8] to be 0.096, 0.077, and 0.119 for chlorine, bromine, and iodine, respectively, compared with values of 0.00084, 0.0010, and 0.0112 for meta substitution of the analogous halobenzenes under the same conditions.

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Since the inductive and resonance effects for halo substituents are opposed, differences between halogen electronic effects will be small and a reactivity order based on these effects could thus be readily modified by other contributing effects.

Clearly, in 5-substituted acenaphthenes, nonbonded interactions occur between the substituent and peri hydrogen. It is likely that, as for 3-*tert*-butylacenaphthene, variation in this interaction energy during formation of the transition state could be largely responsible for the observed reactivity orders. For example, the reactivity of 5-iodoacenaphthene seems anomalous since iodobenzene usually undergoes electrophilic substitution faster in the meta position than does bromo-, chloro-, or even fluorobenzene.[7] This, together with the lower reactivity of, and greater proportion of 8 substitution from, 5-*tert*-butylacenaphthene relative to 5-methylacenaphthene suggests that steric factors are of major importance with these large substituents.

In conclusion, this work provides an extensive account of the directing effect of substituents in electrophilic substitution in monosubstituted acenaphthenes. Previous results on bromination of 5-bromoacenaphthene fit in with the pattern observed in the acetylation reaction. The reason for the observed reactivity orders is not fully apparent to us and is a further instance of the intriguing chemistry of the acenaphthene molecule.

Experimental Section

Glpc analyses were carried out on a GE-SE-30 silicone rubber column at 220–240°. Infrared spectra were run as KCl disks and $CDCl_3$ was employed as the solvent for nmr measurements, with TMS as internal standard. Microanalyses were carried out by the Australian Microanalytical Service.

Materials.—3-Bromo-, 3-chloro-, 5-bromo-, and 5-chloroacenaphthene were prepared as described in part II.[1] 5-Acetylacenaphthene,[9] mp 69° (lit. mp 69–70°), 5-fluoroacenaphthene,[10] mp 93–94° (lit. mp 94–95°), 5-iodoacenaphthene,[11] mp 62–63° (lit. mp 63–63.5°), 5-acetamidoacenaphthene,[12] mp 189–190° (lit. mp 190°), 3-*tert*-butylacenaphthene,[13] mp 63–64° (lit. mp 65–66°),, and 5-methylacenaphthene,[14] mp 93.5–94.5° (lit. mp 95–96°) were prepared by literature methods. The preparation[13] of 5-*tert*-butylacenaphthene was modified in that sublimation of the crude red oily product at *ca.* 0.3 mm (100°) gave, first, acenaphthene, and then 5-*tert*-butylacenaphthene contaminated with a little acenaphthene. Three recrystallizations from ethanol gave the product, mp 98–100° (lit.[13] mp 101.5–102°).

3-Acetylacenaphthene.—The crude mixture of 3-acetyl-5-bromo- and 3-acetyl-6-bromoacenaphthene obtained from acetylation of 10 g of 5-bromoacenaphthene ("standard" conditions; see below) was refluxed for 1.5 hr with cupric oxide (8.0 g), acetic anhydride (6.0 ml), and pyridine (40 ml). The reaction mixture was poured into 5% acetic acid (400 ml) and the product was filtered off. Soxhlet extraction (3 hr) with petroleum ether (bp 60–80°) gave, after evaporation, 3-acetylacenaphthene (5.2 g) containing some 3-acetylacenaphthylene impurity. Hydrogenation at atmospheric pressure in methanol (10% Pd/C catalyst) gave 3-acetylacenaphthene (4.8 g), mp 103.5–104.5° (lit.[15] mp 105°), after recrystallization from methanol–water.

"Standard" Conditions. A. Acetylating Mixture.—Acetic anhydride (0.5 mol) was added dropwise to a stirred mixture (10°) of anhydrous aluminum chloride (1.0 mol) in dry dichloroethane (2.5 mol). Anhydrous zinc chloride replaced the aluminum chloride for reactions of 3-*tert*-butyl-, 5-*tert*-butyl-, and 5-iodoacenaphthene.

B. Acetylation.—The acetylating mixture was added dropwise during 1 hr to a stirred solution of the compound (0.4 mol) in dry dichloroethane (3.5 mol), the temperature being maintained at *ca.* 0° throughout. The mixture was stirred for 1–24 hr (*ca.* 0°), the reaction was quenched by addition of an ice–concentrated hydrochloric acid mixture, and the organic layer was separated.

Analysis.—For acetylation of 5-methyl- and 3-substituted acenaphthenes except 3-*tert*-butylacenaphthene, glpc analysis indicated the presence of only one product, subsequently isolated in high yield. One product only was isolated, in high yield, from the acetylation of 5-acetamidoacenaphthene.

The product ratios from acetylation of 5-acetyl, 3-*tert*-butyl-, 5-*tert*-butyl-, and 5-iodoacenaphthene were obtained by glpc. For 5-bromo-, 5-chloro-, and 5-fluoroacenaphthene, product analysis was carried out by nmr, from knowledge of chemical shifts of the various product acetyl protons (Table III). Analysis of the reaction mixture from 5-fluoroacenaphthene requires more comment. The acetyl region of the reaction product nmr spectrum contained four peaks, two broad and equivalent and two sharp and equivalent. Conversion to the oximes followed by preparative tlc on silica gel with $CHCl_3$ eluent gave two bands (R_f 0.6 and R_f 0.25). The ketone with the R_f 0.25 oxime was shown by comparison with other spectra to be 5-acetyl-6-fluoroacenaphthene. The acetyl region in the nmr contained the two broad equivalent peaks, the splitting (J = 3.2 Hz) being due to the adjacent fluorine. The nmr spectrum of the ketone from the R_f 0.6 oxime contained two sharp and still equal acetyl signals. However, the ir spectrum contained peaks characteristic of both 3,6 [839 (s), 817 (s) cm^{-1}] and 3,5 [778 (s) cm^{-1}] substitution. Thus 3-acetyl-6-fluoroacenaphthene and 3-acetyl-5-fluoroacenaphthene were formed in equal amounts and were not separated. All three isomers had the same glpc retention time.

TABLE III

ACETYL PROTON CHEMICAL SHIFTS (FROM TMS) OF SOME HALOACETYLACENAPHTHENES (INFINITE DILUTION IN $CDCl_3$)

Substituents	Position						
Acetyl	3	3	3	3	3	3	5
Halogen	5-Br	6-Br	5-Cl	6-Cl	5-F	6-F	6-F
δ (ppm)	2.59	2.63	2.61	2.63	2.60	2.63	2.59[a]

[a] J = 3.2 Hz.

Where analysis of the reaction mixture showed the presence of only one major product, the solvent was removed and the residue was recrystallized from ethanol and (except 3-acetyl-6-nitroacenaphthene) vacuum sublimed at *ca.* 120–140°. The following compounds were isolated in this way.

3,6-Diacetylacenaphthene (from 3-acetyl- and 5-acetylacenaphthene) had mp 147–148° (lit.[4] mp 148–149°); ir 1122 (m), 1080 (m), 1018 (m), 988 (m), 963 (s), 837 (s), 814 (s) cm^{-1}. 6-Acetyl-3-bromoacenaphthene (from 3-bromoacenaphthene) had mp 98–100°; ir 1119 (m), 1073 (s), 961 (s), 854 (m), 833 (s), 814 (s) cm^{-1}. *Anal.* Calcd for $C_{14}H_{11}BrO$: C, 61.1; H, 4.0. Found: C, 61.0; H, 3.9. The oxime had mp 175–176°. *Anal.* Calcd for $C_{14}H_{12}BrNO$: C, 58.0; H, 4.2; Br, 27.6; N, 4.8. Found: C, 57.8; H, 4.1; Br, 27.9; N, 4.7. 6-Acetyl-3-chloroacenaphthene (from 3-chloroacenaphthene) had mp 108–109°; ir 1130 (s), 1078 (s), 960 (s), 884 (m), 861 (m), 833 (s), 815 (s) cm^{-1}. *Anal.* Calcd for $C_{14}H_{11}ClO$: C, 72.9; H, 4.8; Cl, 15.4. Found: C, 73.2; H, 5.05; Cl, 15.1. The oxime had mp 178–179°. *Anal.* Calcd for $C_{14}H_{12}ClNO$: C, 68.4; H, 4.9; Cl, 14.4; N, 5.7. Found: C, 68.3; H, 5.1; Cl, 14.5; N, 5.5. 6-Acetyl-3-nitroacenaphthene (from 3-nitroacenaphthene) had mp 217.5–218.5° (not sublimed); ir 970 (m), 956 (m), 935 (m), 845 (m), 839 (s), 800 (s), 755 (m) cm^{-1}. *Anal.* Calcd for $C_{14}H_{11}NO_3$: C, 69.7; H, 4.6; N, 5.8. Found: C, 69.7; H, 4.7; N, 5.55. The 2,4-dinitrophenylhydrazone had mp 259–260°. *Anal.* Calcd for $C_{20}H_{15}N_5O_6$: C, 57.0; H, 3.6; N, 16.6. Found: C, 56.9; H, 3.9; N, 16.5. 3-Acetyl-5-methyl-

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(15) L. F. Fieser and E. B. Hershberg, *ibid.*, **61**, 1272 (1939).

acenaphthene (from 5-methylacenaphthene) had mp 78–79°; ir 1141 (m), 979 (s), 866 (m), 830 (m), 770 (s), 746 (m) cm^{-1}. *Anal.* Calcd for $C_{13}H_{14}O$: C, 85.7; H, 6.7. Found: C, 85.3; H, 6.7. The oxime had mp 152–153°. *Anal.* Calcd for $C_{13}H_{15}NO$: C, 80.0; H, 6.7; N, 6.2. Found: C, 80.2; H, 6.9; N, 5.9. 6-Acetamido-3-acetylacenaphthene (from 5-acetamidoacenaphthene) had mp 218–220°; ir 1123 (m), 1110 (m), 1086 (m), 847 (s), 827 (w), 802 (s) cm^{-1}. *Anal.* Calcd for $C_{16}H_{15}NO_2$: C, 75.9; H, 6.0; N, 5.5. Found: C, 75.85; H, 6.0; N, 5.85.

In acetylations where two products were formed, the pure isomers were isolated by one of the following methods: by recrystallization of (a) the reaction mixture, (b) the oxime mixture prepared from the mother liquor of a, (c) the oxime mixture prepared from the original reaction mixture, or by preparative tlc of (d) the oxime mixture b, or (e) the oxime mixture c. Oximes were reconverted to the respective ketones by heating with 1:1 concentrated hydrochloric acid–water. The ketones were recrystallized from ethanol–water and vacuum sublimed at *ca.* 120–140°.

The following compounds were isolated in these ways.

From 5-chloroacenaphthene.—3-Acetyl-5-chloroacenaphthene (a, EtOH): mp 118–120°; ir 1170 (m), 1101 (m), 989 (m), 881 (m), 849 (m), 832 (m), 770 (s), 742 (m) cm^{-1}. *Anal.* Calcd for $C_{14}H_{11}ClO$: C, 72.9; H, 4.8; Cl, 15.4. Found: C, 72.7; H, 5.0; Cl, 15.5. Oxime. mp 138–139° (lit.[5] 140–141°). 3-Acetyl-6-chloroacenaphthene (b): mp 98.0–98.5°; ir 1080 (m), 978 (m), 863 (w), 841 (s), 822 (w), 810 (s), 724 (m) cm^{-1}. *Anal.* Calcd for $C_{14}H_{11}ClO$: C, 72.9; H, 4.8; Cl, 15.4. Found: C, 72.6; H, 4.8; Cl, 15.6. Oxime, mp 182–183° (EtOH–H_2O) (lit.[5] mp 183–184°).

From 5-bromoacenaphthene.—3-Acetyl-5-bromoacenaphthene (a, EtOH): mp 151–152° (lit.[5] mp 152–153°); ir 1096 (m), 980 (m), 876 (s), 836 (m), 827 (s), 766 (vs), 736 (s) cm^{-1}. 3-Acetyl-6-bromoacenaphthene (b): mp 89–90° (lit.[5] mp 91–92°); ir 1111 (m), 1068 (s), 1020 (w), 1009 (m), 966 (m), 954 (w), 840 (s), 816 (w), 808 (s), 710 (m) cm^{-1}. Oxime, mp 183–184° (EtOH–H_2O) (lit.[5] mp 184–185°).

From 5-fluoroacenaphthene (e, May and Baker silica gel, chloroform eluent).—5-Acetyl-6-fluoroacenaphthene: mp 114°; ir 1144 (m), 1099 (m), 1020 (m), 900 (w), 831 (s), 808 (w) cm^{-1}. *Anal.* Calcd for $C_{14}H_{11}FO$: C, 78.5; H, 5.2; F, 8.9. Found: C, 78.2; H, 5.1; F, 9.0. Oxime, mp 192–193°. *Anal.* Calcd for $C_{14}H_{12}FNO$: C, 73.35; H, 5.3; F, 8.3; N, 6.1. Found: C, 73.0; H, 5.3; F, 8.6; N, 5.9. An inseparable 1:1 mixture of 3-acetyl-5-fluoroacenaphthene and 3-acetyl-6-fluoroacenaphthene, mp 67–69°, was also obtained (see Analysis). *Anal.* Calcd for $C_{14}H_{12}FNO$: C, 78.5; H, 5.2; F, 8.9. Found: C, 78.2; H, 5.3; F, 8.9. Oxime, mp 134–135°.

From 5-iodoacenaphthene.—3-Acetyl-5-iodoacenaphthene (a, EtOH): mp 165–166°; ir 1178 (m), 970 (m), 963 (m), 834 (m), 781 (s) cm^{-1}. *Anal.* Calcd for $C_{14}H_{11}IO$: C, 52.2; H, 3.4; I, 39.4. Found: C, 52.3; H, 3.4; I, 39.3. 3-Acetyl-6-iodoacenaphthene (d, Merck Alumina G, CCl_4 eluent): mp 148°; ir 1110 (m), 990 (s), 840 (s), 805 (s) cm^{-1}. *Anal.* Calcd for $C_{14}H_{11}IO$: C, 52.2; H, 3.4; I, 39.4. Found: C, 52.4; H, 3.6; I, 39.2. Oxime, mp 174–175°.

From 5-*tert*-Butylacenaphthene.—3-Acetyl-5-*tert*-butylacenaphthene (a, EtOH): mp 177–178°; ir 1110 (m), 969 (m), 916 (m), 885 (w), 849 (m), 795 (s), 770 (m) cm^{-1}. *Anal.* Calcd for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found: C, 85.6; H, 8.0. Column chromatography (alumina, 1:1 petroleum ether (bp 60–80°), CCl_4 eluent) of the residue from (a) gave a sample of the minor isomer, contaminated with 3-acetyl-5-*tert*-butylacenaphthene. *Anal.* Calcd for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found: C, 85.3; H, 8.1. From peaks at 833 (s), 818 (m), and 808 (s) in the ir spectrum, this isomer was identified as 3-acetyl-6-*tert*-butylacenaphthene.

From 3-*tert*-butylacenaphthene.—3-Acetyl-8-*tert*-butylacenaphthene (a, EtOH): mp 136–137°; ir 1018 (w), 955 (w), 850 (vs) cm^{-1}. *Anal.* Calcd for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found: C, 85.4; H, 8.0. Column chromatography [alumina, petroleum ether (bp 60–80°) eluent] of the residue from (a) gave 6-acetyl-3-*tert*-butylacenaphthene: mp 57–58° (EtOH); ir 1079 (m), 959 (m), 840 (m), 820 (s) cm^{-1}. *Anal.* Calcd for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found: C, 85.7; H, 8.1. A third, and minor, isomer was not separated.

Registry No.—3,6-Diacetylacenaphthene, 19732-51-5; 6-acetyl-3-bromoacenaphthene, 35210-37-8, 35210-38-9 (oxime); 6-acetyl-3-chloroacenaphthene, 35210-39-0, 35210-40-3 (oxime); 6-acetyl-3-nitroacenaphthene, 35223-25-7, 35223-26-8 (2,4-DNP); 3-acetyl-5-methylacenaphthene, 35223-27-9, 35223-28-0 (oxime); 6-acetamido-3-acetylacenaphthene, 35223-29-1; 3-acetyl-5-chloroacenaphthene, 35223-30-4; 3-acetyl-6-chloroacenaphthene, 35223-31-5; 3-acetyl-5-bromoacenaphthene, 35223-32-6; 3-acetyl-6-bromoacenaphthene, 35223-33-7; 5-acetyl-6-fluoroacenaphthene, 35223-34-8, 35261-94-0 (oxime); 3-acetyl-5-fluoroacenaphthene, 35-223-35-9, 35223-36-0 (oxime); 3-acetyl-6-fluoroacenaphthene, 35223-37-1, 35223-38-2 (oxime); 3-acetyl-5-iodoacenaphthene, 35261-95-1; 3-acetyl-6-iodoacenaphthene, 35223-39-3, 35223-40-6 (oxime); 3-acetyl-5-*tert*-butylacenaphthene, 35223-41-7; 3-acetyl-6-*tert*-butylacenaphthene, 35223-42-8; 3-acetyl-8-*tert*-butylacenaphthene, 35223-43-9; 6-acetyl-3-*tert*-butylacenaphthene, 35223-44-0.

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Cyclohexadienyl Cations. IV. Methoxy Substituent Effects in the Dienone–Phenol Rearrangement

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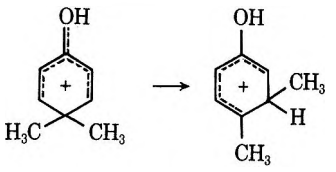
4-Methoxy-4-methylcyclohexadienone has been prepared and has been shown to undergo the dienone–phenol rearrangement in concentrated hydrochloric acid with >95% methyl migration. Rates of rearrangement of this dienone in concentrated perchloric acid from 37.9 to 71.1 wt % acid have been determined. These results, coupled with an estimate of the basicity of 4-methoxy-4-methylcyclohexadienone, are compared to similar data for 4,4-dimethylcyclohexadienone and are discussed in the context of the currently accepted mechanism of the dienone–phenol rearrangement.

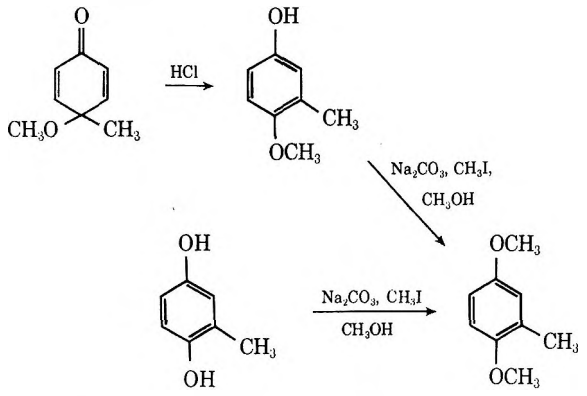
The dienone–phenol rearrangement provides an interesting and useful system for the study of the kinetic acidity dependence of a simple A1 reaction on the one hand while also functioning as a probe system which can be studied to increase our understanding of 1,2 migrations in carbonium ion reactions. For simple alkyl cyclohexadienones such as 4,4-dimethylcyclohexadienone previous work[1-6] has established the mechanism and acidity dependence for this reaction. For example, it has been shown[2] that the rate-determining step for this reaction is



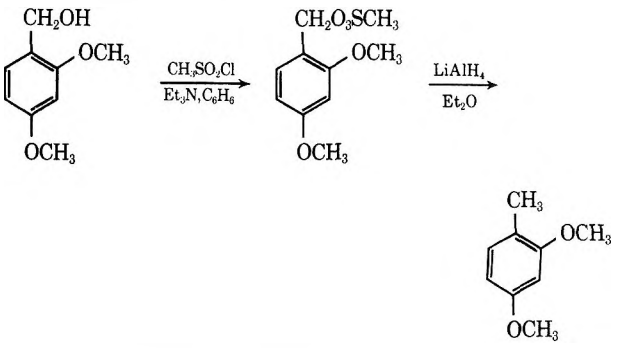
(1)

In this paper we address ourselves to another aspect of this transformation; the effect of a 4-methoxy substituent on the course of the reaction and its effect on individual steps of the reaction sequence.

Results. Product Identification.—4-Methoxy-4-methylcyclohexadienone (**1**) was prepared by the reaction of *p*-cresol with $Pb(OAc)_4$ in methanol as described by Hecker.[7] A sample was isolated by preparative glpc and rearranged in concentrated HCl. The rearrangement product was methylated with Na_2CO_3–CH_3I in methanol and the methylated product purified by glpc. The ir spectrum of this material was identical with that of authentic 2,5-dimethoxytoluene prepared from 2-methylhydroquinone.



A sample of 2,4-dimethoxytoluene was prepared as outlined below and a comparison of its ir spectrum with that of the methylated rearrangement product established that >95% methyl migration had occurred.



These results establish that the methyl group migrates in the acid-catalyzed rearrangement of **1**. Hecker[8] has reported similar results for the rearrangement of **1** in CF_3COOH.

Results. Kinetics.—Rates of rearrangement of **1** in solutions of perchloric acid of varying composition are presented in Table I and Figure 1. The rate is

TABLE I

RATES OF REARRANGEMENT OF 4-METHOXY-4-METHYLCYCLOHEXADIENONE IN AQUEOUS PERCHLORIC ACID AT 25.2 ± 0.1°

$10^5 k_{obsd}$ (sec^{-1})	Wt % $HClO_4$	$-H_0$[a]
8510	71.06	8.06
3060	65.98	6.67
1420	63.17	5.97
330	59.72	5.20
87.0	55.00	4.28
28.9	52.83	3.92
5.90	48.13	3.24
2.54	44.70	2.83
1.58	41.53	2.50
0.601	37.93	2.18

[a] K. Yates and H. Wai, *Can. J. Chem.*, **43** 2131 (1965).

strongly dependent on the proton donating ability of the solvent as measured by the Hammett acidity function H_0. In fact, the first seven data points in Figure 1 provide a good linear relationship between log k_{obsd} and $-H_0$ with slope 0.92 ± 0.04. Historically, this kind of relationship (linear log k_{obsd} *vs.* $-H_0$ plot, slope ≈1) has been taken to be evidence for the operation of an A1 mechanism based on Hammett and Zucker's

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(4) V. P. Vitullo, *J. Org. Chem.*, **35**, 3976 (1970).
(5) K. L. Cook and A. J. Waring, *Tetrahedron Lett.*, 1675 (1971).
(6) K. L. Cook and A. J. Waring, *ibid.*, 3359 (1971).
(7) E. Hecker and R. Lattrel, *Justus Liebigs Ann. Chem.*, **662**, 48 (1963).
(8) E. Hecker and E. Meyer, *Angew. Chem., Int. Ed. Engl.*, **3**, 329 (1964).

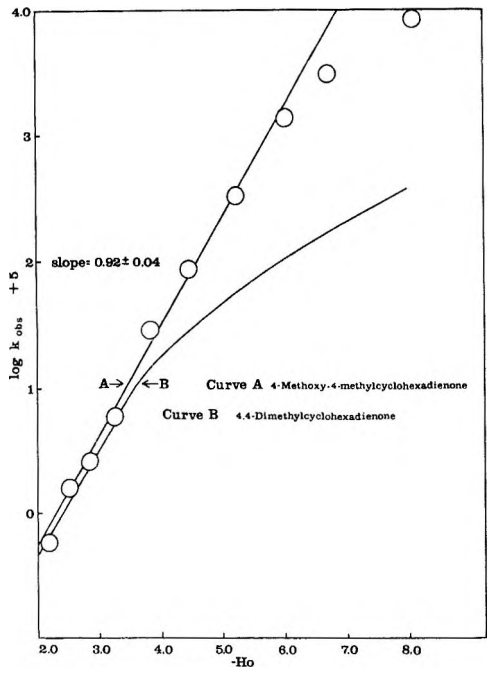


Figure 1.—Plot of log k_{obsd} *vs.* $-H_0$ for 4-methoxy-4-methylcyclohexadienone (upper curve) and 4,4-dimethylcyclohexadienone (lower curve) in perchloric acid at 25°.

original work.[9] Now the underlying assumption of the Zucker–Hammett hypothesis is that the reversible protonation of the substrate undergoing reaction is similar to the protonation of Hammett-type bases, *i.e.*, substituted anilines. However, cyclohexadienones have been shown *not* to be Hammett bases. For example, for six substituted cyclohexadienones thus far investigated[1,4-6]

$$\alpha = (\text{constant})h_0^{0.6} \tag{2}$$

$$D + H^+ \rightleftharpoons DH^+ \qquad \alpha = [DH^+]/[D] \tag{3}$$

In fact, it has been suggested[5,6] that the protonation of cyclohexadienones more nearly parallels the *amide* acidity function h_A[10] although the introduction of yet another unrelated acidity function hardly seems advisable. This is especially true since all acidity functions have been shown to be linear functions of H_0.[11]

Thus, while the dienone–phenol rearrangement is an example of an authentic A1 reaction,[2] the kinetic acidity dependence for the rearrangement of 4-methoxy-4-methylcyclohexadienone is considerably steeper than the equilibrium protonation acidity dependence of other cyclohexadienones.

In earlier work we suggested that over a range of acid concentrations similar to that used in this investigation the rate of the dienone–phenol rearrangement of 4,4-dimethylcyclohexadienone depended not only on the fraction of substrate protonated but also *inversely* on the water activity.

$$k_{obsd} = k[\text{fraction protonated}]/a_{H_2O} \tag{4}$$

(9) For a review of acidity functions and their use in mechanistic organic chemistry, see C. H. Rochester in "Acidity Functions," Academic Press, New York, N. Y., 1970, pp 110–196.

(10) K. Yates, J. B. Stevens, and A. R. Katritzky, *Can. J. Chem.*, **42**, 1957 (1964).

(11) K. Yates and R. A. McClelland, *J. Amer. Chem. Soc.*, **89**, 2686 (1967).

Now

$$k_{obsd} = \frac{k\alpha}{(\alpha + 1)a_{H_2O}} \tag{5}$$

where α is as defined in eq 3. If the amount of substrate protonated is small (*vide supra*) then

$$k_{obsd} = k\alpha/a_{H_2O} \tag{6}$$

and

$$\log k_{obsd} + \log a_{H_2O} = \log k + \log \alpha \tag{7}$$

thus, (log k_{obsd} + log a_{H_2O}) is proportional to log α and the slope of a plot of (log k_{obsd} + a_{H_2O}) *vs.* $-H_0$ should be characteristic of cyclohexadienone protonation. A plot of (log k_{obsd} + log a_{H_2O}) against $-H_0$ for the first seven data points in Figure 1 yielded a slope of 0.66 ± 0.04 in excellent agreement with the equilibrium protonation data for several other dienones.[1,4-6]

Results. Basicity of 1.—To understand the effect of methoxy substitution on individual steps of the dienone–phenol rearrangement it is necessary to estimate the basicity of **1** in concentrated solutions of perchloric acid. For **1** this presents a problem since the half-life for rearrangement in 71% $HClO_4$ is ~8 sec and the absorption spectrum of the fully protonated cyclohexadienone is difficult to obtain. Therefore, we measured the absorbance at zero time in three different perchloric acid solutions by monitoring the absorbance at 295 nm[1,4,5] (a wavelength characteristic of protonated cyclohexadienones of two other similar systems) as a function of time and back-extrapolating to $t = 0$. These results are recorded in Table II.

TABLE II
EQUILIBRIUM PROTONATION DATA FOR **1** IN PERCHLORIC ACID AT 25°

Absorbance[a]	N[b]	Wt % $HClO_4$	$-H_0$[c]	$-a$[d]
0.598 ± 0.032	8	71.06	8.06	(3.60)
0.441 ± 0.044	5	65.98	6.67	3.64
0.310 ± 0.027	7	61.37	5.97	(3.60)

[a] Absorbance at 295 nm; total dienone = 2.68×10^{-4} *M*; path length = 1 cm. [b] Number of independent determinations. [c] Footnote *a* Table I. [d] From eq 10 in text.

In general, the protonation of a weak base in concentrated acid solutions can be expressed by eq 8. The value of m for various dienones[1,4-6] so far investigated is 0.6.

$$\log \alpha = -mH_0 - a \tag{8}$$

In particular the previous discussion of the kinetic acidity dependence for **1** suggests a similar value for this substrate as well. Now α can be related to the measured absorbance through eq 9 where A is the mea-

$$\alpha = A/(A^+ - A) \tag{9}$$

sured absorbance and A^+ is the absorbance of the fully protonated dienone at the same stoichiometric concentration of substrate. Thus

$$\log \frac{A}{A^+ - A} = -0.6H_0 - a \tag{10}$$

Since there are two unknowns in this equation (A^+ and a) two independent measurements of A at two different acidities suffice to evaluate A^+ and a. The values of a and A^+ computed from the first and third entries in

Table II are −3.60 and 0.633, respectively. This value of A^+ yields an extinction coefficient for protonated 1 at 295 nm of 2360 M^{-1} cm^{-1} which is similar to the value of 3680 M^{-1} cm^{-1} reported by us earlier[1,4] for two other dienones differing only in the substituent at the 4 position. When this value of A^+ is used with the second entry in Table II and eq 10 a very similar value of a (−3.64) is obtained. This lends strong support to our assignment of this constant.[12]

In Table III we have summarized the available

TABLE III
H_0 VALUES AT HALF-PROTONATION FOR 4-METHYL-4-X-CYCLOHEXADIENONES IN CONCENTRATED ACID AT 25°

X	H_0
$-CH_3$[a]	−3.66
$-CHCl_2$[b]	−5.54
$-OCH_3$[c]	−6.02
$-CCl_3$[d]	−6.12

[a] Reference 4. [b] Reference 1. [c] This work. [d] N. Grossman, unpublished results.

basicity data for a series of 4-methyl-4-X-cyclohexadienones. The trend is quite clear. As X becomes more electron withdrawing inductively the cyclohexadienyl cation becomes less stable and the parent dienone less basic. In fact there is a good linear relationship between $(-H_0)_{\text{half-protonation}}$ and σ^*.[13]

$$(-H_0)_{\text{half-protonation}} = (0.89 \pm 0.01)\sigma^* + 3.76 \pm 0.03$$

These results suggest that within this series of compounds the basicity of the cyclohexadienone is controlled primarily by the inductive effect of the 4-substituent. It should be noted in this context that a methoxy substituent in the 4 position can only exert a $-I$ effect since resonance stabilization of the cation by this substituent is not possible. The decreased basicity of 1 reflects this electron withdrawing inductive effect.

With $a = -3.62$ it can be estimated that <20% of 1 is protonated at the highest acidity for which the linear correlations discussed above were obtained. This would introduce at most a very modest correction to the computed slope and can be ignored.

Discussion

In Figure 1 along with kinetic data for the acid-catalyzed isomerization of 1 in perchloric acid the lower curve represents kinetic results for the acid-catalyzed rearrangement of 4,4-dimethylcyclohexadienone.[14] At an acidity of $H_0 = -2$ (both substrates are <10% protonated at this acidity) the effect of a methoxy substituent on the free energy of activation is very small; $k_{OCH_3}/k_{CH_3} = 1.2$. Assuming that the neutral dienone reactants have the same free energy this rate factor corresponds to a decrease in free energy of the transition state for methoxy *vs.* methyl of ~100 cal/mol.

It is, however, possible to estimate the relative rearrangement rates for the oxygen-protonated cyclo-

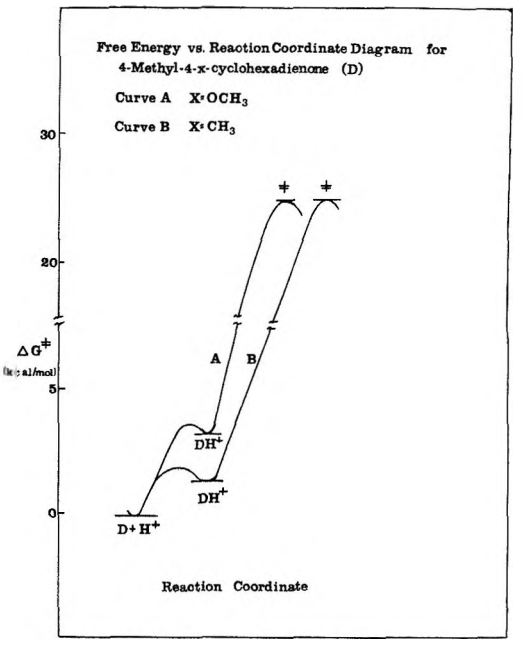


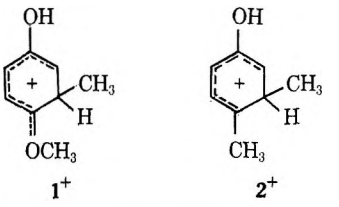
Figure 2.—A free energy *vs.* reaction coordinate profile for the dienone–phenol rearrangement ($H_0 = -2$).

hexadienyl cation intermediates from observed relative rates and an estimate of the fraction protonated for each substrate (eq 11 and 12). Here k_+^X is the specific

$$k_{obsd}^{CH_3O} = k_+^{CH_3O} F_{CH_3O}/a_{H_2O} \quad (11)$$

$$k_{obsd}^{CH_3} = k_+^{CH_3} F_{CH_3}/a_{H_2O} \quad (12)$$

rate of rearrangement of the X-substituted cyclohexadienyl cation and F_X is the fraction of X-substituted dienone protonated at this acidity. We estimate at $H_0 = -2$, $k_+^{CH_3O}/k_+^{CH_3} = 33$. Virtually this entire rate-enhancing effect originates from a destabilization of the intermediate (a factor of 27, 2.0 kcal/mol) by methoxy while only a small stabilization of the transition state is observed (a factor of 1.2, 0.1 kcal/mol). These results are summarized schematically in Figure 2. It is apparent that even though the intermediate cyclohexadienyl cation is destabilized by the electron withdrawing effect of the methoxy substituent this destabilization is not felt in the transition state. This is due to the fact that in the transition state there is some positive charge developed at C-4 and the methoxy substituent can stabilize this partial positive charge by resonance. Now while some positive charge development at C-4 is suggested by our results a very "product-like" transition state (*i.e.*, a transition state with a large fraction of the positive charge at C-4) is considered unlikely because of the



small stabilizing effect observed for the methoxy substituent on the transition state.

From CH_3–CD_3 isotope effects[15] observed in the rearrangement of 4,4-dimethylcyclohexadienone (2) it

(12) In fact, for reasonable variations of m in eq 10 the values of a calculated from the data in Table II are very similar. *E.g.*, for values of m = 0.59–0.63 the average value of a is −3.68 ± 0.09.

(13) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, pp 219–235.

(14) V. P. Vitullo and N. Grossman, *J. Amer. Chem. Soc.*, **94**, 3844 (1972).

(15) V. P. Vitullo and N. Grossman, unpublished results.

appears that the transition state for the rearrangement of this substrate is "product-like," *i.e.*, bearing a close structural resemblance to 2^+. The rearranged cations directly succeeding the transition state for these two substrate should markedly differ in stability with 1^+ being much more stable than 2^+. This should result in a shift in transition state structure[16] for 1^+ toward a more nearly "symmetrical" transition state with an attendant decrease in the amount of positive charge at C-4 in the transition state. This is consistent with the relatively small stabilizing effect of the methoxy group of **1** in the transition state.

Experimental Section

4-Methoxy-4-methylcyclohexadienone (1).—This material was prepared as described by Hecker.[7] The product was produced in 31% yield, purified by preparative glpc (130°, diethylene glycol succinate) and had the following properties: mp 61–61.5° (lit.[7] mp 62–63°); ir (CCl_4) 1675 (>C=O), 1640 (C=C), 1200 cm^{-1} ($COCH_3$); nmr δ 6.15 (d, CH=CHC=O), 6.65 (d, CH=CHC=O), 3.14 (s, OCH_3), 1.38 (s, CH_3).

Rearrangement of 1 in Concentrated Hydrochloric Acid.—A 50-mg portion of **1** was treated with 1 ml of concentrated HCl for 3 days with vigorous stirring. The yellowish solution was extracted with several portions of ether. The ether was dried (Na_2SO_4) and removed on a rotary evaporator. The residue was dissolved in 5 ml of methanol and treated with 106 mg of Na_2CO_3 and 114 mg of CH_3I. After refluxing for 3 days the solution was cooled, filtered, and diluted with ether. The ether solution was washed with water and dried over Na_2SO_4, and the ether removed on a rotary evaporator. The crude product was subjected to glpc analysis (10% diethylene glycol succinate, 140°) and one peak was observed. This peak was collected and its ir spectrum was shown to be virtually identical to that obtained from the methylation of 2-methylhydroquinone (Aldrich Chemical Co).

2,4-Dimethoxytoluene.—2,4-Dimethoxybenzyl mesylate was prepared by allowing 2,4-dimethoxybenzyl alcohol, triethylamine, and methanesulfonyl chloride in benzene to react at room temperature.[17] From 431 mg of 2,4-dimethoxybenzyl alcohol there was obtained 213 mg (35%) of mesylate ester, ir, no OH, 1380 cm^{-1} (sulfonate). The crude mesylate was reduced in refluxing ether for two days with an excess of $LiAlH_4$. A small sample of the reduction product was isolated by preparative glpc (10%, diethylene glycol succinate, 140°). An ir spectrum of this material was substantially different from that of the methylated rearrangement product. In fact, a comparison of ir spectra showed that <5% methoxy migration had occurred in the acid-catalyzed rerrangement of **1**.

Kinetic Procedures.—All rate constants reported in this paper were obtained by monitoring the dissappearance of dienone of 240 nm[7] using either a Beckman DK-1A or Gilford Model 2400 spectrophotometer. The kinetic data were processed by using a nonlinear least-squares program written for the Wang 700 computer. Most of the results reported in Table I are average values based on three or more runs. A concentrated solution of dienone was prepared in ethanol and 2–5 μl of this solution was deposited in the end of a stirring rod. The reaction was initiated by plunging the stirring rod into a cuvette containing acid of the desired strength (previously equilibrated) and monitoring the absorbance as a function of time. Acid concentrations were determined by titrating weighed amounts of acid with previously standardized base.

Basicity of 1 in Perchloric Acid.—To estimate the degree of protonation of **1** we measured the absorbance of solutions of **1** in perchloric acid at 295 nm as a function of time and extrapolated back to the time of mixing either graphically or by using the nonlinear kinetics program. The cyclohexadienyl cations produced by the protonation of 4-dichloromethyl-4-methylcyclohexadienone[1] and 4,4-dimethylcyclohexadienone[2,4] have λ_{max} 295 nm. Neutral **1** has virtually no absorption at this wavelength. These results are presented in Table II.

Registry No.—**1**, 23438-17-7.

Acknowledgment.—We wish to thank the National Science Foundation (Grant No. GP-29738X) for financial support of this work. We also wish to acknowledge several informative discussions with Dr. R. M. Pollack.

(16) G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 334 (1955).

(17) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

Structural Effects on the Acid–Base Properties of Some Closely Related Phosphinic Acids and Phosphine Oxides[1]

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Several isomeric cyclic and acyclic C_8 phosphinic acids and some isomeric cyclic and acyclic C_8 methylphosphine oxides have been synthesized, and their acidity and basicity, respectively, have been determined. The effect of structural branching is acid weakening with the phosphinic acids and base weakening with the phosphine oxides. The presence of a four-membered ring which includes the phosphorus heteroatom tends to be acid strengthening with the phosphinic acids, and it tends to be base weakening with the phosphine oxides. The reasons for these structural effects are discussed.

The acid–base properties of molecules are due to a combination of internal effects and environmental effects,[3] and the relative ability of these effects to stabilize the acids and their conjugate bases or the bases and their conjugate acids. The relative ability of these effects to stabilize the acid or base forms of a molecule are determined only by the structure of the molecule if one uses a constant solvent environment. The structural effects on acid and base properties of some isomeric aliphatic phosphinic acids and phosphine oxides are reported in this study. Since only aliphatic phosphinic acids and phosphine oxides are involved, the important internal effect is an inductive effect, and the important environmental effect is a solvation effect.

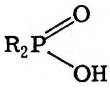
All but one of the phosphinic acids listed in Table I were synthesized by treatment of phosphorus oxychloride or phosphorus trichloride with the appropriate Grignard reagent followed by hydrolysis. The exception was cyclic phosphinic acid (**1**) which was produced by treating 2,4,4-trimethyl-2-pentene with phosphorus trichloride in the presence of aluminum chlo-

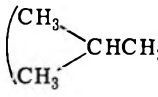
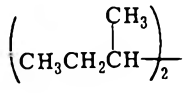
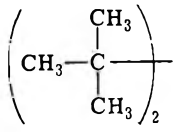
(1) Based on work performed under the auspices of the U. S. Atomic Energy Commission.

(2) Department of Chemistry, Valparaiso University, Valparaiso, Indiana 46383.

(3) E. J. King, "Acid–Base Equilibria," Pergamon Press, Oxford, 1965.

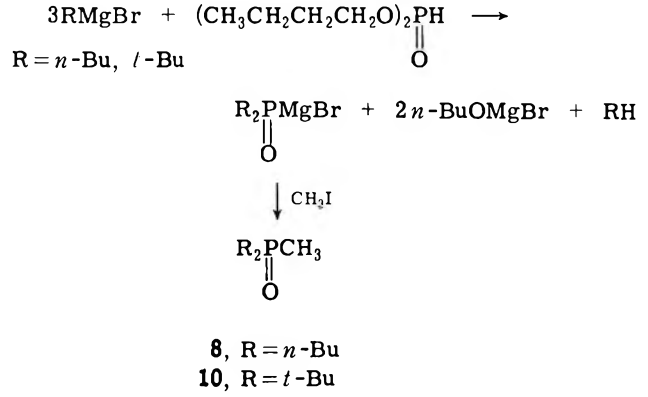
TABLE I
ACIDITIES OF PHOSPHINIC ACIDS IN 75% ETHANOL AND 25% WATER



Compd	R_2	pK_A[a]
1		4.66
2	$(CH_3)_2$	4.72
3	$(CH_3CH_2CH_2CH_2)_2$	5.24
4		5.60
5		5.75
6		6.26

[a] Each value, to be considered followed by ±0.05, was calculated from the average of two or more $pH_{1/2}$ values as read directly from the chart.

ride as described by McBride and coworkers.[4] Cyclic phosphine oxide (**9**) listed in Table II was prepared in a manner similar to phosphinic acid (**1**).[5] Phosphine oxide (**7**) is made by use of the appropriate Grignard reagent with phosphorus oxychloride. Phosphine oxides **8** and **10** were made in 73 and 25% yields, respectively, by use of the appropriate Grignard reagent with di-*n*-butyl phosphite, and the initially formed product is subsequently treated with methyl iodide.



8, R = *n*-Bu
10, R = *t*-Bu

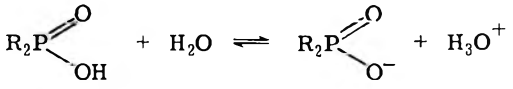
The pK_A values of the series of phosphinic acids given in Table I were determined in 75% ethanol by titration with aqueous sodium hydroxide using a method described previously.[6]

The pK_{BH^+} values of the phosphine oxides listed in Table II were found by nmr chemical shift measurements of methyl protons in sulfuric acid solutions of methyl phosphine oxides.[7-9] Trimethylammonium chloride was used as the internal reference. The H_0 scale was used to determine the effective sulfuric acid concentration.[10,11] The following equation was used in the evaluation of the pK_{BH^+}'s. The slope (m) and

$$\log \frac{\delta_B - \delta_{obsd}}{\delta_{obsd} - \delta_{BH^+}} = \log \frac{[BH^+]}{[B]} = m(pK_{BH^+} - H_0)$$

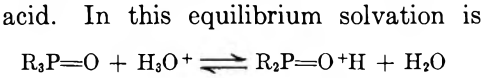
intercept (mpK_{BH^+}) were determined by least-squares analysis.

One of the important factors in the ordering of the pK_A values of the aliphatic phosphinic acids listed in Table I appears to be a solvation effect in a manner similar to that found in aliphatic carboxylic acids.[12a] The equilibrium involved in the exhibition of acid properties by phosphinic acids is an ionogenic one,[3] *i.e.*, one in which the proton transfer is associated with the creation of ions. With this type of equilibrium,



solvation is much more important in the stabilization of the conjugate base anion produced than in the stabilization of the neutral acid.[12b] Therefore any factor that hinders solvation will be acid weakening. The small methyl groups in compound **2** do not effectively interfere with solvation, and the ring structure of compound **1** "pulls back" the methyl groups from the reaction site allowing it to be readily solvated. A strong inductive effect in the form of an electron-withdrawing effect seems to be operative in compound **1** also. This effect stabilizes the anion relative to the free acid even more and makes **1** an even stronger acid than one would predict. The source of this electron withdrawing effect is the strained four-membered ring.[13] The steric hindrance toward solvation increases somewhat with the *n*-butyl, isobutyl, and *sec*-butyl groups of compounds in compounds **3**, **4**, and **5**. The hindrance reaches a maximum with the *tert*-butyl group of compound **6**. The acidity consequently is weakest for this compound as shown by its pK_A.

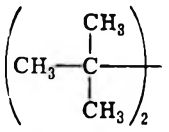
The base properties of phosphine oxides are shown by the equilibrium of the phosphine oxide with its conjugate acid. In this equilibrium solvation is more



important in stabilizing the conjugate acid cation produced than in stabilizing the neutral phosphine oxide. Therefore any factor that hinders solvation will be base weakening for the phosphine oxide. A combination of solvation and inductive effects seems to be the determining factor in the relative basicities of the phosphine oxides listed in Table II. Here it is seen that the trimethylphosphine oxide (**7**) is essentially equal in basicity to di-*n*-butylmethylphosphine

(4) J. J. McBride, Jr., E. Jungermann, J. V. Killheffer, and R. J. Clutter, *J. Org. Chem.*, **27**, 1833 (1962).
(5) S. E. Cremer and R. J. Chorvat, *ibid.*, **32**, 4066 (1967).
(6) D. F. Peppard, G. W. Mason, and C. M. Andrejasich, *J. Inorg. Nucl. Chem.*, **27**, 697 (1965).
(7) P. Haake and G. Hurst, *J. Amer. Chem. Soc.*, **88**, 2544 (1966).
(8) P. Haake, R. D. Cook, and G. Hurst, *ibid.*, **89**, 2650 (1967).
(9) G. C. Levy, J. D. Cargioli, and W. Racela, *ibid.*, **92**, 6238 (1970).
(10) F. A. Long and M. A. Paul, *Chem. Rev.*, **57**, 1 (1957).
(11) M. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963).
(12) (a) G. S. Hammond and D. H. Hogle, *ibid.*, **77**, 338 (1955); (b) G. S. Hammond in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, Chapter 9.
(13) I. J. Miller, *Tetrahedron*, **25**, 1349 (1969).

TABLE II
BASICITIES OF PHOSPHINE OXIDES[a]

Compd	R_2	pK_{BH^+}	Intercept	m	No. of points
7	$(CH_3)_2$	−1.48 ± 0.44	−0.90 ± 0.24	−0.61 ± 0.08	7
8	$(CH_3CH_2CH_2CH_2)_2$	−1.51 ± 0.29	−0.92 ± 0.18	−0.61 ± 0.04	10
9		−2.88 ± 0.17	−1.41 ± 0.07	−0.49 ± 0.01	11
10		−3.41 ± 0.22	−1.63 ± 0.09	−0.48 ± 0.02	10

[a] The slope (m) and intercept (mpK_{BH^+}) were determined by least-squares analysis.

oxide (**8**), but 1,2,2,3,4,4-hexamethylphosphetane 1-oxide (**9**) is a weaker base. The relatively weak basicity of phosphine oxide (**9**) is contrary to what would be expected based on solvation effects. The "tied-back" nature of this cyclic phosphine oxide (**9**) makes it easier to solvate the conjugate acid cation. However, the strained four-membered ring structure in **9** causes a decrease in electron density on the oxygen atom[13] which is the potential protonation site. This decrease in electron density on the oxygen atom of **9** outweighs the improved solvation possibilities for its protonated form resulting in a net decrease in basicity for the phosphine oxide. This decrease in basicity with increasing ring strain has been observed with alicyclic ketones.[14,15] A similar increase in positive charge at phosphorus as ring strain increases has been noted in cyclic phosphates.[16-19] This has been attributed to a lowered occupation of the phosphorus 3d orbitals. The weakest base of the series is di-*tert*-butylmethylphosphine oxide (**10**) whose protonated form is greatly hindered from solvation by the bulky *tert*-butyl groups.

Experimental Section

The instruments used in this work were a modified Precision-Dow Recordomatic titrator and a JEOL C-60HL high resolution nuclear magnetic resonance spectrometer. The elemental analysis was performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Some Phosphine Oxides and Phosphinic Acids.—Trimethylphosphine oxide (**7**) was made by the method of Burg and McKee.[20] 1,2,2,3,4,4-Hexamethylphosphetane 1-oxide (**9**) was synthesized using the procedure of Cremer and Chorvat.[5,21] Dimethylphosphinic acid (**2**) was prepared by the method of Nakamoto, Ferraro, and Mason.[22]

1,1,2,3,3-Pentamethyltrimethylenephosphinic Acid (**1**).—The procedure of McBride and coworkers[4] was followed (on a 1-mole of PCl_3 basis) up to the point at which the water-washed organic phase, containing the acid chloride as the principal product, was separated. One liter of an aqueous solution of 2 *M* NaOH was added (over a period of 30 min) to the stirred organic phase. The aqueous phase was separated, heated at 80° for 1 hr, cooled, and acidified with a slight excess of concentrated hydrochloric acid. A colorless crystalline solid separated from the solution which was isolated by filtration and recrystallized from *n*-heptane, mp 74.5–75°, 85% yield.

Di-*tert*-butylphosphinic Acid (**6**).—This compound was first described as being prepared by the addition of an ether solution of phosphorus trichloride to an ether solution of *tert*-butyl magnesium chloride.[23] We have used a modification of this procedure in which the reagents were added in the reverse order to obtain a much higher yield of product (45%). The purity of the product was such that it could be used in radiometric studies, mp 210°.

Details of the preparation and purification of the compound by this modified procedure are given elsewhere.[24]

Di-*n*-butylphosphinic Acid (**3**).—This compound was prepared in the same manner as di-*tert*-butylphosphinic acid (**6**) except that *tert*-butyl chloride and phosphorus trichloride were replaced by *n*-butyl bromide and phosphorus oxychloride. Consequently the oxidation step was not needed. Also the purification procedure differed markedly from that used for di-*tert*-butylphosphinic acid. The purification was carried out in the following manner. Following completion of the Grignard reaction the ether phase was washed twice with water and extracted with 1 *M* aqueous sodium hydroxide. The aqueous sodium hydroxide extract was heated at 80° for 2 hr, cooled, washed three times with benzene, and acidified with a light excess of concentrated HCl. The aqueous solution was extracted with isobutyl alcohol, and the alcoholic extract was washed with four portions of water. Upon evaporation of the alcohol a colorless crystalline solid product was obtained. It was recrystallized from *n*-heptane (60% yield), mp 68.5–69.5° (lit.[23] mp 68.5–69°).

Diisobutylphosphinic Acid (**4**).—The same procedure as was given above for making di-*n*-butylphosphinic acid (**3**) was fol-

(14) E. M. Arnett, R. P. Quirk, and J. W. Larsen, *J. Amer. Chem. Soc.*, **92**, 3977 (1970).
(15) H. J. Campbell and J. T. Edward, *Can. J. Chem.*, **38**, 2109 (1960).
(16) R. L. Collin, *J. Amer. Chem. Soc.*, **88**, 3281 (1966).
(17) D. B. Boyd, *ibid.*, **91**, 1200 (1969).
(18) G. M. Blackburn, J. S. Cohen, and I. Weatherall, *Tetrahedron*, **27**, 2903 (1971).
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(20) A. B. Burg and W. E. McKee, *J. Amer. Chem. Soc.*, **73**, 4590 (1951).
(21) The methylphosphonous dichloride used in this procedure was kindly provided by the Ethyl Corporation.
(22) K. Nakamoto, J. R. Ferraro, and G. W. Mason, *Appl. Spectrosc.*, **23**, 521 (1969).
(23) P. C. Crofts and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 3379 (1953).
(24) G. W. Mason, S. Lewey, and D. F. Peppard, *J. Inorg. Nucl. Chem.*, in press.

lowed here using isobutyl bromide to give a colorless crystalline product in a 60% yield, mp 46–47° (lit.[25] mp 38–40°).

Di-*sec*-butylphosphinic Acid (5).—The same procedure as was reported above for making di-*n*-butylphosphinic acid (**3**) was followed here for making **5** by using *sec*-butyl chloride to give product in a 60% yield. The final recrystallization step was omitted since the product is a liquid at room temperature. This is the first time a pure sample of this compound has been reported, the only other report being that of a crude sample.[26]

Anal. Calcd for $C_8H_{19}O_2P$: C, 53.92; H, 10.75; P, 17.38. Found: C, 54.10; H, 10.84; P, 17.51.

Di-*n*-butylmethylphosphine Oxide (8).—To a stirred Grignard solution prepared from 411 g (3.0 mol) of *n*-butyl bromide and 73 g (3.0 mol) of magnesium in 1 l. of diethyl ether was added dropwise (over a period of 1 hr) 194 g (1.0 mol) of di-*n*-butyl phosphite. A total of 142 g (1.0 mol) of methyl iodide was added and the mixture heated under reflux for 1.5 hr. The cooled solution was stirred with 500 ml of concentrated HCl and the organic phase (upper layer) was separated. The organic phase was washed successively with two 250-ml portions of water, one 250-ml portion of 1 *M* NaOH, and one 250-ml portion of water. The ether, *n*-butyl alcohol, and water were removed from the organic phase (the latter two under high vacuum since they were quite difficult to remove) to give 128.7 g (73%) of colorless solid product, mp 34–35° (lit.[27] mp 35°).

Di-*tert*-butylmethylphosphine Oxide (10).—The same procedure as was reported above for making di-*n*-butylmethylphosphine oxide (**8**) was used here for making **10** by using *tert*-butyl chloride in place of *n*-butyl bromide. The final product was purified by fractional distillation, and the purified product was obtained in a 25% yield. This is a vastly improved yield over the 2% yield of product reported from the reaction of *tert*-butylmagnesium chloride with methylphosphonic dichloride.[28]

Registry No.—**1**, 35210-25-4; **2**, 3283-12-3; **3**, 866-32-0; **4**, 15924-57-9; **5**, 35210-27-6; **6**, 677-76-9; **7**, 676-96-0; **8**, 14062-37-4; **9**, 16083-94-6; **10**, 18351-81-0.

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(26) P. J. Christen and L. M. van der Linde, *Rec. Trav. Chim. Pays-Bas*, **78**, 543 (1959).

(27) G. M. Kosolapoff and R. F. Struck, *Proc. Chem. Soc., London*, 351 (1960).

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Notes

Birch Reduction of Biphenylene. Formation of 4,5-Benzobicyclo[4.2.0]octa-2,4-diene

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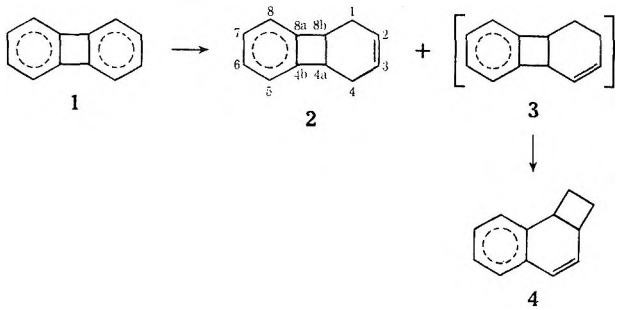
Braun's report[1] of the characterization of the products from the reaction of benzyne and 1,3-cyclohexadiene prompts us to report our findings in the Birch reduction of biphenylene (**1**).



Baker reported[2] that reduction of **1** by sodium in liquid ammonia yielded 30% biphenyl plus unsaturated oil. Atkinson[3] found that the mixture of products obtained by alkali metal reduction in liquid ammonia underwent disproportionation during distillation, reforming a small amount of biphenylene (**1**). Barton[4] found reduction with lithium in ethylamine–diethylamine (1:4 ratio) at 0° to give 85% biphenyl plus small amounts of 1-phenylcyclohexene and a tetrahydrobiphenylene.

Our results differ from those cited. Reduction of **1** using sodium or lithium in liquid ammonia plus anhydrous ether plus ethanol yielded a mixture which glc indicated was composed of unreacted **1**, 1,4,4a,8b-tetrahydrobiphenylene (**2**), and 4,5-benzobicyclo[4.2.0]-octa-2,4-diene (**4**), with the latter two in a ratio of about 4:1. Biphenyl was specifically sought by nmr and glc, but none was found.

Braun[1] isolated **4** from the reaction of benzyne and 1,3-cyclohexadiene and proposed its formation by the rearrangement of 1,2,4a,8b-tetrahydrobiphenylene (**3**), which was the expected minor 1,2 addition product. Thus, our obtaining **4** instead of **3** by a different route supports Braun's proposed rearrangement of **3**. However, neither we nor Braun have isolated **3** or established whether the rearrangement occurs spontaneously or is caused by the glc work-up. It may be significant that two tetrabromo compounds with the same skeletal structure as **3** have been reported[5] and seem stable.

Braun[1] characterized **4**, which exhibits a uv absorption spectrum typical of styrene derivatives rather than benzocyclobutene derivatives.[6] Previously unreported **2** exhibits the uv spectrum (ETOH) typical of a benzocyclobutene derivative and a molecular

(1) A. M. Braun, *J. Org. Chem.*, **35**, 1208 (1970).

(2) W. Baker, M. P. V. Boarland, and J. F. W. McOmie, *J. Chem. Soc.*, 1476 (1954).

(3) E. R. Atkinson and F. E. Granchelli, private communication cited in M. P. Cava and M. J. Mitchell, "Cyclobutadiene and Related Compounds," Academic Press, New York, N. Y., 1967, pp 267 and 283.

(4) J. W. Barton and D. J. Walsh, unpublished work mentioned by Barton in "Nonbenzenoid Aromatics," Vol. I, J. P. Snyder, Ed., Academic Press, New York, N. Y., 1969, pp 56–57.

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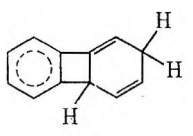
(6) M. P. Cava, R. J. Pohl, and M. J. Mitchell, *J. Amer. Chem. Soc.*, **85**, 2080 (1963).

weight of 156 by mass spectral analysis. Nmr (CCl_4) indicates the following protons: four aromatic, two vinyl, two benzylic methinyl, and four allylic methylene. The benzylic hydrogens (δ 3.65) are further downfield than usual[7] for benzylic hydrogens, which is in agreement with their location on a cyclobutene ring.[7,8] Equivalency of the benzylic hydrogens is indicated, as they have the same chemical shift and do not split one another (a J of 6–10 magnitude[7] would be required). Also absence of mutual splitting and identical chemical shift indicate equivalency of the vinyl hydrogens. The absence of carbon-to-carbon double bond stretching in the 1600–1680-cm^{-1} region of the ir spectrum, as well as the overall simplicity of the ir and nmr spectra, agrees with the symmetrical structure of **2**.

The most likely structures for the dihydro intermediate which must form first and then go on to tetrahydro products **2** and **4** are 2,4a-dihydrobiphenylene (**5**), 4a,8b-dihydrobiphenylene (**6**), and 1,4-dihydrobiphenylene (**7**). **5** is the product predicted[9] by Streitwieser, who used molecular orbital theory based on protonation at sites of highest electron density in the radical anion and anion intermediates. Further reduction of **5** would be expected to form **3**. Isomerization of **5** to 1,8b-dihydrobiphenylene (**8**) by the ethoxide ion present is reasonable and further reduction would lead to **2** and **3**.



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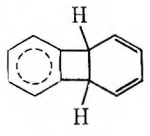

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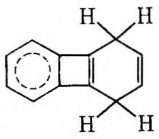

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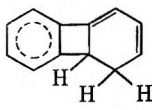

8

Experimental Section[10]

Biphenylene (1) was prepared in 25% yield by the procedure of Friedman,[11] mp 108–110°.

Reduction of Biphenylene (1).—To a stirred, refluxing (−33°) mixture of 500 ml of liquid ammonia, 150 ml of anhydrous ether, and 2.00 g of **1** (0.0132 mol) was added 0.90 g of sodium (0.039 mol). The blue solution was stirred for 15 min and then 15 ml of absolute ethanol was added over a 5-min period. The blue color disappeared and the NH_3 was allowed to evaporate. The residue was mixed with 150 ml of water and extracted with ether. Evaporation of the ether from the dried extracts ($MgSO_4$) yielded 1.70 g of a mixture of solid and liquid. Glc analysis indicated that **1**, **2**, and **4** were present in the ratio of 11:4:1 and that biphenyl was absent. Nmr confirmed the absence of biphenyl. Preparative glc gave enough material for spectral and elemental analysis.

Use of lithium instead of sodium required no ethanol but gave the same results. When the amount of sodium was increased to 4.5 equiv, then no unreacted **1** remained and the amounts of **2** and **4** were increased proportionally.

1,4,4a,8b-Tetrahydrobiphenylene (2): nmr (CCl_4) δ 2.35 ("filled-in" t, J = <3 Hz, 4 H), 3.65 ("filled-in" t, J = <3 Hz, 2 H), 5.60 ("filled-in" t, J = <3 Hz, 2 H), 6.95 (m, 4); ir (neat) 3.3, 3.4, 3.5, 6.9, 13.5 (ortho-disubstituted benzene), and 14.8 μ (*cis*-HC=CH); uv max (ethanol) 214 (ε 5184), 261 (ε 1410), 266.5 (ε 2150), and 273 nm (ε 2570); mol wt 156 (mass spectrum).

Anal. Calcd for $C_{12}H_{12}$: C, 92.25; H, 7.74. Found: C, 92.10; H, 7.71.

The dibromide of **2** was prepared by addition of bromine in CCl_4, mp 87–88°, recrystallized from ethanol.

Anal. Calcd for $C_{12}H_{12}Br_2$: C, 45.60; H, 3.83; Br, 50.57. Found: C, 45.37; H, 3.98; Br, 50.50.

4,5-Benzobicyclo[4.2.0]octa-2,4-diene (4): nmr (CCl_4) same as published spectrum[1] δ 1.8–2.7 (m, 4, two CH_2), 2.9–3.9 (m, 2, methyl CH), 5.75 (double d, 1, J_{AB} = 10 Hz, J = 3 Hz, vinyl CH), 6.30 (d, 1, J_{AB} = 10, vinyl CH), 6.93 (m, 4, aromatic CH); ir (neat) 13.2 μ; uv max (ethanol) 219.5 nm (ε 22,265), 226 (ε 17,877), 248.5 (ε 7801), 271 nm (ε 6825), lit.[1] max 248 nm (ε 8600); mol wt 156 (mass spectrum).

Anal. Calcd for $C_{12}H_{12}$: C, 92.25; H, 7.74. Found: C, 92.15; H, 7.55.

Registry No.—**1**, 259-79-0; **2**, 35031-03-9; **2** dibromide, 35031-04-0; **4**, 21367-71-5.

Acknowledgment.—The authors are indebted to the Research Corp. for a Frederick Gardner Cottrell grant, which purchased some of the equipment used, and to Dr. D. K. Wedegaertner and the University of Rochester, N. Y., for the nmr and mass spectra.

(7) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, pp 136–145.

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(9) (a) A. Streitwieser, Jr., "Molecular Orbital Theory," Wiley, New York, N. Y., 1961, p 429; (b) A. Streitwieser, Jr., and S. Suzuki, *Tetrahedron*, **16**, 153 (1961).

(10) Analyses were by Bernhardt Mikroanalytisches Laboratorium, Elbach uber Engelskirken, West Germany. Ir spectra were obtained on Perkin-Elmer 137B. Nmr spectra were obtained in CCl_4 on Joel JNM-C-60HL with tetramethylsilane as internal standard. Molecular weights were obtained using a Hitachi Perkin-Elmer RNV-6E mass spectrometer. Uv spectra were obtained on a Perkin-Elmer 202. Glc analysis and separations were done using Aerograph Model A-90-P instrument and a 1/4 in. × 10 ft column of 10% Carbowax on 80–100 mesh firebrick treated with HMDS at 190°. The ammonia for the reductions was distilled from its metal cylinder and condensed in the reduction flask, but not dried before use. The sodium was cut free of oxide and hydroxide just before use.

(11) F. M. Logullo, A. H. Seitz, and L. Friedman, *Org. Syn.*, **48**, 12 (1968).

Hydrogenolysis of the Acetal 6,8-Dioxabicyclo[3.2.1]octane by Aluminum Chloride Hydride. Evidence for the Preferred Direction of Ring Cleavage in the Course of α-Bromination of This Acetal

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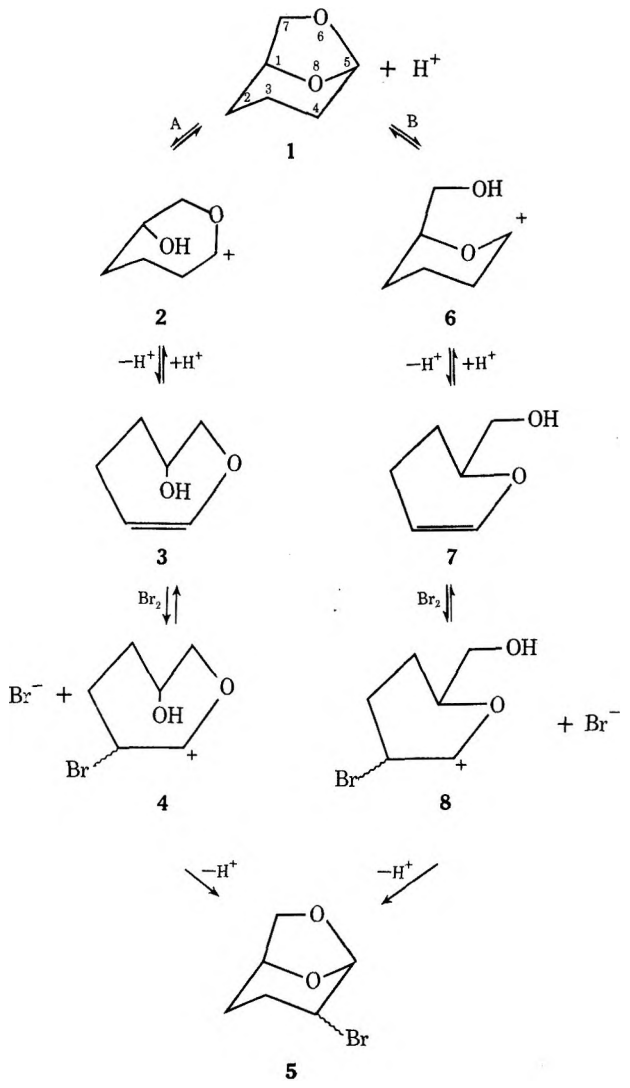
A recent report[2] has suggested that bromination of acetals is acid catalyzed and that the exclusive attack of bromine on the α position of the acetal 6,8-dioxabicyclo[3.2.1]octane (**1**) is the result of initial cleavage of the protonated acetal to give the oxocarbonium ion **2** and/or **6** (path A and/or B of Scheme I) which in turn would lose a proton to form an intermediate α,β-unsaturated ether **3** and/or **7**. Bromine attack on **3** and/or **7** would produce the species **4** and/or **8** which would then suffer intramolecular attack by the hydroxyl group to re-

(1) Author to whom correspondence should be directed.

(2) T. P. Murray, C. S. Williams, and R. K. Brown, *J. Org. Chem.*, **36**, 1311 (1971).

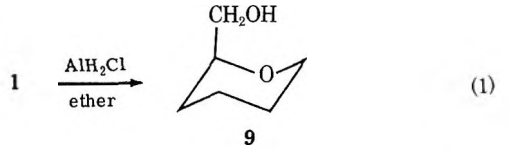
SCHEME I



generate the bicyclic molecule **5** now containing the bromine atom in the α position. Both the exo and endo monobromo isomers are obtained. No firm decision could be made as to which path of reaction (A or B) is preferred or whether both routes are followed, one giving the exo and the other the endo monobromo isomer. However, path B was considered[2] to be the preferred route on the basis of the apparent greater ease of cleavage of the C-5–O-6 bond in the hydrolysis or alcoholysis of substituted bicyclic structures such as **1**.

Work on the hydrogenolysis of acetals and ketals by mixtures of $LiAlH_4$ and $AlCl_3$ in ether[3] has indicated that, as is the case for the hydrolysis of acetals, the rate-controlling step of the hydrogenolysis reaction is the cleavage of the C–O bond, weakened by the association of its oxygen atom with the Lewis acid. However, the subsequent addition of the hydride ion to the resulting oxocarbonium ion is very fast and irreversible. Product analysis then provides clear evidence of the preferred route of bond cleavage.

We have subjected **1** to hydrogenolysis by AlH_2Cl, prepared from the appropriate quantities of $LiAlH_4$ and $AlCl_3$,[4] and found that 2-hydroxymethyltetrahydropyran (**9**, eq 1) was produced in excellent yield.



No other product could be detected by gas–liquid chromatography (glc) of the reaction mixture. Since the model of **1** shows that both oxygen atoms are readily accessible to the Lewis acid (AlH_2Cl), this reaction provides evidence to support our view that acid-catalyzed bromination of **1** occurs by path B.

Experimental Section

To a stirred solution of lithium aluminum hydride (0.427 g, 0.01125 mol) in 10 ml of dry ether kept at 5° by an ice bath, was added dropwise 10 ml of ether solution of aluminum chloride (1.49 g, 0.01125 mol). After the addition, the solution was stirred at room temperature for 15 min. To this stirred mixture was then slowly added a solution of 1.71 g (0.015 mol) of 6,8-dioxabicyclo[3.2.1]octane (**1**) in 10 ml of dry ether. The mixture was then stirred at room temperature for 2 hr whereupon a 15% aqueous solution of potassium hydroxide was slowly added until no further reaction occurred. The solids were removed by filtration and washed with ether. The combined ether solutions were dried (Na_2SO_4) and freed from solvent. The residue was analyzed by glc with a column of 20% butanediol succinate on Chromosorb W 60–80 mesh. The compound 2-hydroxymethyltetrahydropyran was obtained in 93% yield as the only detectable product.

Registry No.—**1**, 280-16-0.

Acknowledgment. We thank the National Research Council of Canada for financial assistance in this work.

(3) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **42**, 990 (1964); **43**, 1030 (1965).

(4) U. E. Diner, H. A. Davis, and R. K. Brown, *ibid.*, **45**, 207 (1967).

Alumina-Catalyzed Dehydration of Substituted Cyclohexanones. Comments on the Mechanism of Hydrocarbon Formation

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Received October 26, 1970

Over the past several years, our investigations of alumina-catalyzed dienol dehydration[1,2] have led us to investigate the formation and subsequent reactions of various 1,3-cyclohexadienes.[3] Several workers[4,5] have alluded to the possibility of the intermediacy of 1,3-cyclohexadiene in the alumina-catalyzed dehydration of cyclohexanone, even though it is found only as a minor product. Most of the reported product analyses, however, were incomplete, due mainly to difficulties in the separation of complex hydrocarbon mix-

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(2) C. Spangler, *ibid.*, **31**, 346 (1966).
(3) C. Spangler and R. Hennis, *ibid.*, **36**, 917 (1971).
(4) H. Adkins and S. Watkins, *J. Amer. Chem. Soc.*, **73**, 2184 (1951).
(5) G. Woods, *U. S. Dept. Com., Office Tech. Serv. AD 278,110*, 29 (1962).

TABLE I

Ketone, catalyst[a] (temp, °C, column length, cm)	% conversion[b]	% of total hydrocarbon[c] product						
								
2, A (400, 26)	45.5	0.0	27.5	34.4	2.3	8.8	7.5	11.9
2, A (300, 26)	20.2	0.0	32.0	67.3	Trace	0.6	0.1	0.0
2, A (300, 18)	1.5	0.0	28.8	66.7	Trace	1.7	Trace	2.8
2, A (400, 18)	26.4	0.0	37.2	57.6	1.3	3.0	0.6	0.3
2, B (300, 18)	8.9	0.0	28.0	72.0	0.0	0.0	0.0	0.0
2, B (400, 18)	38.6	Trace	36.3	53.1	0.2	3.8	4.6	0.1
2, C (300, 18)	13.5	0.0	30.0	69.9	0.0	0.0	0.0	0.0
2, C (400, 18)	36.6	0.0	33.6	57.3	2.2	3.5	0.2	2.6
3, A (300, 26)	40.0	98.7	0.0	0.0	0.4	0.0	0.0	0.9
3, A (400, 26)	60.3	81.0	0.0	0.0	2.1	5.0	4.6	6.0
3, A (300, 18)	36.0	99.8	0.0	0.0	0.2	0.0	0.0	0.0
3, A (400, 18)	58.3	95.0	0.0	0.0	2.6	0.5	0.9	1.0
3, B (300, 18)	12.4	99.9	0.0	0.0	0.1	0.0	0.0	0.0
3, B (400, 18)	42.0	91.5	Trace	2.7	1.1	1.8	0.1	1.9
3, C (300, 18)	25.5	99.9	0.0	0.0	0.1	0.0	0.0	0.0
3, C (400, 18)	37.0	80.0	Trace	16.3	0.2	0.4	0.6	2.0
								
1, A (300, 26)	51.6	98.6	1.3	0.1				
1, A (400, 26)	78.2	90.0	8.2	1.8				
1, A (300, 18)	19.0	99.2	0.8	0.0				
1, A (400, 18)	42.2	96.0	2.8	0.6				
1, B (300, 18)	21.2	98.7	1.3	0.0				
1, B (400, 18)	55.4	95.4	4.1	0.5				
1, C (300, 18)	9.8	99.7	0.3	0.0				
1, C (400, 18)	49.0	97.0	2.8	0.2				

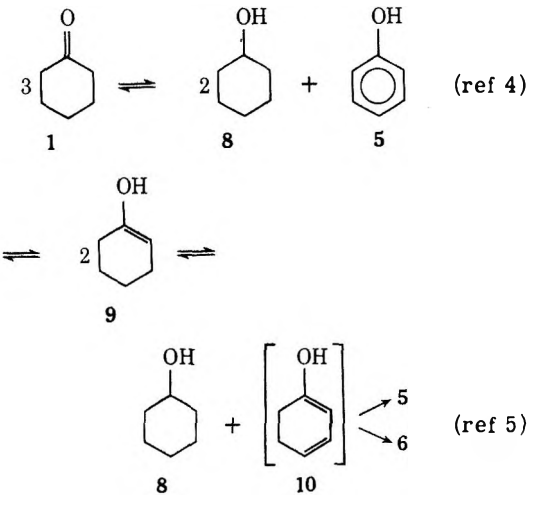
[a] Catalyst A is KA 101 (Kaiser Chemicals); B is AL-0104 (Harshaw Chemical Co.); C is Houdry HA-100S (Houdry Process and Chemical Co.). [b] Expressed as percentage of original ketone converted to dehydration products, including phenolic material. [c] Methylenecyclohexene and unconjugated dienes make up the balance to equal 100% of total hydrocarbon content.

tures into their respective components. Our recent experience with such complex mixtures of this type prompted us to reinvestigate the dehydration of cyclohexanone and to extend our studies to include the methylcyclohexanones.

In the present study, cyclohexanone (**1**) was dehydrated over alumina at 300 and 400°. Three different alumina catalysts were utilized to determine the presence or absence of specific catalytic effect on our product distributions. Conversions of the cyclohexanone to products varied from 10 to 78%, enabling us to determine if product distributions varied significantly with percentage conversion. Glpc analysis of the lower temperature dehydration products showed them to be quite similar to those reported previously;[4,5] however, dehydration at 400° produced much greater amounts of 1,3-cyclohexadiene than had been indicated earlier. Similarly, 2-methylcyclohexanone (**2**) and 4-methylcyclohexanone (**3**) were also dehydrated as described for **1**. Product distributions (Table I) of both of these at 400° also revealed much greater concentrations of dienes than one would expect from the simple disproportionation mechanisms proposed earlier.[4,5]

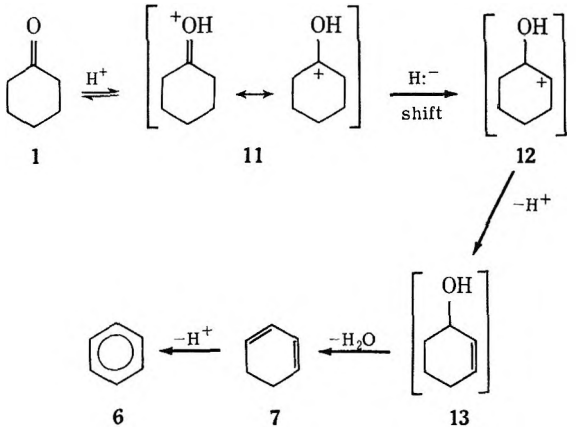
In Table I we have indicated only the product distribution for the hydrocarbon fraction. In all cases phenolic and, to a lesser extent, polymeric materials were also formed. As we did not intend to discuss this aspect of the mechanism, no effort was made to quantitatively determine the phenolic fraction of the total crude product. Thus dehydration of **1**, **2**, or **3** yields a mixture of hydrocarbons (see Table I), a phenol, traces of the corresponding cyclohexanol, and residual ketone, as reported previously.[4,5] Table I emphasizes the make-up of the hydrocarbon fraction *only*.

Adkins and Watkins[4] initially reported that alumina dehydration of cyclohexanone (**1**) yielded a mixture of cyclohexene (**4**), phenol (**5**), and unchanged **1**. Woods,[5] in a more detailed study, also confirmed the presence of both benzene (**6**) and 1,3-cyclohexadiene (**7**) in the product mixture, but was unable to obtain

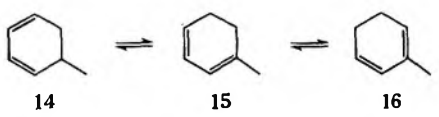


accurate quantitative product distributions. In both studies, however, the major products were cyclohexene and phenol. These results prompted the above workers to postulate disproportionation schemes for these reactions prior to catalytic dehydration. Thus, dehydration of **8** would yield **4**, the normal dehydration product, while either dehydration or dehydrogenation of **10** would yield **6** or **5**, respectively. Both the dehydration and dehydrogenation steps are well-known reactions over alumina at elevated temperature. Presumably, any 1,3-cyclohexadiene in the product would be formed by direct dehydration of **1**, probably *via* the enol **9**. Our results indicate that the Adkins–Watkins mechanism is probably the first step in the reaction, as only this pathway can account for the total quantity of hydrocarbons observed (theoretical limit is 67 mol% for 100% dehydration).

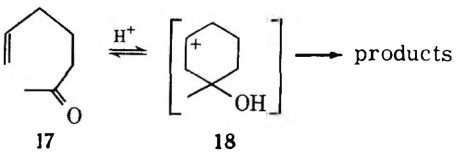
These observations raise the question of whether cyclohexanols are the precursors of all nonaromatic products, or if some pathway other than cyclohexanone disproportionation is operative. Corkern and Fry[6] have recently reported the partial dehydration of both **1** and **2** over polyphosphoric acid at elevated temperature, obtaining benzene and toluene, respectively, although in low yield (3 and 5%). They postulate that dehydration occurs through rearrangement of an α-hydrogen or α-alkyl group to the conjugate acid of the carbonyl, followed by dehydration and dehydrogenation. This mechanism can easily be adapted to the production of a conjugated cyclic diene, proceeding *via* a 2-cyclohexen-1-ol.



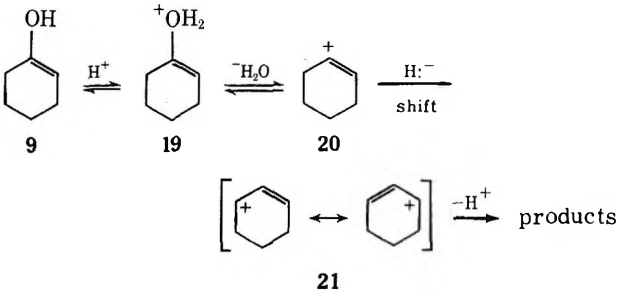
Similarly, **2** and **3** would yield 2-methyl-1,3-cyclohexadiene and 5-methyl-1,3-cyclohexadiene, respectively, as well as toluene. Under the conditions of methylcyclohexanone dehydration (300–400°), however, either of these dienes would rapidly isomerize either by thermal [1,5] sigmatropic migration of hydrogen or by acid-catalyzed routes,[7] by which methylenecyclohexene and the 1,4-dienes may also be obtained. The data in Table I clearly show that the dienes are more extensively isomerized at 400 than at 300°. This is in agreement with our previous work regarding thermal and acid-catalyzed isomerization of methyl-1,3-cyclohexadiene mixtures in this temperature range.[3]



Similar intermediates have been postulated by Descotes, *et al.*,[8] in the cyclodehydration of δ,ϵ-unsaturated ketones over both alumina and polyphosphoric acid, yielding product mixtures composed of aromatics, 1,3-cyclohexadienes, monoolefins, and some 1,4-cyclohexadienes.



An alternate pathway to the cyclic dienes might also occur through the enol (however, we feel that **20** would only form with great difficulty in the vapor phase) and is not as likely as a reaction proceeding through intermediates such as **12** or similar intermediates.



In order to eliminate the possibility that dienes were being formed by direct dehydrogenation of the monoolefins, 4-methyl-1-cyclohexene (**22**) was passed over all three of the catalysts employed in this study at 400°. No dienes or aromatic products were obtained, although between 2 and 5% of the olefin was isomerized to 1-methyl-1-cyclohexene. We conclude from our experiments that diene formation is a process totally unrelated to the disproportionation–dehydrogenation sequence yielding the monoolefins and phenolic products and, in fact, is much more important than any previous workers had indicated, especially under conditions of high conversion. It is probable that dienes result from an acid-catalyzed dehydration route similar to that proposed by Corkern and Fry,[6] followed by isomerization *via* consecutive sigmatropic hydrogen shifts and/or acid-catalyzed isomerization.[3]

Experimental Section[9]

Nature of Catalysts.—The three catalysts employed in this study have different characteristics. Catalyst A (Kaiser Chemi-

(6) W. Corkern and A. Fry, *J. Amer. Chem. Soc.*, **89**, 5888 (1967).

(7) R. Bates, E. Caldwell, and H. Klein, *J. Org. Chem.*, **34**, 2615 (1969).

(8) G. Descotes, M. Fournier, and R. Mugnier, *Bull. Soc. Chim. Fr.*, 382 (1968).

(9) Gas–liquid partition chromatography was performed with an Aerograph Model 202-1B dual-column instrument equipped with a Hewlett-Packard Model 3370A electronic integrator for peak area measurement; dual 15–15% TCEP on 60–80 mesh Chromosorb W columns were utilized for the analysis of the hydrocarbon fraction; dual 6 ft–15% Carbowax 20M on 60–80 mesh Chromosorb W columns were utilized for total analysis of the product mixtures. Ultraviolet spectra were obtained with a Perkin-Elmer Model 202; nmr spectra were obtained with a Varian A60-A using TMS as an internal standard ($CDCl_3$ solvent). All compounds were identified by both uv and nmr spectra and glpc retention times, and comparison to authentic samples.

cals, KA-101)[10] is a quasiamorphous alumina, as determined by X-ray diffraction,[11] which can be referred to as χ-ρ alumina. The X-ray pattern is diffuse and intermediate between amorphous ρ and the more crystalline χ, but distinct from each.[11] A minor phase (*ca.* 20–30%) which coexists with the above dominant phase resembles γ-alumina but is more diffuse. The catalyst is supplied as pellets, 8–14 mesh, with a surface area of 360 m^2/g. Sodium content is 0.40%, expressed as Na_2O.

Catalyst C (Houdry HA-100S)[12] is a γ-alumina catalyst which has been described as essentially nonacidic,[13] while catalyst B (Harshaw AL-0104)[14] is also a γ-alumina, classed as weakly acidic. Both B and C have been utilized as dehydration catalysts in a large number of published examples by several different workers.[13] C has a sodium content of 0.1–0.2%, while B has a content of 0.4% expressed as Na_2O.

Catalysts were prepared by heating at the dehydration temperature for a period of 1 hr under reduced pressure (20–25 mm). After this period they were used directly as described below.

Dehydration of Cyclohexanone (1).—Cyclohexanone[15] (20 g, 0.21 mol) was added dropwise at a rate of 0.25 ml/min through a 22-mm Pyrex tube packed to a depth of either 18 or 26 cm with alumina and externally heated with a Lindberg Hevi-Duty split-tube furnace. A pressure of 20–25 mm was maintained in the system to facilitate rapid removal of the product from the column. The product was trapped in a flask immersed in a Dry Ice–acetone bath, and subsequently warmed to room temperature, washed with water, filtered through anhydrous magnesium sulfate, and analyzed immediately by glpc (12.8 g, 72%).[16] No attempt was made to maximize this yield, although we recognize that this method discriminates against isolating phenolic-type products. High-boiling materials were also condensed on the inside of the exit tube from the dehydration chamber. This was shown to consist mainly of phenolic material and higher-boiling residues. Since our main interest was in the hydrocarbon fraction, we made no further effort at a complete material balance for all products.

The dehydration products were identified by collecting each peak emanating from the chromatograph in glass V tubes immersed in cooling baths: (1) in isooctane for uv analysis, and (2) in $CDCl_3$ for nmr analysis. In each case, the product was identified by comparison of the uv, nmr, and glpc retention times to those of authentic samples in our laboratories.

Dehydration of 4-Methylcyclohexanone (3).—Methylcyclohexanone[17] (20 g, 0.18 mol) was dehydrated at 400° as described above for cyclohexanone, yielding 14.9 g (87%)[18] of the product, which was analyzed immediately by glpc.

Dehydration of 2-Methylcyclohexanone (2).—2-Methylcyclohexanone[19] (15 g, 0.13 mol) was dehydrated at 400° as described above, yielding 9.3 g (73%)[20] of product, which was immediately analyzed by glpc.

Thermolysis of 4-Methyl-1-cyclohexene (22).—4-Methyl-1-cyclohexene (10 g) was thermolyzed by passage through an 18-cm column packed with either A, B, or C, at 400°. Immediate glpc of the recovered product (>95% in all three cases) revealed that the only new product was 1-methyl-1-cyclohexene (2–5%).

Registry No.—1, 108-94-1; 2, 583-60-8; 3, 589-92-4; alumina, 1344-28-1.

(10) Kaiser Chemicals, Division of Kaiser Aluminum and Chemical Corp.

(11) Private communication, Dr. Robert B. Emerson, Staff Research Associate, Chemical Aluminas, Kaiser Chemicals, Baton Rouge, La.

(12) Houdry Process and Chemical Co.

(13) See, for example, L. Klemm, J. Shabtai, and D. Taylor, *J. Org. Chem.*, **33**, 1480 (1968), and references therein.

(14) The Harshaw Chemical Co., Division of Kewanee Oil Co.

(15) J. T. Baker Chemical Co.

(16) For catalyst A (26-cm column) the following total product analysis was obtained: recovered **1**, 21.8%; total dehydration products, 78.2%. The hydrocarbon analysis is shown in Table I, recalculated on the basis of 100% total hydrocarbon content.

(17) Chemical Samples Co.

(18) For catalyst A (26-cm column) the following total product analysis was obtained: recovered **3**, 39.7%; total dehydration products, 60.3%. The hydrocarbon analysis is shown in Table I, recalculated on the basis of 100% total hydrocarbon present.

(19) Aldrich Chemical Co.

(20) For catalyst A (26-cm column) the following total product analysis was obtained: recovered **2**, 54.5%; total dehydration products; 45.5%. The hydrocarbon analysis is shown in Table I, recalculated on the basis of 100% total hydrocarbon present.

Mechanism of Redox Decomposition of Oxymercurated *cis*-2-Butene in Aqueous Solution

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Received October 1, 1971

Olefins are oxidized by mercuric ion in aqueous acid to yield unsaturated aldehydes,[1-4] saturated aldehydes,[2,3] allylic alcohols,[4] or saturated ketones.[5] Saturated ketones are obtained under milder conditions than unsaturated aldehydes or allylic alcohols. For example, acetone is obtained from propene at about 50° and methyl ethyl ketone from *trans*- or *cis*-2-butene below room temperature,[6] whereas acrolein and crotonaldehyde are formed at about 80°[1] and allyl alcohol at 90°.[4] These reactions proceed as the redox decomposition of hydroxymercurated olefins,[7] and their reaction rates are first order with respect to the mercurials,[1,8] without depending on free mercuric ion in the case of ketone formation.[8]

Since hydroxymercurated *cis*-2-butene is sufficiently stable at low temperatures, the reaction process can be pursued by nmr spectroscopy *in situ* after the temperature of the solution is raised abruptly. Time-sequential spectra following the redox decomposition of hydroxy- and deuteroxymercurated *cis*-2-butene are shown in Figure 1.[9]

It is obvious in Figure 1 that methyl ethyl ketone is the sole product and, interestingly, no deuterium is incorporated into the product from the solvent D_2O. Therefore, reaction equations are presented as follows, where the mechanism of two electron transfer, *i.e.*, no association of free mercuric ion, is postulated on the basis of the reaction kinetics.[8]

$$CH_3CH(OH)CHCH_3Hg^+ \xrightarrow[H_2O]{} CH_3COCH_2CH_3 + H^+ + Hg(0) \quad (1)$$

$$CH_3CH(OD)CHCH_3Hg^+ \xrightarrow[D_2O]{} CH_3COCH_2CH_3 + D^+ + Hg(0) \quad (2)$$

The reaction product from the D_2O solution was analyzed by mass spectroscopy and the following deuterium distribution was obtained: $d_0 = 97.3\%$, $d_1 = 2.4\%$, $d_2 = 0.3\%$, $d_3 = d_4 = \cdots = d_8 = 0.0\%$. Thus the result shown in eq 2 was confirmed unequivocally. A concerted mechanism is, therefore, suggested, whereby an intramolecular hydrogen shift occurs and

(1) B. C. Fielding and J. Roberts, *J. Chem. Soc. A*, 1627 (1966).

(2) J. C. Strini and J. Metzger, *Bull. Soc. Chim. Fr.*, 3145, 3150 (1966).

(3) B. Charavel and J. Metzger, *ibid.*, 4865 (1968).

(4) H. B. Tinker, *J. Organometal. Chem.*, **32**, C25 (1971).

(5) Y. Saito and M. Matsuo, *ibid.*, **10**, 527 (1967).

(6) Y. Saito, 1st Japan–U. S. S. R. Seminar on Catalysis, Novosibirsk, July 1971.

(7) W. Kitching, *Organometal. Chem. Rev.*, **3**, 61 (1968).

(8) M. Matsuo and Y. Saito, *Bull. Chem. Soc. Jap.*, **44**, 2889 (1971).

(9) Chemical shifts of α, β, γ, and β' protons of both hydroxy- and deuteroxymercurated *cis*-2-butenes were δ 3.01, 3.86, 1.19, and 1.38, respectively, and their coupling constants for the sets of $\alpha\beta$, $\beta\gamma$, and $\alpha\beta'$ protons were 4.0, 6.0, and 7.6 Hz, respectively, where designation of α, β, β', etc., was made from the mercurated carbons.

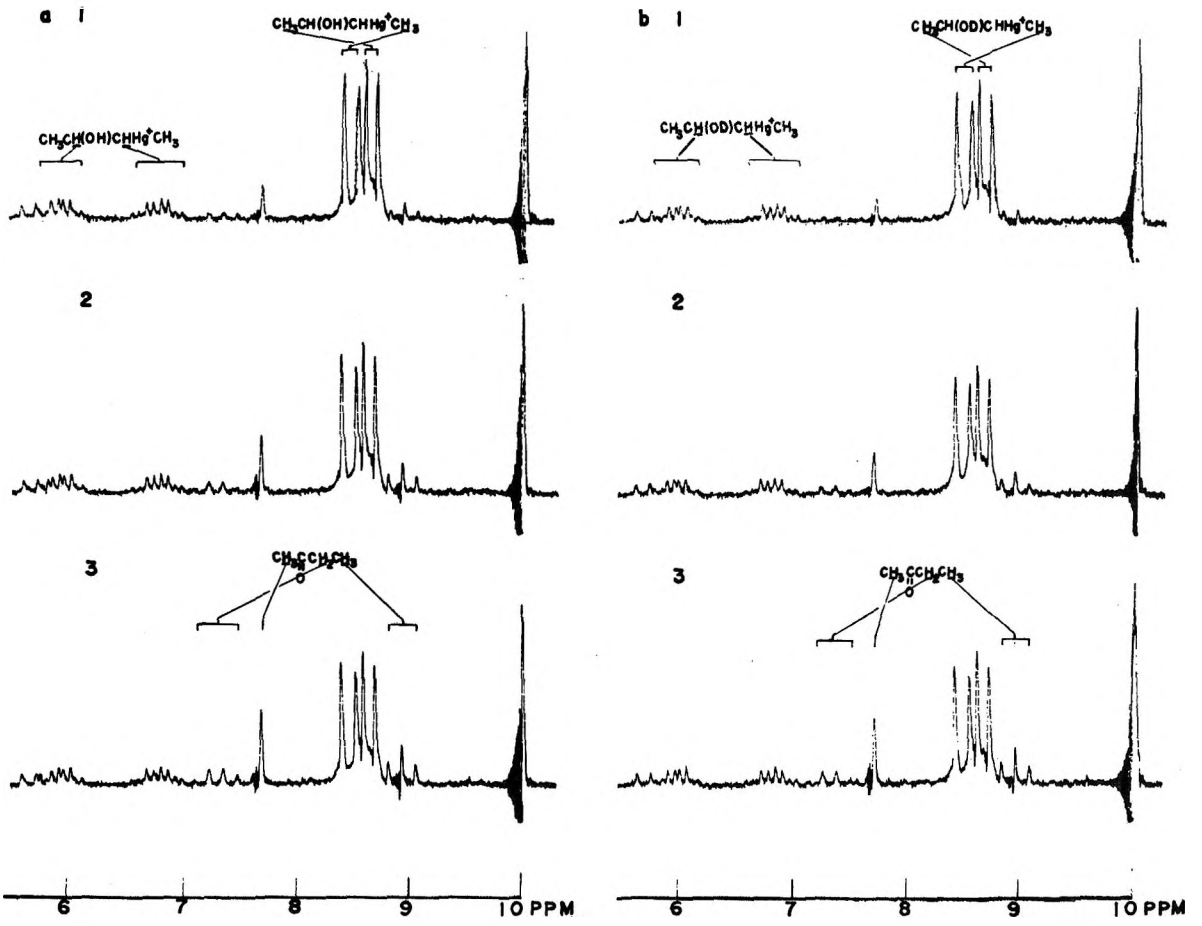

Figure 1. The time-sequential nmr spectra obtained *in situ* for the redox decomposition of oxymercurated *cis*-2-butene in H_2O solution (a) and D_2O solution (b). These spectra were taken after (a) (1) 20.0 min, (2) 38.0 min, (3) 57.5 min, and (b) (1) 5.5 min, (2) 28.0 min, (3) 55.0 min from the moment of raising the solution temperature.

two electrons are transferred along the carbon–mercury bond simultaneously.

As is well known, undeuterated acetaldehyde is obtained by palladium(II) oxidation of ethylene in D_2O solution.[10] Redox decomposition of the 2-hydroxyethylpalladium(II) σ complex to acetaldehyde is sufficiently fast that no deuterium isotope effect is observed for deuterated ethylene.[11] The rate-determining step in this reaction is ascribed to the σ-complex formation from an olefin–palladium(II) π complex.[12] This is in sharp contrast to the mercury(II) case, since hydroxymercuration of olefin is much more rapid[13] than the redox decomposition.[6] A resemblance can be seen, therefore, between mercury(II) and palladium(II) oxidation of olefins to ketones not only because of the common reaction mechanism of intramolecular hydrogen shift during the redox decomposition process but also because of the reaction scheme olefin → π complex → σ complex → saturated ketone.

The reaction rates of the redox decomposition were obtained as first order with respect to the mercurials, as reported previously,[5,6,8] with the rate constants determined as 2.8×10^{-5} and 2.7×10^{-5} sec^{-1} for the H_2O and D_2O solutions, respectively.

Large solvent isotope effects were reported for the reaction of deoxymercuration affording the original olefins. For example, the value of $k(D_2O)/k(H_2O)$ for the dehydroxymercuration of 2-hydroxypropylmercuric iodide was 2.16.[14] Similar results were obtained for deoxymercuration affording ethylene,[15] propylene,[14] and cyclohexene;[16] they are $k(D_2O)/k(H_2O)$ = 3.32, 2.80, and 3.2, respectively. These large inverse solvent isotope effects can be explained by assuming fast prototropic preequilibrium during deoxymercuration.[7] Since the magnitude of the solvent isotope effect for the present reaction is negligibly small, no acidic assistance during the redox decomposition of hydroxymercurated *cis*-2-butene could be concluded.

Experimental Section

Materials.—All the reagents were of GR grade, prepared by Tokyo Kasei Kogyo Co. Ltd. (Tokyo), and were used without further purification. Absence of impurities was confirmed by gas chromatography using a β,β'-dioxypropionitrile column for *cis*-2-butene prepared by Takachiho Kagaku Kogyo Co. Ltd. (Tokyo).

Procedure.—Mercuric solutions were prepared by dissolving mercuric nitrate in concentrated nitric acid and diluting with ion-exchange water to a given concentration. The concentration of mercuric ion was determined by titration with potassium thiocyanate. *cis*-2-Butene was introduced from the cylinder into the solution maintained at 0°. In order to prepare $CH_3CH(OH)CHCH_3Hg^+$, a solution consisting of 0.25 g (4.00 mmol) of HNO_3, 1.32 g (4.00 mmol) of $Hg(NO_3)_2$, and 1.80 g (100 mmol) of H_2O was used, while a solution consisting of 0.25 g (4.00 mmol)

(10) J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, and A. Sabel, *Angew. Chem., Int. Ed. Engl.*, **1**, 80 (1962).
(11) P. M. Henry, *J. Amer. Chem. Soc.*, **86**, 3246 (1964).
(12) P. M. Henry, *Advan. Chem. Ser.*, **No. 52**, 126 (1968).
(13) J. Halpern and H. B. Tinker, *J. Amer. Chem. Soc.*, **89**, 6427 (1967).
(14) M. M. Kreevoy, *ibid.*, **81**, 1099 (1959).
(15) M. M. Kreevoy and L. T. Ditsch, *J. Org. Chem.*, **25**, 134 (1960).
(16) M. M. Kreevoy and F. R. Kowitt, *J. Amer. Chem. Soc.*, **82**, 739 (1960).

of DNO_3, 1.32 g (4.00 mmol) of $Hg(NO_3)_2$, and 2.00 g (100 mmol) of D_2O was used to prepare $CH_3CH(OD)CHCH_3Hg^+$.

A part of the solution maintained at 0° was quickly transferred to an nmr sample tube and put in the probe of the spectrometer kept at 4.3°, with the temperature regulated by blowing cooled nitrogen gas and nmr calibrated by the relative chemical shifts of 1,3-propanediol. The redox decomposition reaction was pursued by taking spectra in sequence with a JEOL C-60 nmr spectrometer. The concentrations of oxymercurated *cis*-2-butene and methyl ethyl ketone were determined from the peak intensities by comparing them with that of the external tetramethylsilane reference. A Hitachi RMU-S mass spectrometer was used for analysis of methyl ethyl ketone produced in D_2O solution, which was separated from the solution by vacuum distillation at 0°.

Registry No.—$CH_3CH(OH)CHCH_3Hg^+$, 35184-47-5; $CH_3CH(OD)CHCH_3Hg^+$, 35184-48-6.

Acknowledgment. The authors are grateful to Professor Y. Yoneda for his encouragement and helpful discussion.

A Mild and Effective Two-Step Conversion of Disubstituted Cyanamides to Secondary Amines

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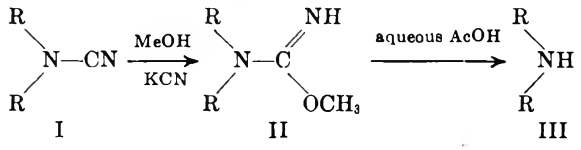
Received February 7, 1972

One limitation in the synthesis of secondary amines by the cyanamide method arises from the frequent difficulty of cleaving the N-CN bond.

In a previous paper,[1] we have reported on a KCN-promoted addition of methanol to disubstituted cyanamides to give isourea-type compounds (II), which could be hydrolyzed easily to secondary amines by refluxing in aqueous acetic acid.



In this manner, we were able to prepare some secondary terpenylamines not available by the usual decyanation procedures.[1,2]

This note reports further results (Table I) and experimental details from the application of this method to the synthesis of various secondary amines (including cyclic amines III-10, III-11), as well as an elucidation of the mechanism involved in the formation of the intermediate *O*-methylisoureas (II).

Satisfactory yields of disubstituted cyanamides are obtained from halides and cyanamide using sodium methylsulfinylmethide in dimethyl sulfoxide as deprotonating agent. Besides the mildness of the reaction conditions, one important advantage of this procedure over the conventional method[3] is the avoidance of isomeric products arising from allylic rearrangements or from cyclopropylcarbinyl interconversion reactions. The intermediate *O*-methylisoureas (II) are obtained by heating the corresponding cyanamides with potassium cyanide in methanol. In practice, these intermediates can be isolated, purified, and then hydrolyzed in the subsequent step, or hydrolyzed directly as crude products. The second step is carried out by refluxing the intermediates II in aqueous acetic acid. Under these conditions, the *O*-methylisoureas undergo a facile hydrolysis to secondary amines.

The formation of isoureas (II) may be regarded as a base-catalyzed addition of methanol to the cyano group, the role played by potassium cyanide being to provide a low, but sufficient, concentration of MeO^- ions.

$$CN^- + MeOH \rightleftharpoons MeO^- + HCN$$

$$R_2NCN + MeO^- \longrightarrow R_2NC(OMe)=N^- \xrightarrow{MeOH} R_2NC(OMe)=NH + MeO^-$$

This mechanism is supported both by the successful replacement of equimolar potassium cyanide with catalytic amounts of sodium methoxide and by the analogy with the mechanism observed for the base-catalyzed conversion of nitriles to methyl imidates.[4]

The absence of strong acids or bases in the two steps makes this modification of the cyanamide method suitable to be used with sensitive substrates. Furthermore, the fact that disubstituted cyanamides are also key intermediates in the von Braun degradation suggests potential applications.[5]

Experimental Section

Boiling points are uncorrected. Melting points are uncorrected and were taken on a Büchi capillary melting point apparatus. Ir spectra were run on a Perkin-Elmer 337 spectrophotometer, nmr spectra on a Varian A-60A spectrometer (Me_4Si) (0.00 ppm).

Materials.—All the halides used for the synthesis of disubstituted cyanamides were bromides, except for 3,4,5-trimethoxybenzyl chloride and 3,4-methylenedioxybenzyl chloride. They were synthesized by known procedures. Dimethyl sulfoxide was dried by distillation from calcium hydride.

General Methods. Disubstituted Cyanamides (I).—Cyanamide (0.1 mol) was added portionwise to a stirred suspension of sodium methylsulfinylmethide[6] prepared *in situ* from 0.22 mol of a 80% dispersion of sodium hydride in mineral oil and 150 ml of dry dimethyl sulfoxide. The mixture was stirred at room temperature for 30 min and then 0.22 mol of the appropriate halide (0.11 mol for I-10 and I-11) was added slowly. Generally, the reaction temperature rose to 50–60° while a white precipitate formed. After an additional 1-hr stirring at room temperature, the mixture was poured into ice–water and extracted with ether. The ether extract was washed with water, dried over $MgSO_4$, and concentrated, and the residue was distilled or crystallized from a suitable solvent.

N,N-Disubstituted *O*-Methylisoureas (II).—A mixture of 0.1 mol of the appropriate I, 0.1 mol of potassium cyanide, and 200

(1) A. Donetti, A. Omodei-Salè, and A. Mantegani, *Tetrahedron Lett.*, 3327 (1969); for decyanation procedures, see references therein.

(2) V. Prelog, B. C. McKusick, J. R. Merchant, S. Julia, and M. Wilhelm, *Helv. Chim. Acta*, **39**, 498 (1956); V. Cerny, L. Dolejs, and F. Sorm, *Collect. Czech. Chem. Commun.*, **29**, 1591 (1964); H. Rapoport, C. H. Lovell, H. R. Reist, and M. E. Warren, *J. Amer. Chem. Soc.*, **89**, 1942 (1967).

(3) E. B. Vliet, "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1946, p 203.

(4) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

(5) Following the conditions we had previously reported,[1] Professor J. Pecher (Faculté des Sciences, Université Libre de Bruxelles) succeeded in carrying out the decyanation step during a von Braun degradation on the ajmaline molecule. Previous attempts by conventional procedures had been unsuccessful. Personal communication.

(6) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

TABLE I[a]

SYNTHESIS OF SECONDARY AMINES

$$RRNCN \longrightarrow RRNC(=NH)OCH_3 \longrightarrow RRNH$$

I II III

Compd[b,c]	R	Disubstituted Cyanamides (I) Mp or bp, °C (mm)	Yield, %	O-Methylisoureas (II) Mp or bp, °C (mm)	Yield, %	Secondary amines (III) Mp or bp, °C (mm)	Yield, %
1	$(CH_3)_2C{=}CHCH_2$	146–148 (15)	63	142–144 (15)	75	92–94 (15)[d]	65
2	$(CH_3)_2C{=}CHCH_2CH_2$	96–98 (0.15)	55	92–94 (0.1)	63	116–118 (14)	61
3	$(CH_3)_2C{=}CH(CH_2)_2C(CH_3){=}CHCH_2$	166–168 (0.08)	61	165–168 (0.07)	76	134–137 (0.04)[e]	60
4	$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2CH_2$	154–157 (0.05)	72	147–149 (0.03)	81	123–125 (0.03)	71
5	Cyclopropylmethyl	141–143 (15)	90	74–75 (0.07)	83	63–64 (15)	85
6	Cyclobutylmethyl	157–159 (15)	75	85–88 (0.05)	78	97–98 (15)	83
7	Benzyl	55–56[f]	88	145–147 (0.05)	90	291–292 (760)[g]	65
8	3,4,5-Trimethoxybenzyl	85–86[h]	83	106–107[h]	43	87–88[i]	60
9	3,4-Methylenedioxybenzyl	106–107[h]	85	*j*	89	72–73[k]	78
10	CH_2 (RR)	239–240[l]	69	151–152[m]	72	124–125[n]	80
11	$(CH_2)_2$ (RR)	127–129[o]	72	118–119[m]	70	150–152[p]	91

[a] Satisfactory analytical values (±0.4% for C, H, and N) were reported for all compounds: Ed. [b] Consistent ir and nmr spectra were obtained for all products. [c] Yields are based on distilled or crystallized products, unless otherwise specified. Purity was also checked by vpc or tlc analyses, or by comparison with the literature data, when available. [d] Lit.[7] bp 80° (10 mm). [e] Lit.[8] bp 135–137° (0.03 mm). [f] Lit.[9] mp 47–50°. [g] Lit.[10] bp 298–300°. [h] Crystallized from Et_2O. [i] Crystallized from Et_2O–petroleum ether (bp 40–70°). [j] Waxy product. [k] Lit.[11] mp 72–73°. [l] Lit.[12] mp 239–240°. [m] Recrystallized from 50% aqueous EtOH. [n] Lit.[12] mp 124.5–125°. [o] Lit.[13] mp 128–129°. [p] Lit.[13] mp 152.5°.

ml of methanol was refluxed for 24 hr. The methanol was removed, water was added to the residue, and the mixture was extracted with ether. The ether layer was washed with water, dried over $MgSO_4$, and concentrated, and the residue was purified or used as crude product in the subsequent step.

The structure of these compounds was determined by ir and nmr spectra. For instance, the ir spectrum (film) of II-1 showed absorption at 3370 (NH), 1630 (C=N), and 1270 cm^{-1} (COC). The nmr spectrum (CCl_4) had peaks at δ 1.66, 1.72 [each 6 H, s, $(CH_3)_2C{=}$], 3.63 (3 H, s, $-OCH_3$), 3.70 (4 H, d, CH_2NCH_2), 4.57 (1 H, s, =NH), 5.15 (2 H, t, 2 =CH).

Secondary Amines (III).—A solution of 0.1 mol of the appropriate II in 80% acetic acid (300 ml) was refluxed for 24 hr. The reaction mixture was allowed to cool to room temperature and was then poured into ice–water. The mixture was washed with ether, the aqueous layer was made alkaline with 10% sodium hydroxide, and the basic material was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$, and concentrated, and the residue was purified (Table I).

Literature[7-13] melting points or boiling points of some of the compounds are also given in Table I.

Registry No.—I-1, 24339-01-3; I-2, 24339-02-4; I-3, 35211-92-8; I-4, 24339-03-5; I-5, 35140-75-1; I-6, 35140-76-2; I-7, 2451-91-4; I-8, 35140-78-4; I-9, 35140-79-5; I-10, 27016-63-3; I-11, 31486-22-3; II-1, 24339-04-6; II-2, 24339-05-7; II-3, 35191-83-4; II-4, 24381-82-6; II-5, 35140-84-2; II-6, 35191-85-6; II-7, 35140-85-3; II-8, 35140-86-4; II-9, 35140-87-5; II-10, 35140-88-6; II-11, 35191-86-7; III-1, 5122-42-9; III-2, 24339-06-8; III-3, 35146-71-5; III-4, 24381-83-7; III-5, 26389-68-4; III-6, 35146-74-8; III-7, 103-49-1; III-8, 35146-75-9; III-9, 6701-35-5; III-10, 16031-95-1; III-11, 31486-25-6.

Acknowledgment.—The authors are grateful to Professor S. Casadio for his interest in this work. They are also indebted to Dr. A. Gallazzi for physicochemical data.

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An Anomalous Reaction of Aceto-4- (or 6-) nitro-2,5-xylidides with Hydrochloric Acid

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In an attempt to prepare 4-nitro- and 6-nitro-2,5-xylidine by hydrolysis of a mixture of 4-nitro- and 6-nitro-2,5-acetoxylidide,[1,2] an oil was obtained which, upon steam distillation, fractionated into two components, neither of which contained nitrogen. Only a small amount of organic tars remained as a residue in the steam distillation flask.

The major component from the oil, melting at 82–84°, gave ir and nmr spectra having absorption bands identical with those of an authentic sample of

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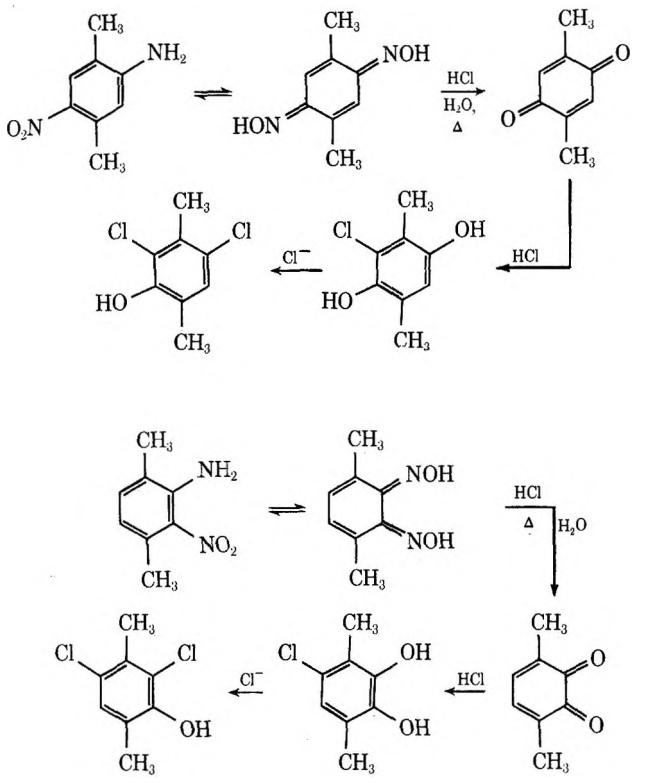

4,6-dichloro-2,5-xylenol.[3] The minor component, isolated by fractionation, and boiling at 220–222°, was identified as a dichloroxylene by mass spectrometry. The ir spectrum of the neat compound exhibited a strong absorption band at 850 cm^{-1}, typical of the aromatic CH wag of the isolated meta hydrogens of a 1,3,4,5-tetrasubstituted benzene.[4] The nmr spectrum of the compound in $CDCl_3$ had singlets for two methyl groups at δ 2.26 and 2.45. The two ring hydrogens were seen as a singlet at δ 7.05. Therefore, we have assigned it the structure of 2,6-dichloro-*p*-xylene (lit.[5] bp 220°).

A third component was found as an impurity in the 2,6-dichloro-*p*-xylene fraction and was separated by preparative glpc. This compound was identified as 2,3,5-trichloro-*p*-xylene by mass spectrometry, based upon a parent peak of *m/e* 208 and an isotopic cluster pattern characteristic of three ring chlorines.[4]

Discussion

The results obtained during the attempted hydrochloric acid hydrolysis of the two acetonitroxylidides appear to be anomalous and certainly not general for nitroanilines. This was borne out by the fact that only the expected nitroanilines were obtained upon similar hydrochloric acid treatment of *o*- and *p*-nitroacetanilide and of aceto-4-nitro-2,6-xylidide.

Boyer, *et al.*,[6] demonstrated that, in 12 *N* hydrochloric acid and in the presence of copper, *o*-benzoquinone dioxime was rapidly isomerized to *o*-nitroaniline. They were not, however, able to show this same isomerization phenomenon with *p*-benzoquinone dioxime. Since these observations were published, Docken, *et al.*,[7] were able to show that, when *p*-benzoquinone dioxime was heated in polyphosphoric acid at 130–140°, it rearranged to *p*-nitroaniline.

Therefore, a suggested rationale which could account for the isolated products assumes that the appropriate nitroaniline, in acid solution, exists to some degree in equilibrium with the benzoquinone–dioxime. Hydrolysis of the benzoquinone dioxime to the analogous benzoquinone and subsequent reactions with hydrochloric acid would account for the formation of 4,6-dichloro-2,5-xylenol. Nucleophilic displacement of the hydroxyl group of 4,6-dichloro-2,5-xylenol by chloride ion can account for the presence of 2,3,5-trichloro-*p*-xylene. At present, however, we are not able to offer any rationale for the presence of 2,6-dichloro-*p*-xylene in the hydrolysate.

When the nitration, hydrolysis and separation, following the procedure of Van Helden, *et al.*,[8] was carried out using 7 *N* instead of 12 *N* hydrochloric acid, the expected 4- and 6-nitro-2,5-xylidines were obtained in reasonable yields. The different course of the reaction was attributed to the lower concentration of acid used in the reaction scheme.

Experimental Section[9]

Nitration of 2-Aceto-*p*-xylidide.—Following a modification of a procedure by Noelting and Thesmar,[1] a flask was fitted with a mechanical stirrer, thermometer, dropping funnel, and reflux condenser. To the flask was added 135 g (0.83 mol) of 2-aceto-*p*-xylidide and 225 mol of sulfuric acid, sp gr 1.84. The contents of the flask were cooled to 20° by means of an ice–water bath and a solution of 70 ml of HNO_3, sp gr 1.42, and 70 ml of H_2SO_4, sp gr 1.84, was added dropwise. The temperature of the reaction was controlled between 30 and 40° by means of ice cooling, and by controlling the addition rate of the acid solution. After acid addition, the reaction mixture was allowed to stir at room temperature for an additional hour, then poured over ice. The pale yellow product was collected and placed in a flask. 500 ml of concentrated hydrochloric acid was added while stirring, and the mixture was refluxed for 2 hr. Following this period, 800 ml of water was added and the product was subjected to steam distillation. There was obtained in the distillate 58 g of an orange oil. Fractionation of the oil gave 8 g of 2,6-dichloro-*p*-xylene, bp 220–222° (lit.[5] bp 222°), and 36 g of 4,6-dichloro-2,5-xylenol, mp 80–84° (lit.[3] mp 84°). The 4,6-dichloro-2,5-xylenol was further purified and gave 32 g of 4,6-dichloro-2,5-xylenol as pale yellow crystals, mp 82–84°. Glpc analysis of the 2,6-dichloro-*p*-xylene fraction resolved a peak amounting to ~2% of the total volatiles. Mass spectral analysis of this material revealed the structure to be 2,3,5-trichloro-*p*-xylene.

Registry No.—Aceto-4-nitro-2,5-xylidide, 6954-69-4; aceto-6-nitro-2,5-xylidide, 35182-75-3; hydrochloric acid, 7647-01-0; aceto-*p*-xylidide, 103-89-9.

Acknowledgment.—The authors are indebted to the National Aeronautics and Space Administration for support of this research under NAS2-4893.

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(9) Ir spectra were taken on a Beckman IR-5A spectrometer. The nmr spectra were determined on a Varian T-60 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Glpc analyses and separations were carried out on a Varian Aerograph Model A90-P3. The mass spectra were obtained using an Atlas CH-4 Mass Spectrometer.

Isomeric Products in the Diacetylation of Dibenzothiophene

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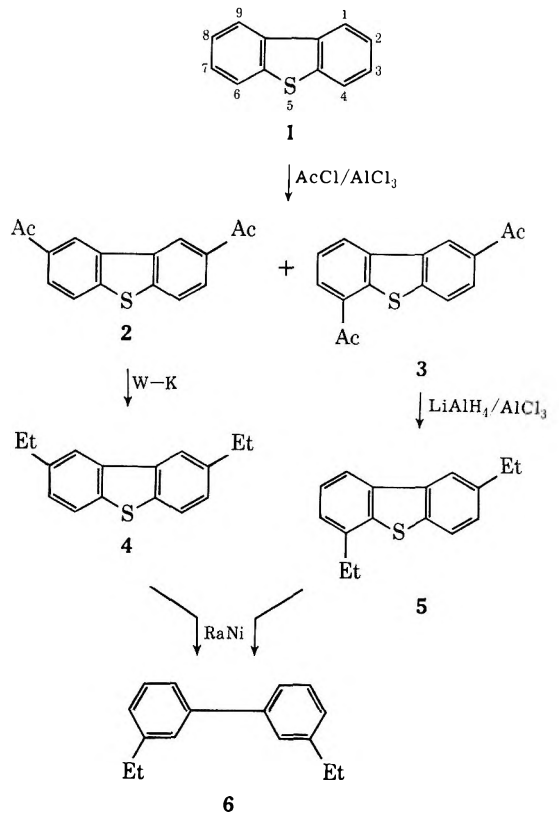
In the course of our work, it was necessary to prepare 2,8-diacetyldibenzothiophene (**2**), previously synthesized by Burger, *et al.*,[1] in a single-step Friedel–Crafts diacetylation reaction. These workers also prepared **2** in a stepwise fashion by employing two successive monoacetylation reactions, first preparing 2-acetyldibenzothiophene and subsequently converting the monoacetyl derivative into **2**. Later Burger and Bryant[2] investigated the mixture of ketones obtained in the monoacetylation of dibenzothiophene. In addition to the major product, 2-acetyldibenzothiophene, they were able to characterize a second monoacetylated isomer, 4-acetyldibenzothiophene. It was noted earlier by these workers that mixtures of ketones were also obtained in the diacetylation reaction. Considering the previous evidence, it was then realistic to anticipate the presence of the 2,6-disubstituted isomer in the diacetylation reaction.

Our original goal was to improve the synthesis of **2** in a single-step diacetylation by varying the reaction conditions. This was accomplished when methylene chloride was used as the reaction solvent and gave 47% of **2**. Continuing our investigation, we chose tetrachloroethane as the reaction solvent from which 11% of a pure diacetylated material could be isolated. Although this compound melted near the reported melting point of **2**, its nmr spectrum was considerably different from that of **2** and the mixture melting point with **2** was depressed. This paper is concerned with the structure proof of this new diacetyl dibenzothiophene, shown to be 2,6-diacetyldibenzothiophene (**3**) by chemical transformation and nmr spectroscopy.

The sequence of reactions used to elucidate the structure of **3** is shown in Scheme I. The course chosen was to convert **2** and **3** to the same biphenyl derivative. The initial attempt to convert both compounds to 3,3′-diacetylbiphenyl was only partially successful in that **2** was readily desulfurated but **3** was resistant to desulfurization. The next approach was to reduce **2** and **3** to 2,8-diethyldibenzothiophene (**4**) and 2,6-diethyldibenzothiophene (**5**), respectively. The Wolff–Kishner reduction of **2** gave **4**. Under identical conditions, **3** was not reduced to **5** but instead a yellow solid, mp > 300°, was obtained. The conversion of **3** to **5** was finally achieved by modifying the $LiAlH_4/AlCl_3$ reduction procedure of Nystron and Burger.[3] Compounds **4** and **5** were subsequently desulfurated with T-1 Raney nickel catalyst[4] to the known 3,3′-diethylbiphenyl (**6**).[5,6] The ir, uv, and nmr spectra of **6** obtained from both **4** and **5** were identical.

SCHEME I



The aromatic region of the nmr spectra of compounds **2** through **5** are shown in Figures 1 and 2. The two patterns of symmetrically substituted **2** and **4** and unsymmetrically substituted **3** and **5** are readily apparent. The former are assigned the 2,8 structure and the latter are assigned the 2,6 structure. These assignments are based on the detailed interpretation of the nmr spectra[7] and the chemical transformation outlined in Scheme I. In all compounds, the area ratios of aromatic to aliphatic protons, as well as the relative intensities of the separated aromatic peaks, agreed with theory.

The assignment of the 2,8 structure for the symmetrically substituted compounds is obvious. The assignment of the 2,6 structure to the unsymmetrical compounds is based on the observance of both an ABX and ABC pattern for the aromatic protons of **3** and **5** and the conversion to 3,3′-diethylbiphenyl. The 4,6-disubstituted isomer, which could also be converted to the 3,3′-diethylbiphenyl, would show *only* an ABC pattern in the nmr spectrum. The possibility that **3** and **5** are actually the 1,8-disubstituted dibenzothiophene, which would have a similar nmr spectrum, is eliminated by the chemical conversion of **5** into a 3,3′-disubstituted biphenyl.

The aliphatic region of the nmr spectra also re-

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(7) The detailed interpretation of the nmr spectra will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-3355. Remit $3.00 for photocopy or $2.00 for microfiche.

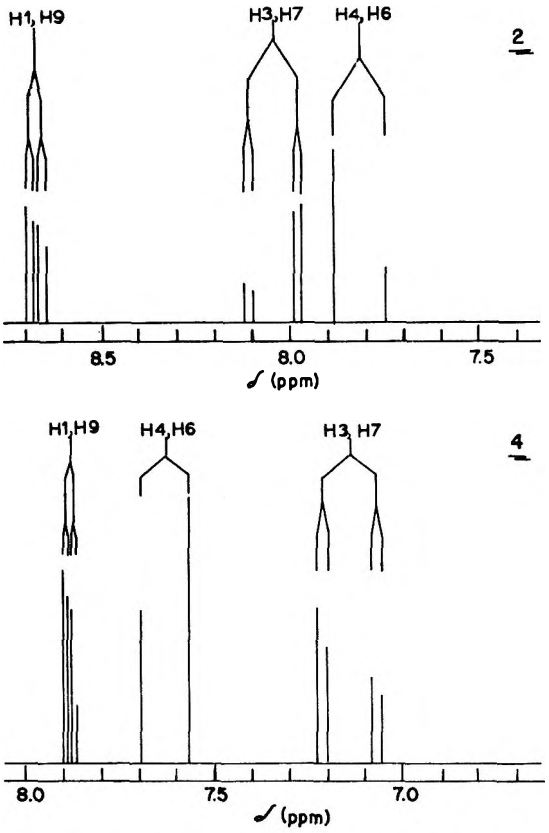

Figure 1.—Nmr spectra of aromatic region of **2** and **4**.

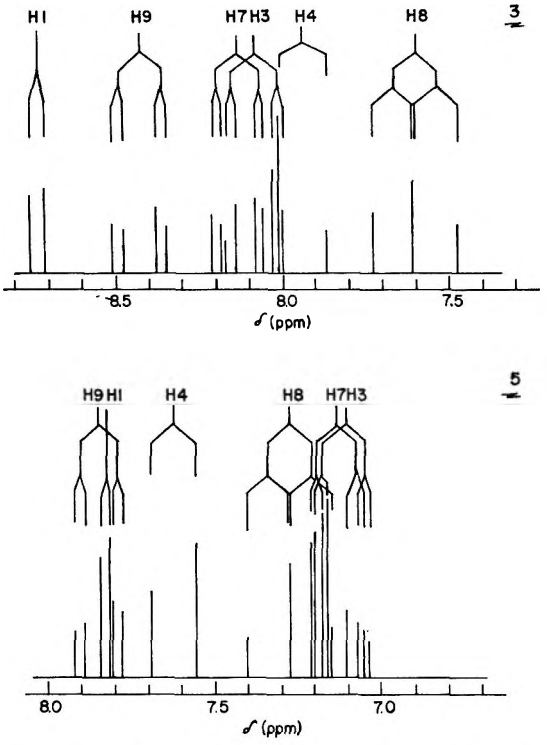

Figure 2.—Nmr spectra of aromatic region of **3** and **5**.

flects the symmetry of substitution. The unsymmetrical compounds **3** and **5** show an additional methyl and ethyl resonance shifted *ca.* 0.1 ppm downfield from the single resonances observed for **2** and **4**. Thus it is possible to determine the symmetry of substitution from examination of the high-field region of these nmr spectra. The ultimate structural assignment must be determined by the detailed analysis of the aromatic region of these spectra and appropriate chemical transformation.

The sulfones **7** and **8** were also prepared. A rigorous interpretation of their nmr spectra was of no additional value in establishing structure.

Experimental Section

All melting points were determined in open capillary tubes using a Thomas–Hoover apparatus and are uncorrected. All boiling points are uncorrected. The infrared spectra were recorded on a Perkin-Elmer 521 recording spectrophotometer. The ultraviolet spectra were recorded on a Perkin-Elmer 350 recording spectrophotometer. The nuclear magnetic resonance spectra were obtained from $CDCl_3$ solution unless otherwise noted at 60 MHz on a Varian A-60A spectrometer. Tetramethylsilane (TMS) was used as the internal standard and all signals are given in parts per million (δ) relative to TMS. Indices of refraction were determined on a Carl Zeiss Model A Abbe refractometer.

2,8-Diacetyldibenzothiophene (2).—A stirred mixture of 196 g (2.5 mol) of acetyl chloride, 280 g (2.1 mol) of $AlCl_3$ and 2 l. of CH_2Cl_2 was cooled in an ice bath while a solution of 184 g (1.0 mol) of dibenzothiophene (J. T. Baker) in 1 l. of CH_2Cl_2 was added dropwise over a period of 1 hr. The reaction mixture was stirred overnight at room temperature, refluxed for 1 hr, cooled, and then decomposed by pouring onto ice–concentrated HCl. The crude product was crystallized from butanone to yield 127 g (47%) of **2**: mp 204–205.5° (lit.[1] mp 208–209°); uv max ($CHCl_3$) 262 mμ (ϵ 67,600); ir (KBr) 1675 cm^{-1} (C=O); nmr.[7]

2,6-Diacetyldibenzothiophene (3).—The above reaction was repeated with $(CHCl_2)_2$ as solvent and the crude product was crystallized from $(CHCl_2)_2$ to give 30 g (11%) of **3**: mp 205–206°; uv max ($CHCl_3$) 257 mμ (ϵ 45,500); ir (KBr) 1675, 1665 cm^{-1} (C=O); nmr.[7]

Anal. Calcd for $C_{16}H_{12}O_2$: C, 71.63; H, 4.51; S, 11.93. Found: C, 71.57; H, 4.44; S, 11.88.

The mixture melting point of **2** and **3** is 170–185°.

2,8-Diethyldibenzothiophene (4).—A mixture of 5.0 g of **2**, 25 ml of 85% H_2NNH_2, and 100 ml of diethylene glycol was stirred and heated at 110° for 1 hr in an open flask, followed by the addition of 18 g of KOH. After stirring at reflux for 18 hr, the mixture was poured into 1 l. of H_2O and then extracted with benzene. The benzene extracts were combined, washed with water and saturated NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo* on a steam bath. The residue obtained was vacuum distilled. The yield of **4** was 1.8 g (40%): bp 193–195° (2.0 mm); uv max (95% EtOH) 238 mμ (ϵ 53,100); ir (neat) 2960, 2925, 2865 (aliphatic CH), 1550 cm^{-1} (C=C); nmr.[7]

Anal. Calcd for $C_{16}H_{16}S$: C, 79.94; H, 6.71; S, 13.34. Found: C, 79.86; H, 6.62; S, 13.12.

2,6-Diethyldibenzothiophene (5).—A solution of 6.7 g of **3** in 400 ml of $CHCl_3$ was added dropwise to a stirred mixture of 6.7 g of $LiAlH_4$, 49.5 g of $AlCl_3$, and 400 ml of anhydrous Et_2O. After stirring at reflux for 18 hr, the reaction mixture was treated with H_2O, followed by concentrated HCl. The organic layer was separated, washed with H_2O and saturated NaCl solution, dried ($MgSO_4$), and evaporated *in vacuo* on a steam bath. The residue obtained was vacuum distilled. The yield of **5** was 4.1 g (69%): bp 174° (0.8 mm); mp 35–39°;[8] uv max (95% EtOH) 233 mμ (ϵ 52,900); ir (neat) 2970, 2935, 2880 (aliphatic CH), 1610, 1578, 1558 cm^{-1} (C=C); nmr.[7]

Anal. Calcd for $C_{16}H_{16}S$: C, 79.94; H, 6.71; S, 13.34. Found: C, 79.99; H, 6.65; S, 13.28.

Desulfurization of 4.—A mixture of 5.0 g of **4**, 100 g of T-1 Raney nickel catalyst,[3] and 100 ml of ethyl acetate was refluxed for 24 hr. After filtration to remove the catalyst, the filtrate was evaporated *in vacuo* on a steam bath. The residue obtained was vacuum distilled to give 2.4 g (55%) of 3,3′-diethylbiphenyl (**6**): bp 131–132° (0.5 mm); n^{20}D 1.5773; uv max (95% EtOH) 251 mμ (ϵ 16,100); ir (CS_2) 2960, 2925, 2870 (aliphatic CH), 885, 790, 705 cm^{-1} (aromatic meta substitution) [lit.[5,6] bp 154–155° (9–10 mm); n^{25}D 1.5768; uv max (95% EtOH) 251 mμ (ϵ 16,100); ir (CS_2) 2960, 2925, 2870, 890, 795, 710 cm^{-1}]; nmr ($CDCl_3$) δ 7.28 (m, 8, Ar), 2.68 (q, 4, J = 8 Hz, CH_2), 1.23 (t, 6, J = 8 Hz, CH_3).

(8) Corrected melting point determined using a Perkin-Elmer Differential Scanning Calorimeter Model DSC-1B.

Desulfurization of 5.—By the same procedure described for desulfurization of **4**, 3.0 g of **5** was desulfurated to yield 1.3 g (48%) of 3,3′-diethylbiphenyl (**6**): bp 135–137° (1.3 mm); $n^{20}D$ 1.5762; uv max (95% EtOH) 251 mμ (ε 16,745). The ir and nmr were identical in all respects to the ir and nmr of **6** obtained in the desulfurization of **4**.

2,6-Diacetyldibenzothiophene 5,5-Dioxide (7).—A mixture of 3.0 g of **3**, 10 ml of 30% H_2O_2, and 50 ml of HOAc was refluxed for 1 hr and cooled to room temperature, and the product was filtered. Recrystallization from acetonitrile gave 3.1 g (92%) of **7**: mp 303° dec; uv max (DMF) 333 mμ (ε 844); ir (KBr) 1695, 1681 (C=O), 1310, 1162 cm^{-1} (sulfone); nmr (CF_3COOH/$CDCl_3$) δ 2.83 (s, 3, CH_3), 2.87 (s, 3, CH_3).

Anal. Calcd for $C_{16}H_{12}O_4S$: C, 63.99; H, 4.03; S, 10.67. Found: C, 64.19; H, 3.95; S, 10.72.

2,8-Diacetyldibenzothiophene 5,5-Dioxide (8).—By the same procedure used in the oxidation of **3**, 6.0 g of **2** was oxidized, yielding 5.7 g (84%) of **8** after crystallization from acetonitrile: mp 272–277°; uv max (DMF) 377 mμ (ε 1430); ir (KBr) 1690 (C=O), 1312, 1169 cm^{-1} (sulfone); nmr (CF_3CO_2H/$CDCl_3$) δ 2.87 (s, 6, CH_3).

Anal. Calcd for $C_{16}H_{12}O_4S$: C, 63.99; H, 4.03; S, 10.67. Found: C, 64.24; H, 4.05; S, 10.64.

Registry No.—**1**, 132-65-0; **2**, 35105-75-0; **3**, 35105-76-1; **4**, 35105-77-2; **5**, 35105-78-3; **6**, 13049-38-2; **7**, 35105-80-7; **8**, 35105-81-8.

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Synthesis of 1-(*p*-Iodobenzenesulfonyl)-3,5-di-*n*-propyl Isocyanurate

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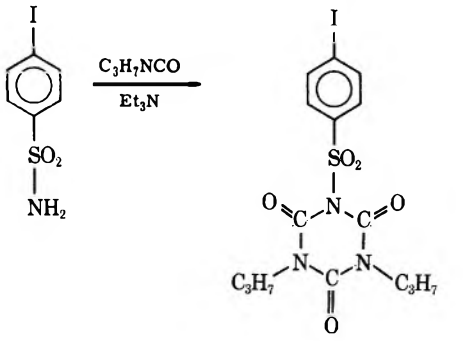
The base-catalyzed reaction of arylsulfonamides with alkyl isocyanates is a valuable synthetic method for the preparation of arylsulfonylureas. During studies aimed at the synthesis of 1-(*p*-iodobenzenesulfonyl)-3-*n*-propylurea-^{125}I, we found that a base-insoluble product was formed when the reaction was carried out with an excess of *n*-propyl isocyanate.[1] This base-insoluble product was identified as 1-(*p*-iodobenzenesulfonyl)-3,5-di-*n*-propyl isocyanurate (**1**).

Tri-N-substituted, di-N-substituted, and mono-N-substituted isocyanurates have been synthesized[2-4] and studied, but no 1-arylsulfonyl-3,5-dialkyl isocyanurates have been reported. The formation of **1**, therefore, represents not only a novel reaction but also a new chemical entity. The reaction most likely involves the base-catalyzed condensation of *p*-iodobenzenesulfonamide with a threefold excess of *n*-propyl isocyanate with the subsequent elimination of *n*-propylamine. The transient existence of a series of anionic intermediates can be justified on the basis of a delocalization of the developing negative charge as proposed by Ulrich[5] for analogous reactions.



1

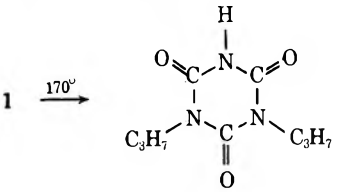
No mass ion occurred in the high-resolution mass spectrum of this compound under normal conditions; however, a small peak did occur at *m/e* 479 when the instrument was overloaded with sample. The prominent high mass ion in the mass spectrum occurred at *m/e* 415. This differs by sulfur dioxide from the proposed structure. The loss of sulfur dioxide upon electron impact has previously been reported in sulfonylureas[6] and in *O*-alkyl-*N*-arylsulfonyl carbamates.[7] The prominent ions in the mass spectrum of **1** (Table I) can be accounted for by fragmentation of the molecule in a manner analogous to that reported for tolbutamide[6] and for ethyl *N*-methyl-*N*-(*p*-toluenesulfonyl)carbamate.[7]

TABLE I

PROMINENT IONS IN THE MASS SPECTRUM OF 1-(*p*-IODOBENZENESULFONYL)-3,5-DI-*n*-PROPYL ISOCYANURATE

m/e	Ion	Per cent total ionization
415	$C_{15}H_{18}IN_3O_3^+$	12.50
374	$C_{12}H_{13}IN_3O_3^+$	8.75
332	$C_9H_7IN_3O_3^+$	2.70
288	$C_8H_5IN_2O_2^+$	13.25
267	$C_6H_4IO_2S^+$	22.50
245	$C_7H_4INO^+$	26.25
203	$C_6H_4I^+$	50.50
56	$C_2H_2NO^+$	51.25
43	$C_3H_7^+$	61.25

Heating **1** at 170° in DMF–H_2O afforded 1,3-di-*n*-propyl isocyanurate (**2**), thus providing chemical evidence in support of the proposed structure of **1**.



2

(1) G. N. Holcomb, C. M. Boyd, R. E. Counsell, W. H. Beierwaltes, R. A. Szczesniak, D. R. K. Murty, and G. A. Bruno, *J. Pharm. Sci.*, **60**, 390 (1971).

(2) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Rev.*, **57**, 47 (1957).

(3) W. Close, *J. Amer. Chem. Soc.*, **75**, 3617 (1953).

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(5) H. Ulrich, *Accounts Chem. Res.*, **2**, 186 (1969).

(6) M. R. Grostic, R. J. Wnuk, and F. A. MacKellar, *J. Amer. Chem. Soc.*, **88**, 4664 (1966).

(7) W. H. Daly and C. W. Heurtevant, *Org. Mass Spectrom.*, **4**, 165 (1970).

Experimental Section

Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich. Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Ir spectra were taken on a Perkin-Elmer 337 spectrophotometer. Nmr spectra were obtained with a Varian A-60 spectrometer in $CDCl_3$ at a concentration of 10% with TMS as an internal reference. Mass spectra were obtained on an Associated Electrical Industries MS902 Double Focusing High Resolution Mass Spectrometer equipped with a Honeywell 7600 Frequency Modulated Analog Tape Reader. The spectra were run at 70 eV. Chromatogram strips (K301R) were used for tlc, and the spots were detected with uv light.

1-(*p*-Iodobenzenesulfonyl)-3,5-di-*n*-propyl Isocyanurate (1).—A solution of 0.5 g (0.0018 mol) of *p*-iodobenzenesulfonamide in 5 ml (0.052 mol) of *n*-propyl isocyanate and 0.1 ml of triethylamine was refluxed with stirring for 96 hr. The excess *n*-propyl isocyanate and triethylamine were removed and the residue was dissolved in 15 ml of ethyl acetate. The ethyl acetate solution was filtered and 5 g of silica gel (80–200 mesh) was added to the filtrate. The ethyl acetate was removed *in vacuo* and 50 ml of benzene was added to the resin and evaporated *in vacuo* to remove the last traces of ethyl acetate. The dried silica gel with the reaction mixture adsorbed on it was added to the top of a silica gel column (60 × 2.5 cm), and the column was eluted with benzene at a rate of 4 ml/min. The product was eluted in the fractions between 500 and 600 ml. Aliquots of these fractions were chromatographed on tlc with benzene and only one spot (R_f 0.55) was observed. The benzene was removed from these fractions *in vacuo*. The resulting solid was recrystallized (EtOH–H_2O) to yield 0.363 g (44.4%) of product: mp 186–187°; ir (KBr) 1725, 1700 (C=O), 1168 cm^{-1} (SO_2); nmr ($CDCl_3$) 0.91 (t, 6, J = 7 Hz, CH_3), 1.63 (m, 4, $-CH_2-$), 3.75 (t, 4, J = 7 Hz, CH_2N), and 7.85 ppm (s, 4, aromatic).

Anal. Calcd for $C_{15}H_{18}IN_3O_5S$: C, 37.59; H, 3.79; N, 8.77. Found: C, 37.75; H, 3.83; N, 8.83.

Thermal Degradation of 1-(*p*-Iodobenzenesulfonyl)-3,5-di-*n*-propyl Isocyanurate (1).—A solution of 0.2 g (0.0004 mol) of 1 in 9.8 ml of dimethylformamide and 0.2 ml of water was heated at 170° for 48 hr. The solvent was removed *in vacuo*, and the residual oil was dissolved in 10 ml of 1 *N* NaOH. The pH of the solution was adjusted to 6 with HCl and a solid precipitated. The product was recrystallized (H_2O) to yield 0.06 g (71%) of 1,3-di-*n*-propyl isocyanurate (2): mp 137–138° (lit.[8] mp 138°); ir (KBr) 3200 (NH), 1730, 1710 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 213 (41).

Registry No.—1, 35105-49-8.

Acknowledgment.—The authors wish to express their appreciation to Dr. A. I. Cohen for the mass spectra. We are grateful to Dr. R. L. Jacoby for the stimulating discussions and the helpful suggestions. This research was partially supported by a grant from The Squibb Institute for Medical Research. One of us (T. J. S.) was supported by a National Science Foundation Undergraduate Research Participation Grant.

(8) British Patent 928,637 (June 12, 1963); *Chem. Abstr.*, **60**, 2988 (1964).

The Synthesis and Reactions of a Tetrachlorodioxopiperazine

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For a projected synthesis, we required the amino acid derivative *N*-trifluoroacetyl-α-chlorosarcosyl chloride (2). When we applied the usual two-step procedure[2] for the synthesis of α-chloroacyl chlorides to *N*-trifluoroacetylsarcosine (1), using first thionyl then sulfuryl chloride, we isolated the α,α-disubstituted sarcosyl chloride 3 (~18% yield) in some reactions. The unexpected instability of 3[3] and the identification of

$CH_3N(TFA)CXX'COX''$

1, X = X′ = H; X″ = OH
2, X = H; X′ = Cl; X″ = Cl
3, X = X′ = X″ = Cl

(TFA = F_3CCO-)

several of its decomposition products as fully chlorinated or ketalized diketopiperazines seemed of sufficient interest to warrant this interim report, especially so since *N*-trifluoroacetyl-α-chlorosarcosyl chloride (2), which we obtained recently, is stable and does not yield diketopiperazines on standing.

As expected the ir spectrum of 3 showed acid chloride (1775 cm^{-1}) and trifluoroacetylamide (1660 cm^{-1}) carbonyl absorptions (CCl_4), the nmr spectrum displayed the *N*-methyl signals only slightly shifted from 1, but the signal for the α hydrogen was absent. Finally the electron-impact mass spectrum with the highest *m/e* peak at 236 corresponds to the molecular ion of 3 less one chlorine atom, behavior which might be expected for a geminal halide.

On standing in a stoppered flask at room temperature for 24 hr, however, the original colorless liquid changed largely to a crystalline mass (mp 128–130°) whose ir spectrum now showed only one absorption (1728 cm^{-1}) in the carbonyl region and a single *N*-methyl signal (singlet, δ 3.51) in the nmr spectrum. An electron-impact mass spectrum showed as the highest peak *m/e* 243; the true parent ion (*m/e* 278) could be detected with chemiionization techniques.[4] These data and the elemental analysis ($C_6H_6N_2O_2Cl_4$) suggested the sarcosine anhydride structure 6 for this product.

The route to 6 starts with loss of trifluoroacetyl chloride from 3 to give the imidoyl chloride 4, which, being a reactive bifunctional species, could dimerize *via* 5 (Scheme I). The addition of acyl halides to imines has precedents.[5] To prove that the distillate (3) still had an intact *N*-trifluoroacetyl linkage, a sample was refluxed with octadecylamine (10) in benzene. *N*-Trifluoroacetyloctadecylamine (11) was isolated in 62% yield, identical in all respects with a sample prepared from 10 and trifluoroacetic anhydride. Low temperature trapping experiments designed to demonstrate the presence of trifluoroacetyl chloride in decomposing samples of 3 have so far been unsuccessful.

The diketopiperazine 6 possessed appreciable reactivity, as might be expected.[6] The addition of 1 equiv of triethylamine to a slurry of 6 in methanol initiated a rapid exothermic reaction to produce a 1:3 mixture of the soluble mono- and diketals 7 and 8, which were separated by fractional crystallization. The mono-

(1) University at Nijmegen, Toernooiveld, Nijmegen, The Netherlands.

(2) E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **70**, 3626 (1948).

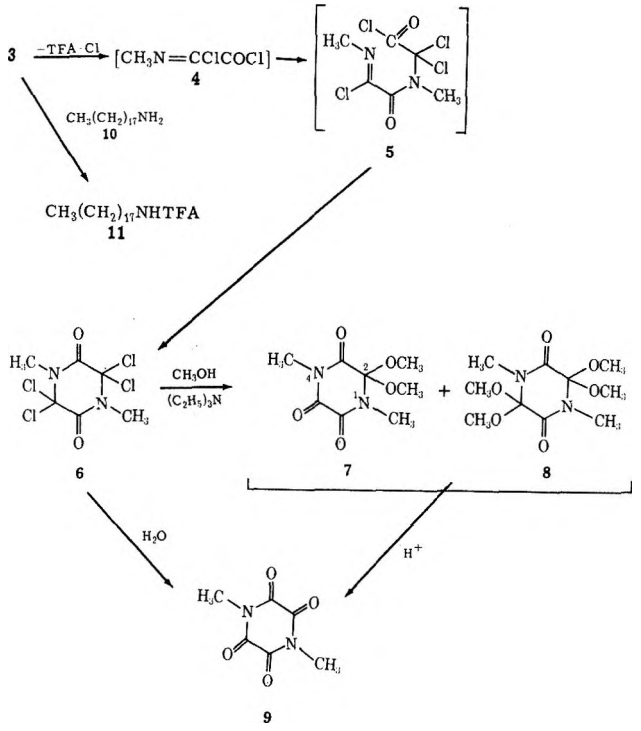
(3) F. Weygand and U. Glöckler, *Chem. Ber.*, **89**, 653 (1956).

(4) We thank Dr. Henry Fales, National Heart and Lung Institute, for this spectrum.

(5) A. H. Leuchs and A. Schlötzer, *Chem. Ber.*, **67**, 1572 (1934), and references cited therein.

(6) (a) P. W. Trown, *Biochem. Biophys. Res. Commun.*, **33**, 402 (1968); (b) H. Poisel and U. Schmidt, *Chem. Ber.*, **104**, 1714 (1971); (c) H. Böhme and K. Hartke, *ibid.*, **96**, 600 (1963).

SCHEME I



ketal **7**, mp 124–125°, exhibited nmr signals at δ 3.40, 3.34, and 3.05 in a 2:1:1 ratio (assigned to CH_3O, N_4 CH_3, and N_1 CH_3, respectively); the diketal **8**, mp 137–138°, had signals at δ 3.38 and 2.98 in a 2:1 ratio as expected for CH_3O and CH_3N protons. Surprisingly *both* **7** and **8** had only one amide carbonyl absorption in the ir region at 1702 and 1680 cm^{-1}, respectively. Finally, electron-impact mass spectrometry showed the parent molecular ions for **7** and **8** at *m/e* 216 and 262, respectively, as the highest peaks in the spectra.

When crystalline **6** was allowed to stand for 2 weeks in contact with the humid atmosphere, it decomposed to a material of the formula $C_6H_6N_2O_4$. A sample recrystallized from acetic acid had the characteristic melting point behavior of *N,N*-dimethyltetraketopiperazine **9**.[7] The ir spectrum (Nujol mull) showed one single carbonyl band (1695 cm^{-1}), the mass spectrum exhibited *m/e* 170 as the highest peak, and the nmr spectrum (trifluoroacetic acid) showed only one *N*-methyl singlet at δ 3.51. Exposure of the mixture of ketals **7** and **8** to acid also produced **9**. The tetrachlorodiketopiperazine **6** gave an immediate precipitate with silver nitrate and also a positive starch–iodide test.

Experimental Section

Ir spectra were measured with Perkin-Elmer spectrophotometers, Models 237B ($CHCl_3$ or CCl_4) and 421 (KBr). Mass spectra were obtained with the double-focusing Hitachi RMU-6E mass spectrometer. Pmr spectra were measured on the Varian Associates spectrometer, Model A-60. Chemical shifts are reported as δ values (parts per million) relative to tetramethylsilane as an internal standard; deuteriochloroform was used as solvent unless stated otherwise. Melting points were taken on a Koefler hot stage and are corrected. Thin layer chromatography (tlc) was carried out on 0.25-mm Merck precoated silica gel F-254 plates; spots were visualized with a hand uv lamp or iodine vapor.

N-**Trifluoroacetylsarcosine** (**1**).—The procedure of Weygand[8] was used. To a cooled solution (−10°) of 8.9 g (0.10 mol) of sarcosine in 60 ml of dry trifluoroacetic acid, 17.6 ml (0.12 mol) of trifluoroacetic anhydride was added over a period of 30 min. The mixture was stirred at −20° for 16 hr, then at room temperature for 1 hr, after which excess reagent and solvent were removed (bath temperature kept below 35°). The yellow residue was purified by vacuum distillation [bp 119–120° (1.1 mm)], yielding 11.0 g (0.59 mol, 59%) of a light yellow viscous oil which solidified upon cooling. This material was pure enough to be used in further experiments. A sample, crystallized from ethanol–hexane, had mp 54.5–55.5°. Tlc (acetic acid–benzene 7:1) showed one spot, R_f 0.25; ir (CCl_4) 1740 (amide), 1710 cm^{-1} (acid); nmr δ 10.7 (s, 1 H, COOH), 4.23 (s, 2 H, CH_2), 3.26 and 3.13 (4 lines, 1 line, respectively, 3 H, NCH_3, cis and trans isomers); mass spectrum (120°) *m/e* 185 (M^+), 141 ($M^+ - CO_2$), 140 ($M^+ - CO_2H$, base peak), 126, 112, 110, 97 (TFA), 90, 88 ($M^+ - TFA$), 78, 69, 60.

Anal. Calcd for $C_5H_6NO_3F_3$: C, 32.46; H, 3.27; N, 7.57. Found: C, 32.49; H, 3.50; N, 7.47.

N-**Trifluoroacetyl-α,α-dichlorosarcosyl Chloride** (**3**).—A solution of 19.0 g (0.103 mol) of **1** in 30 ml of freshly distilled thionyl chloride was refluxed for 2 hr. To the refluxing solution was then added 30 ml of freshly distilled sulfuryl chloride and refluxing was continued for another 2 hr. Excess reagents were removed by careful distillation and the light yellow residue was vacuum distilled, yielding 4.67 g (182 mmol, 18%) of a colorless liquid: bp 52–58° (16–18 mm); ir (CCl_4) 1865 (w), 1775 (s), 1660 cm^{-1} (m); mass spectrum (135°) *m/e* 236 ($M^+ - Cl$), 233, 174 ($M^+ - COCl_2$), 167 ($M^+ - Cl_3$), 140 ($M^+ - CF_3COCl$), 140 (CH_3N-$CCl{=}C{=}O$), 97 (TFA), 69 ($CH_3NC{=}C{=}O$).

2,2,5,5-Tetrachlorosarcosine Anhydride (**6**).—When 1.0 g of the above distillate was stored at room temperature in a stoppered flask for 24 hr, a crystalline mass formed, a sample of which on washing with dry hexane had mp 128–130°; ir (CCl_4) 1728 (s), 1420 (w), 1335 cm^{-1} (br m); nmr δ 3.51 (s); mass spectrum (200°), chemical ionization with 1 mm of methane, *m/e* 307 ($M^+ + C_2H_5$), 279 ($M^+ + 1$), 243 ($M^+ - Cl$), 216 ($M^+ - COCl$), 210, 209, 182, 181 ($M^+ - COCl_2$), 169, 168, 154, 147, 146, 141.

Anal. Calcd for $C_6H_6N_2O_2Cl_4$: C, 25.74; H, 2.16; N, 10.01. Found: C, 25.45; H, 2.19; N, 9.97.

N-**Trifluoroacetyloctadecylamine** (**11**).—To 4.0 g (15 mmol) of octadecylamine dissolved in the minimal amount of refluxing dry benzene was added 0.80 g (2.9 mmol) of distillate **3**. An exothermic reaction was observed. The clear solution was refluxed for 16 hr and cooled, and unreacted octadecylamine removed by filtration. The yellow filtrate was concentrated to dryness and then subjected to vacuum sublimation [105° (0.5 mm)] to yield 602 mg (1.8 mmol, 62%) of a colorless solid. Recrystallization from methanol gave needles: mp 73–74°; ir ($CHCl_3$) 3460 (sharp, NH), 2950, 2870, 1730 (CO), 1550, 1470 cm^{-1}; mass spectrum (160°) *m/e* 365 (M^+), 296 ($M^+ - CF_3$, base peak), 268 ($M^+ - TFA$), 97 (TFA), losses of *m/e* 14 and 28.

Authentic **11** was prepared as follows. To 4.0 g (15 mmol) of octadecylamine dissolved in the minimal amount of dry benzene was added, dropwise, 5 ml (excess) of trifluoroacetic anhydride. The solution was stirred at room temperature for 16 hr and for 1 hr at reflux. Solvent and excess reagent were removed and the colorless residue was recrystallized from methanol to yield 4.1 g (11.2 mmol, 75%) of a material that was identical in all respects with the amide described above.

2,2,5,5-Tetramethoxysarcosine Anhydride (**8**) **and 2,2-Dimethoxy-5-ketosarcosine Anhydride** (**7**).—To a stirred suspension of 40 mg of **6** in 3 ml of absolute methanol at room temperature was added 0.4 ml of triethylamine (hydrochloride vapors noted above the suspension). An exothermic reaction occurred resulting in a clear solution within 5 min. The solution was stirred at room temperature for 24 hr, and then the solvent was removed. The solid residue was extracted with ethyl acetate and water, the organic layer was dried (Na_2SO_4) and evaporated, and the residue was subjected to vacuum sublimation [90° (0.5 mm)] to yield 36 mg of a colorless solid which had the same nmr spectrum as the unsublimed material. The sublimate was recrystallized from chloroform–hexane which was allowed to evaporate slowly to yield 26 mg of large, cubic crystals (mp 137–138°) on the bottom and 8 mg of long, fine needles (mp 124–125°) on the wall of the flask.

(7) M. O. Forster and W. B. Saville, *J. Chem. Soc.*, **121**, 816 (1922).

(8) F. Weygand and R. Geiger, *Chem. Ber.*, **89**, 647 (1956).

The higher melting material was identified as the diketal **8**: ir ($CHCl_3$) 2940, 2830, 1680, 1380 cm^{-1}; nmr δ 3.38 (s, 12 H, OCH_3), 2.98 (s, 6 H, NCH_3); mass spectrum (160°) *m/e* 262 (M^+), 247 ($M^+ - CH_3$), 231 ($M^+ - OCH_3$), 216 ($M^+ - CH_3OCH_3$), 203, 201, 190, 185, 157, etc.

The lower melting material was assigned structure **7**: ir ($CHCl_3$) 2940, 2830, 1702, 1340 cm^{-1}; nmr δ 3.40 (s, 6 H, OCH_3), 3.34 (s, 3 H, N_4CH_3), 3.05 (s, 3 H, N_1CH_3); mass spectrum (160°) *m/e* 216 (M^+), 201, 185, 157, 144, 142, 131, 116, 103, 88.

2,3,5,6-Tetraketo-1,4-dimethylpiperazine (9).—The appearance of a sample of 6 (40 mg), stored in an open flask for 2 weeks, changed drastically and the original big cubic crystals had become brittle and calcified. The material was now found to be insoluble in most organic solvents, but soluble in DMF, DMSO, water, acetic acid, and CF_3COOH. This material was subjected to vacuum sublimation [130° (0.4 mm)]; a sample of the sublimate on recrystallization from glacial acetic acid yielded rhomboid plates of dec pt 320° (sample rapidly sublimed around 270°). The rest of the sublimate was used for spectral analysis: ir (Nujol) 1695 cm^{-1} (br); nmr (CF_3COOH) δ 3.51 (s); mass spectrum (140°) *m/e* 170 (M^+), 142 ($M^+ - CO$), 114 ($M^+ - 2CO$), 113 ($M^+ - CONHCH_3$), 86 ($M^+ - 3CO$), 85 ($M^+/2$), 70, 58, 57, 56.

Anal. Calcd for $C_6H_6N_2O_4$: C, 42.36; H, 3.56; N, 16.47. Found: C, 41.91; H, 3.37; N, 16.58.

Registry No.—**1**, 35141-11-8; **3**, 35191-65-2; **6**, 35191-66-3; **7**, 35141-12-9; **8**, 35141-13-0; **9**, 35141-14-1; **11**, 10574-23-9.

The Preparation of Some 1,3,4,6-Tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxides[1]

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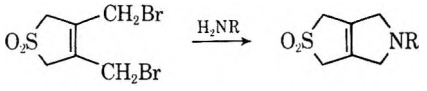
In a recent report,[3] it was indicated that, when 3,4-bis(bromomethyl)-2,5-dihydrothiophane 1,1-dioxide (**1**) was reacted with various amines even under



1 **2**

very mild conditions, in either protic or aprotic solvents, intractable mixtures were obtained. Only the weakly basic *p*-chloroaniline was reported to react with **1** over a 3-day period to yield the corresponding bicyclic pyrrolidine. We felt that it was important to report the successful preparation, without apparent difficulty, of several 1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-dioxides (**2**) by the reaction of alkyl and aryl primary amines with the dibromo sulfone (**1**) in both protic and aprotic solvents. These reactions were completed, for the most part, in less than 2 hr.

Gschwend and Haider[3] had proposed that the difficulty with the reaction lay with the fact that the strongly acidic character of the sulfolene (**1**) protons toward the basic amine strongly favored proton abstraction and suppressed the nucleophilicity of the amines. Although we had earlier reported[4] that this abstraction process was predominant when strong nucleophiles such as hydroxides, sulfides, and alkoxides were reacted with **1**, this does not appear to occur to any great extent with those primary amines we have studied.

By reacting the dibromo sulfone (**1**) with aniline (pK_a 4.63) or *p*-anisidine (pK_a 5.34) in methanol (in the presence of anhydrous sodium carbonate, which neutralized the amine hydrobromide salts as they were formed), the corresponding bicyclic pyrrolidines were obtained in moderately good yields (38–78%). These reactions were complete in less than 2 hr, yielding white crystalline products which gave decomposition points and nmr and ir spectra similar to those obtained by Gschwend and Haider[3] for the *p*-chloroaniline derivative (Table I). In our preparation of the *p*-chloroaniline derivative, the reaction rate was so slow at room temperature under these conditions that the reaction mixture was heated at 55° for 1 hr.

TABLE I

AMINES REACTED WITH 3,4-BIS(BROMOMETHYL)-2,5-DIHYDROTHIOPHENE 1,1-DIOXIDE

Amine	pK_a[b]	Solvent	Reaction time, hr	% yield
Aniline	4.63	MeOH	2	38–74
p-Anisidine	5.34	MeOH	2	73–83
p-Chloroaniline[a]	4.15	MeOH	2	34
Benzylamine	9.33	CH_3CN	1	47–60
Methylamine	10.81	CH_3CN	1	37
Ethylamine	10.66	CH_3CN	1	32

[a] This was also prepared by Gschwend and Haider.[3] [b] "CRC Handbook of Chemistry and Physics," 50th Ed., Chemical Rubber Co., Cleveland, Ohio, 1969, pp 115–116.

The much stronger primary amines such as methylamine (pK_a 10.81) and ethylamine (pK_a 10.66) also gave reasonable yields of the corresponding bicyclic pyrrolidines with **1**. These amines reacted in acetonitrile to yield a mixture of bicyclic free amine and the corresponding HBr salt. The latter is treated with Na_2CO_3 to liberate the bicyclic amine product.

In contrast to the arylamine bicyclic pyrrolidines, which decomposed on heating, the alkyl compounds gave sharp melting points. Another difference between the alkylamines and the arylamines was that the former appeared to have a much faster reaction rate. The side products from both of these reactions, other than the corresponding primary amine hydrobromide salt, were intractable polymeric gums or oils.

Experimental Section[5,6]

5-Phenyl-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The dibromo sulfone[7] (3.04 g, 10 mmol) was dissolved in 200 ml of boiling methanol. Sodium carbonate (0.53 g) and 0.93 g (10

(1) This work was supported in part by the National Science Foundation Grant GP26616.

(2) A Texaco Fellow.

(3) H. W. Gschwend and H. Haider, *J. Org. Chem.*, **37**, 59 (1972).

(4) R. M. Ottenbrite, *Va. J. Sci.*, **21**, 196 (1970).

(5) Melting points were obtained in a Thomas–Hoover melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60 instrument with TMS internal reference, and ir spectra were recorded on a Perkin-Elmer 337.

(6) We wish to thank Texaco, Inc., Research Laboratories, Richmond, Va., for the analytical analyses.

(7) G. B. Butler and R. M. Ottenbrite, *Tetrahedron Lett.*, 4873 (1967).

mmol) of aniline were added to the hot methanol solution. The mixture was stirred and allowed to cool, during which time all of the sodium carbonate was consumed (about (0.5 hr). Another 0.53-g portion of Na_2CO_3 was added to completely neutralize the amine hydrobromide being formed in the reaction. The reaction mixture was stirred for another 90 min, during which time all of the sodium carbonate was consumed and most of the bicyclic product precipitated. The reaction mixture was allowed to stand in a freezer overnight and the bicyclic product was recovered by filtration. Recrystallization from hot methanol yielded from 38 to 74% (dec pt 156–157°): ν^{KBr} 1580, 1490, 1370, 1287, 1188, 1111, 745, 686 cm^{-1}; nmr (CF_3COOD) δ 4.3 (s, 4 H), 5.02 (s, 4 H), 7.67 (s, 5 H); nmr ($CDCl_3$) δ 3.87 (s, 4 H), 4.19 (s, 4 H), 6.4–6.84 and 7.09–7.34 (broad phenyl absorption, 5 H).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5 95. Found: C, 61.77; H, 5.52; N, 5.83.

5-(*p*-Methoxyphenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The 5-(*p*-methoxyphenyl) product was prepared by a procedure similar to that described above: yield 73–83%; dec pt 156°; ν^{KBr} 2825, 1520, 1314, 1253, 1238, 1185, 1119, 1038, 811 cm^{-1}; nmr (CF_3COOD) δ 3.95 (s, 3 H), 4.26 (s, 4 H), 4.95 (s, 4 H), 7.16 and 7.59 (AB, J = 9 Hz, 4 H); nmr (DMSO-d_6), δ 3.67 (s, 3 H), 4.07 (broad peak, 8 H), 6.41 and 6.89 (AB, J = 9 Hz, 4 H).

Anal. Calcd for $C_{13}H_{15}NO_3Si$: C, 58.85; H, 5.69; N, 5.28. Found: C, 59.36; H, 5.58; N, 5.14.

5-(*p*-Chlorophenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—This bicyclic pyrrole was obtained by following a procedure similar to that above, with the exception that the reaction mixture was held at 55° for 1 hr. Recrystallization from hot methanol yielded 0.8 g (34%), dec pt 153° (lit.[3] 153°).

5-Methyl-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The dibromo sulfone (12.11 g, 40 mmol) and 130 mmol of anhydrous methylamine in 300 ml of acetonitrile were stirred at room temperature for 60 min. The reaction mixture was filtered to remove the methylamine hydrobromide which precipitated, and the filtrate was evaporated to dryness. The residue was triturated in 100 ml of ether, and the ethereal solution was reduced in volume to 25 ml and allowed to stand in a freezer overnight; 1.1 g of the bicyclic product was obtained. The residue that remained after the ether washing was dissolved in methanol and neutralized with sodium carbonate. The methanol was removed under reduced pressure and the resultant residue was also triturated with 100 ml of ether. From this ether solution 1.5 g of the bicyclic product was obtained: total yield 2.8 g (37%); mp 89–90°; ν^{KBr} 1297, 1262, 1174, 1143, 1100, 848, 792 cm^{-1}; nmr (CF_3COOD) δ 3.37 (s, 3 H), 4.10–5.17 (s, 4.22 with broad AB pattern, 8 H; nmr ($CDCl_3$) δ 2.51 (s, 3 H), 3.56 (s, 4 H), 3.75 (s, 4 H).

Anal. Calcd for $C_7H_{11}NO_2S$: C, 48.53; H, 6.39; N, 8.08. Found: C, 48.92; H, 6.07; N, 7.95.

5-Ethyl-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The 5-ethyl product was prepared by the same procedure as the 5-methyl product. The only deviation from the procedure is that the ethylamine hydrobromide did not precipitate: 32%; mp 98–99°; ν^{KBr} 1285, 1264, 1184, 1154, 1166, 1100, 1032, 847, 793, 770 cm^{-1}; nmr (CF_3COOD) δ 1.52 (t, J = 7 Hz, 3 H), 3.64 (q, J = 7 Hz, 2 H), 4.06–5.04 (s, 4.18 with a broad AB pattern, 8 H); nmr ($CDCl_3$) δ 1.12 (t, J = 7 Hz, 3 H), 2.75 (q, J = 7 Hz, 2 H), 3.59 (s, 4 H), 3.80 (s, 4 H).

Anal. Calcd for $C_8H_{13}NO_2S$: C, 51.35; H, 6.98; N, 7.48. Found: C, 51.08; H, 6.76; N, 7.30.

5-Benzyl-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide.—The 5-benzyl product was prepared by the same procedure as the 5-methyl product: 46–60%; mp 100°; ν^{KBr} 2780, 1298, 1263, 1110, 1091, 740, 700 cm^{-1}; nmr (CF_3COOD) δ 4.16 (s, 4 H), 4.37–4.77 (s, 4.69 and broad peak, 6 H), 7.57 (s, 5 H); nmr ($CDCl_3$) δ 3.60 (s, 4 H), 3.73 (s, 4 H), 3.86 (s, 2 H), 7.31 (s, 5 H).

Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.07; N, 5.62. Found: C, 62.63; H, 5.86; N, 5.38.

Registry No.—1, 18214-57-8; 2 (R = phenyl), 35105-69-2; 2 (R = *p*-methoxyphenyl), 35105-70-5; 2 (R = *p*-chlorophenyl), 32515-66-5; 2 (R = methyl), 35105-72-7; 2 (R = ethyl), 35105-73-8; 2 (R = benzyl), 35105-74-9.

The Preparation of 17β-Hydroxyestra-4,6-dien-3-one and Its Stereospecific β-Face Reduction at Carbons 6 and 7[1]

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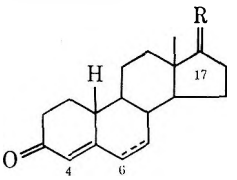
In connection with studies on the metabolism of 19-nor steroids we required estr-4-ene-3,17-dione (**1a**) labeled with a hydrogen isotope in a stable position. We decided to introduce the lable at C-7 by reducing 17β-hydroxyestra-4,6-dien-3-one (**1c**) with tris(triphenylphosphine)rhodium(I) chloride as was done in the steroidal C_{19} series.[2] Usual one-step procedures for the preparation of the diene starting material proved unsatisfactory. Reaction of chloranil (2,3,5,6-tetrachloroquinone) with estr-4-ene-3,17-dione or the corresponding 17β-hydroxy compound in refluxing *tert*-butyl alcohol gave a negligible yield of the desired $\Delta^{4,6}$-3-one compound, although the procedure gives reasonable results with C_{19} steroids.[3,4] Use of DDQ (dichlorodicyanoquinone) and acid catalysis was somewhat better, but was still unsatisfactory. Although the reaction goes to completion in 0.5 hr using a C_{19} compound,[5] only 75% of 17β-hydroxyestr-4-en-3-one (**1b**) was dehydro-



1a, R = O
b, R = 17β-OH, 17α-H
c, Δ^6-**1b**

genated in 1.5 hr and gave product mixtures that required extensive purification. However, we succeeded in obtaining complete reaction of 17β-hydroxyestr-4-en-3-one using chloranil in *tert*-butyl alcohol, ethanol, or methanol by heating to only 50° for 2–3 hr. The products were separated readily from the reagent materials by alumina column chromatography and further purification of the steroid fraction by tlc gave the pure $\Delta^{4,6}$-diene in good yield. A small amount of a mixture also was isolated and was tentatively identified as the phenolic ethyl ethers of estradiol-17β and the corresponding Δ^6 compound. This indicated that some C-1,2 dehydrogenation took place also and suggested that the same conditions, but with DDQ as oxidant, might bring about dehydrogenation at C-1 as occurs with testosterone, rather than at C-6 which occurs with 17β-hydroxyestr-4-en-3-one (19-nortestosterone).[6] How-

(1) (a) An outline of portions of this work has appeared in a communication: H. J. Brodie and C. E. Hay, *Biochem. J.*, **120**, 667 (1970). (b) Supported by U. S. Public Health Service, NIH Grants AM 14625, AM 6894, and GM 16928.

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ever, dehydrogenation under these conditions also occurred preferentially at C-6 as judged by gas–liquid chromatographic analysis of the products.

Preliminary experiments on the reduction of 17β-hydroxyestra-4,6-dien-3-one (**1c**) to 17β-hydroxyestr-4-en-3-one (**1b**) with the rhodium catalyst and hydrogen gas showed that complete reduction in benzene was obtained in 12 hr, while in dioxane only 3 hr was required. Dioxane was used subsequently for reductions with isotopic hydrogen. With deuterium gas, 7 hr was required for uptake of 1 mol equiv and, under the somewhat different conditions of reduction with stoichiometric amounts of tritium gas,[7] 40 hr was required for an apparent 33% uptake of tritium. Material from the latter experiment was chromatographed on silver nitrate impregnated silica gel plates to separate the 17β-hydroxyestr-4-en-3-one (**1b**) from unreacted 6-dehydro material. A portion of the product, after dilution with carrier, was refluxed with base to remove exchangeable tritium at C-6 and tlc of the 17β-hydroxyestrenone-7-^3H product gave a radiochemically pure material as judged by subsequent paper chromatography and crystallization. The 6,7-tritiated material was diluted with ^{14}C-labeled and unlabeled 17β-hydroxyestr-4-en-3-one (**1b**) and was crystallized repeatedly. There was insignificant loss of tritium, showing that reduction with the rhodium catalyst gives material readily obtainable in a radiochemically pure state. This was confirmed by the preparation of the acetate derivative. Equilibration with base caused the $^3H/^{14}C$ ratio to decrease 50% (presumably due to loss of tritium at C-6), and indicates that the label was equally distributed at C-6 and C-7 (Table I). Similar

Table I

Demonstration of Purity of 17β-Hydroxyestrenone-6,7-^3H and -7-^3H after Reverse Isotope Dilution and Crystallization

17β-Hydroxyestrenone-	dpm/μmol		
6,7-^3H,4-^{14}C	$^3H \times 10^{-3}$	^{14}C	Ratio ($^3H/^{14}C$)
$n - 3$	105	2940	35.6
$n - 2$	106	3010	35.1
n	106	2970	35.6
Base refluxed			18.3 (loss, 51%)
17β-Acetate, diluted and crystallized	12.2	352	34.8

results were obtained with deuterium reduction where 92% of the product was dideuterated, accompanied by an insignificant amount of trideuterated material. These are in contrast to results with heterogeneous catalysis where the distribution of the label across the double bond often is not uniform[8] or where an appreciable amount of label may be exchanged into positions α to the double bond.[9,10]

The configuration of the label at C-7 was determined by microbiological hydroxylation at C-7β, a transformation we determined occurs readily with the microorganism *B. malorum* using estrenedione as the substrate.[11] The 7β-labeled materials were converted to estrenedione by Jones oxidation. When estrenedione-7β-^3H, 4-^{14}C and estrenedione-7β-^2H, both diluted with carrier, were incubated separately with the microorganism, the hydrogen isotope label in the 7β-hydroxyestrenedione product decreased by over 97%. Since hydroxylation occurs by direct replacement of hydrogen,[12] the data show that the label at C-7β was almost exclusively β oriented. We[13] and others[14] showed that reduction with the rhodium catalyst occurs by cis addition, from which we may conclude that the label at C-6 also is essentially β oriented. Support for this assignment was obtained from nmr spectra. In estrenedione, no splitting of the 4-H signal is noted, presumably due to a broadening brought about by coupling with both the 6β and 10β hydrogens. In contrast, the 4-H signal is split when the 6β hydrogen is replaced by methyl[15] or hydroxyl,[11] due to coupling with only the C-10β proton. A similar signal for the C-4 proton is noted in the 6,7-dideuterated estrenedione, indicating that the deuterium is at C-6β as expected.

Experimental Section

Infrared spectroscopy was recorded with a Perkin-Elmer Model 137 from KBr disks; ultraviolet spectroscopy was recorded from a Perkin-Elmer Model 202 spectrophotometer, using a methanol solvent. Nmr spectra were obtained on a Varian DA-60 (60 MHz) or Varian HA100-15 (100 MHz) spectrometer; peaks are quoted in δ (parts per million) downfield from tetramethylsilane internal standard. Mass spectrometry was determined with a Varian M-66 spectrometer. Conditions for deuterium analysis have been described.[13] Radioactivity was measured by double-label scintillation counting on a Packard Tri-Carb Model 314 EX as before.[16] Melting points were taken on a Fisher–Johns hot stage. Thin layer chromatography used Merck silica gel PF-254, with preparative layers PR-254 + 366. Gas chromatography was performed with 2% QF-1 on Gas-Chrom Q (Applied Science Laboratories). 17β-Hydroxyestr-4-en-3-one was purchased from Searle Chemical Co.

17β-Hydroxyestra-4,6-dien-3-one (1c). Method A. DDQ and Acid Catalysis.—Dry HCl gas was bubbled for 1.5 hr into a stirred solution of 1 g (3.65 mmol) of 17β-hydroxyestr-4-en-3-one (**1b**) and 944 mg (3.98 mmol) of DDQ in 30 ml of purified dioxane.[17] After filtering and diluting with dichloromethane, the filtrate was washed with potassium carbonate and then with water. Analysis of a sample at this point indicated 75% conversion, as judged by the relative absorbance at 240 and 283 nm. Purification by silica gel column chromatography using ethyl acetate–benzene mixtures followed by preparative layer (5 mm) silica gel chromatography using benzene–acetone (9:1, v/v) and crystallization from benzene–hexane–diethyl ether gave 308 mg of product still contaminated with starting material. Subsequent chromatography on preparative layer silica gel–silver nitrate coated plates (30:5, v/v) in the system cyclohexane–chloroform–acetic acid (48:50:10, v/v) gave the diene free from the less polar Δ4-3 ketone. Elution with chloroform–methanol (9:1, v/v) and washing with 1% aqueous NaCl, 2% $Na_2S_2O_3$, and then water[18] gave pure material used subsequently for reduction with tritium gas: λ_{max} 283 nm [ε 26,219 (lit.[19] 26,920)]; ν 3500 (OH), 1655 (3-one), 1620, 1575 (vinylic H).

Method B. Chloranil. A solution of 5 g of 17β-hydroxyestr-4-en-3-one (**1b**) and 3.35 g of chloranil in 500 ml of ethanol was stirred at 50° for 2 hr and then was evaporated to dryness under

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reduced pressure. The residue was chromatographed on a column containing 400 g of neutral alumina (Woelm) using increasing percentages of ethyl acetate in benzene for development. The fractions containing material absorbing at 283 nm were combined to give a yield of 2.7 g of 17β-hydroxyestra-4,6-diene-3,17-dione (1c) based on uv analysis. This material was purified further by preparative tlc using benzene–acetone (9:1, v/v). The $\Delta^{4,6}$ product and a less polar material were eluted. The mass spectrum of the latter showed highest mass peaks of equal intensity at m/e 298 and 300. The infrared spectrum was similar to that of the 3-methyl ether of estradiol-17β and glc analysis indicated the presence of two compounds of approximately equal amounts. However, these could not be separated on several thin layer and paper systems and the problem was not investigated further. It appeared that they were ethyl ethers of estradiol-17β and the corresponding Δ^6 compound.

Preparation of Catalyst.—A solution of 1 g of rhodium chloride trihydrate and 6 g of triphenylphosphine in 120 ml of ethanol was refluxed for 30 min.[20] Upon cooling, the precipitated tris(triphenylphosphine)rhodium(I) chloride was collected, washed with cold ethanol and ether, and then stored at 4° in a stoppered vial.

Preparation of 6,7-Labeled 17β-Hydroxyestr-4-en-3-one (1b). A. Tritium Labeling.—A solution of 27.2 and 14 mg of tris(triphenylphosphine)rhodium(I) chloride in 2 ml of dioxane was stirred under 1 mol equiv of tritium gas. There was an apparent 3.5-Ci uptake in 7 days. After removal of tritium gas and solvent, the residue was chromatographed on silver nitrate impregnated silica gel plates as detailed above using chloroform–methanol (98:2, v/v). A radioscan of a small sample chromatographed in a similar fashion showed major radioactive peaks at the origin and in the area corresponding in mobility to 17β-hydroxyestr-4-en-3-one (1b). Material in this zone was eluted to give 273 mCi (7.7% yield based on tritium uptake). A portion was diluted with 4-^{14}C-labeled and unlabeled testosterone and was crystallized from benzene–hexane to constant specific activity. This was diluted further with carrier and then was acetylated with 50% acetic anhydride in pyridine at room temperature for 3 hr. After tlc and crystallization, analysis for ^{3}H and ^{14}C again was carried out on weighed crystals. Another portion of the double-labeled testosterone was refluxed with 2% KOH in methanol–water (1:1, v/v), and was analyzed by scintillation counting after purification by tlc as described previously.[4] The results are in Table I.

B. Deuterium Labeling.—A dioxane solution containing 2.5 g of 17β-hydroxyestr-4,6-dien-3-one (1c) and 1.25 g of the rhodium catalyst was stirred in a deuterium atmosphere 16 hr at ambient temperature and pressure. The residue from evaporation was chromatographed on 400 g of silica gel using benzene–ethyl acetate mixtures. 17β-Hydroxyestr-4-en-3-one (1b) came off the column with a 9:1 mixture and was purified further by preparative plate chromatography in benzene–ethyl acetate (9:1 and then 8:2, v/v) to give a material which was homogeneous on gas chromatographic analysis (QF-1): mp 172–173°; λ_{max} 241 nm; mass spectrometric analysis of the molecular ion (d_0 = 274) d_0 (3%), d_1 (4%), d_2 (93%). Oxidation with Jones reagent[21] gave estr-4-ene-3,17-dione: nmr δ 0.94 (s, 3 H, 18-methyl), 5.89 (d, J = 1.7 Hz, 1 H, 4-H).

Preparation of 7-Labeled Estrenedione.—6,7-Labeled 17β-hydroxyestr-4-en-3-one (1b) was refluxed with base and was purified by tlc in benzene–ethyl acetate (3:1, v/v). Oxidation with Jones reagent[21] gave 7-labeled estr-4-ene-3,17-dione (1a). Material which had been tritiated was diluted with estr-4-ene-3,17-dione-4-^{14}C and was crystallized repeatedly. There was an insignificant change in the ^{3}H/^{14}C ratio. Similarly, the deuterated product, after dilution with carrier (1:1), isolation, and crystallization showed one peak on gas chromatography [d_0 (51%), d_1 (3%), d_2 (47%)]. Mass spectrometric analysis of the molecular ion showed only d_0 and d_1 species [d_0 (51%)].

Incubation with *B. malorum*.—Estrenedione-7-^3H,4-^{11}C (^{14}C sp act., 2700 dpm/mg; ^{3}H/^{14}C ratio, 28.6) was incubated with respiring cultures of *B. malorum* for 20 hr and the 7β-hydroxyestrenedione product was isolated as described[11] and the acetate derivative was crystallized from benzene–hexane three times. Loss of tritium as judged by decrease in the ^{3}H/^{14}C ratio was 98%. The product from the 7β-deuterated substrate [d_1 (34%)] was analyzed by mass spectrometry directly as the alcohol, since the highest m/e value for the acetate was 270 ($M^+ - 60$). There was no detectable amount of deuterium on mass spectrometric analysis of the 7β-hydroxy product after three crystallizations from ethyl acetate.

Registry No.—**1a**, 13209-45-5; **1a** (7-T, 4-^{14}C), 31031-84-8; **1b** (6-T, 4-^{14}C), 35140-96-6; **1b** (7-T, 4-^{14}C) 35140-97-7; **1b** (6-D), 35140-98-8; **1b** (7-D), 35140-99-9; **1c**, 14531-84-1.

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The Use of Propionic Acid–Hydrochloric Acid Hydrolysis in Merrifield Solid-Phase Peptide Synthesis

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Merrifield solid-phase peptide synthesis[2-5] procedure is useful for the synthesis of peptides in high yield. However, several cases have been reported of incomplete couplings (for examples see ref 6–10). As work continues with the synthesis of larger peptides and proteins, the need for quick accurate analysis is becoming more important.

During the last 4 years we have been using anaerobic and aerobic propionic acid–hydrochloric acid (HCl) hydrolysis as an analytical tool. Our previous report[11] showed that blocked amino acids could be hydrolyzed easily from the resin used in Merrifield synthesis using this technique. This communication reports the results of 70 peptides hydrolyzed by these procedures, as compared to hydrogen fluoride–anisole cleavage from the resin, followed by constant boiling HCl hydrolysis.[12]

Table I gives the ratios, R, of moles of amino acids obtained from peptide resins hydrolyzed by 1:1 propionic acid–12 *N* HCl at 130° for 2 hr, and the moles of amino acids obtained from peptide resins treated with hydrogen fluoride–anisole[13,14] and then hydrolyzed by

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TABLE I

Amino acid	Side chain blocking group	Number of residues used[15]	$R_{aerobic}$[a]	95% confidence level[b]	R anaerobic[a]	95% confidence level[b]
Alanine		29	1.00	0.023	1.01	0.018
Arginine	Nitro	18	0.99	0.025	0.99	0.015
Aspartic	*O*-Benzyl	2	0.95	0.381	0.96	0.597
Cysteine	Methoxybenzyl	1	0.97		0.98	
Glutamic	*O*-Benzyl	17	0.99	0.015	1.01	0.013
Glycine		46	1.00	0.008	1.00	0.006
Histidine	Dinitrophenyl	7	0.81	0.076	0.98	0.047
Isoleucine		10	0.99	0.045	0.99	0.027
Leucine		14	1.00	0.019	0.99	0.011
Lysine	Carbobenzoxy	9	1.00	0.030	0.98	0.032
Methionine		3	0.94	0.133	0.98	0.120
Phenylalanine		19	1.01	0.017	1.00	0.021
Serine	*O*-Benzyl	54	0.73	0.018	0.85	0.014
Threonine	*O*-Benzyl	10	0.94	0.050	0.95	0.016
Tyrosine	*O*-Benzyl	8	0.80	0.061	0.90	0.045
Valine		13	0.99	0.024	0.99	0.009
Asparagine		15	0.97	0.051	1.01	0.041
Glutamine		15	1.00	0.017	1.00	0.013
Proline		3	0.93	0.013	0.97	0.022

[a] R is the average of the ratios of moles of amino acids obtained from resin peptides hydrolyzed by 1:1 propionic acid–12 *N* HCl at 130° for 2 hr to the moles of amino acids obtained from resin peptides by using hydrogen fluoride–anisole followed by HCl:H_2O hydrolysis at 100° for 24 hr. The ratios used for the calculation of R are normalized to the expected ratios in the synthetic peptide. No assumption about absolute yield of the peptide from the resin is used in the calculation. [b] The error limits for R were calculated using the Student's t distribution of $s = \sqrt{\Sigma(R - R_i)^2/n(n-1)}$ for $n - 1$ degrees of freedom and 95% confidence of the value R, where R is the mean value of the individual value R_i. These error limits, therefore, include errors in the single amino acid analyses,[16] as well as all other random errors in our experiments.

1:1 H_2O:12 *N* HCl at 100° for 24 hr. A wide variety of peptides were hydrolyzed in these experiments.[15] As would be expected, anaerobic propionic–HCl acid hydrolysis gives better results than aerobic hydrolysis. However, the aerobic procedure certainly can be used with excellent results. The only amino acids giving low recoveries by our procedure are serine, tryptophan, tyrosine, and threonine—all of which give low values with 6 *N* HCl hydrolysis. Tryptophan is, of course, completely destroyed by acid hydrolysis. The serine value seems to be quite temperature dependent.

The histidine values reported in Table I are rather uncertain. Several of the peptide resins examined contained incompletely coupled histidine. Some of the peptide molecules on these resins, therefore, contain histidine and some do not. It is known[10] that hydrogen fluoride–anisole will not cleave sterically hindered resin peptide molecules, whereas the propionic acid–HCl procedure cleaves all resin peptide molecules completely. The peptide molecules lacking histidine are expected to be those in the most sterically hindered positions on the resin and, therefore, the inaccuracy in the histidine values is understandable.

Hyrolysis of propionic acid–HCl at 130° facilitates quick, reliable analysis. The peptide doesn't require prior cleavage from the resin, and the preparation for amino acid analysis requires only 2 hr.

(15) Gly-Gln-Tyr-Ser-Trp-Ile-Ile-Asn-Gly-Ile-Glu-Trp-Ala-Ile-Ala-Asn-Asn-Met-Asp-Val; Asn-Ser-His-Gly-Thr-His-Val-Ala-Gly-Thr-Val-Ala-Ala-Leu-Asn-Asn-Ser-Ile-Gly; Ser-Met-Ala-Ser-Pro-His-Val-Ala-Gly-Ala-Ala-Ala-Leu-Ile-Leu-Ser-Lys-His-Pro; Asn-Trp-Thr-Asn-Thr-Gln-Val-Arg-Ser-Ser-Leu-Gln-Asn-Thr-Thr-Thr; Ser-Arg-Phe-Ser-Phe-Gly-Ala-Glu-Gly-Gln-Lys; Ser-Arg-Val-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Lys; Ser-Arg-Phe-Ala-Trp-Gly-Ala-Glu-Gly-Gln-Lys; Ser-Arg-Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Arg; Ser-Arg-Phe-Ser-Trp-Gly-Ala-Glu-Gly-Ile-Lys; Ser-Arg-Phe-Gly-Ser-Trp-Gly-Ala-Glu-Gly-Gln; Ser-Arg-Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Ile; Ser-Arg-Phe-Ser-Trp-Gly-Ala-Ile-Gly-Gln-Lys; Ser-Arg-Phe-Ser-Val-Gly-Ala-Glu-Gly-Gln-Lys; Ser-Arg-Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Lys; Ser-Arg-Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln; Glu-Trp-Ala-Ile-Ala-Asn-Asn-Met-Asp-Val; Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Gly-Arg; Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gly-Gln-Arg; Phe-Ser-Trp-Ala-Ala-Glu-Gly-Gln-Arg; Gly-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Arg; Phe-Ser-Trp-Gly-Ala-Glu-Gly-Glu-Arg; Act-Ser-Trp-Gly-Ala-Glu-Gly-Gln-Arg; Phe-Gly-Trp-Gly-Gly-Gly-Gly-Gln-Arg; Gly-Gly-Trp-Gly-Gly-Gly-Gly-Gln-Arg; Ser-Thr-Gly-Ser-Ser-Ser-Thr-Val-Gly; Ser-Arg-Phe-Ser-Trp-Gly-Ala-Glu-Gly; Phe-Ser-Trp-Gly-Ala-Glu-Gly-Gln; Ser-Arg-Phe-Gly-Ser-Trp-Gly-Ala; Thr-Ser-Ala-Ala-Ser-Ser-Ser-Asn; Arg-Ala-Ser-Phe-Ser-Ser-Val-Gly; Ser-Trp-Gly-Ala-Glu-Gly-Gln-Arg; Gly-Trp-Gly-Gly-Gly-Gly-Gln-Arg; Phe-Ser-Tyr-Ala-Glu-Gly-Gln-Arg; Ser-Arg-Phe-Ser-Trp-Gly-Ala-Glu; Phe-Ser-His-Ala-Glu-Gly-Gln-Arg; Trp-Gly-Ala-Glu-Gly-Gln-Arg; Ser-Arg-Phe-Ser-Trp-Gly-Ala; Pro-Gly-Asn-Lys-Tyr-Gly; Ala-Ala-Ser-Ser-Ser-Asn; Val-Glu-Gly-Leu-Tyr-Leu; Glu-Ala-Leu-Tyr-Leu-Val; Ser-Arg-Phe-Gly-Ser-Trp; Gly-Ala-Gln-His-Gly; Gly-Ala-Gln-Gly-Gly; Gly-Gly-Gln-Lys-Gly; Gly-Lys-Gln-Ile-Gly; Gly-Lys-Gln-Ala-Gly; Gly-Gly-Gln-Ser-Gly; Gly-Ser-Gln-Arg-Gly; Gly-Asp-Gln-Pro-Gly; Gly-Pro-Gln-Asp-Gly; Gly-Gln-Asn-Lys-Gly; Phe-Ser-Trp-Gly-Ala-Glu; Ser-Arg-Phe-Ser-Trp; Phe-Ser-Trp-Gly-Ala; Val-Glu-Gly-Leu-Tyr; Glu-Gly-Leu-Tyr-Leu; Asn-Gln-Ala-Ser-Phe; Gly-Gly-Leu-Tyr; Ala-Asp-Cys-Ser; Gly-Leu-Tyr; Leu-Gly-Glu; His-Gly; His-Glu; Pro-Glu; Tyr-His; His-Arg; Glu-His; Glu-Pro; Glu-Gly.

Experimental Section

The peptides were synthesized on chloromethylated copolystyrene crosslinked with 2% divinyl benzene resin by the procedure of Merrifield,[2-4] with occasional small modifications.[6] The resin was substituted with 0.2–0.5 mmol/g of the carboxyl terminal amino acid. The α amino groups of the amino acids were blocked by the *tert*-butoxycarboxyl groups, and the side chain groups were blocked as shown in Table I. One milliliter of propionic acid and 1 ml of 12 *N* HCl were placed in a small test tube with 1–3 μmol of the resin peptide, and the test tube was sealed. For anaerobic propionic–HCl acid hydrolysis, the acid mixture was frozen and thawed under vacuum three times, and then sealed under vacuum. The tube was later placed in either a heating block or a thermostated oil bath for 2 hr at 130°. The tubes were cooled and opened, and the samples were dried by rotary evaporation in 100-ml round-bottomed flasks at 40°. Amino acid analyses were then performed.[16] In separate experiments the same peptides were removed from the resin using anhydrous hydrogen fluoride and anisole.[13,14] After freeze drying, the peptides were hydrolyzed anaerobically with constant boiling HCl and analyzed. For aerobic hydrolysis the experimental procedure was the same, except that the tubes were sealed in air without exposure to vacuum.

(16) Amino acid analyses were performed by Mrs. R. M. Smith; see K. Dus, S. Lindroth, R. Pabst, and R. M. Smith, *Anal. Biochem.*, **14**, 41 (1966).

Registry No.—Propionic acid, 79-09-4; hydrochloric acid, 7647-01-0.

Acknowledgment.—This work was supported by NSF Grant BG-7033X and NIH Grant HD-01262 to Professor M. D. Kamen, NIH Grant GM-10928 to Professor J. Kraut, and NIH Grant AM 14879-02.

The Origin of the $[M - 56]\cdot^+$ Ion in the Mass Spectra of Trimethylsilyl Ethers of Dehydroepiandrosterone and Related Compounds

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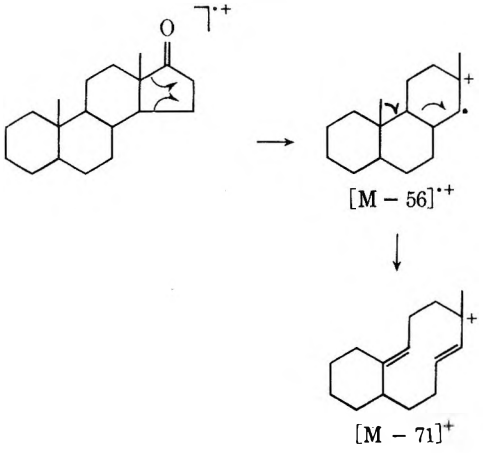
The mass spectra of many 16- and 17-keto steroids contain ions $[M - 56]\cdot^+$, the formation of which has been ascribed to cleavages of the bonds C-13/17 and C-14/15.[1] These ions are often accompanied by ions $[M - 71]^+$ formed by subsequent loss of a methyl radical[2] (Scheme I). During a survey of the mass

SCHEME I

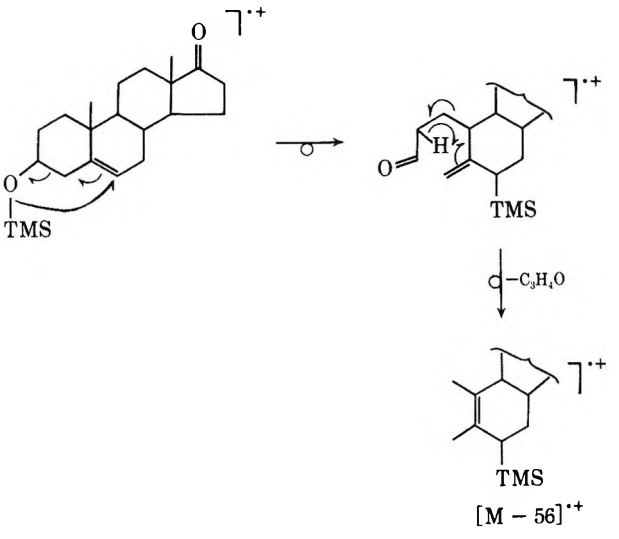


spectra of trimethylsilyl (TMS) ethers of a number of Δ^5-3β-hydroxy steroids it was found that $[M - 56]\cdot^+$ ions, unaccompanied by $[M - 71]^+$ ions, were present in the spectra of 16 and 17 ketones. It has been demonstrated that these $[M - 56]\cdot^+$ ions are formed by electron-impact-induced rearrangement, and not by D-ring cleavage.

The first indication of a duality of mechanisms for the formation of such ions was the presence of $[M - 56]\cdot^+$ ions in the spectra of the TMS ethers of *15,15,-17,17-d_4*-3β-hydroxyandrost-5-en-16-one, *16,16-d_2*-3β-hydroxyandrost-5-en-17-one, and *9,12,12,16,16-d_5*-3β-hydroxyandrost-5-ene-11,17-dione.[3] When the 17-oxo group of the TMS ether of 3β-hydroxyandrost-5-en-17-one (dehydroepiandrostereone, DHEA) was selectively replaced[4] by ^{18}O, this atom was found to be retained in the $[M - 56]\cdot^+$ ion. All nine deuterium atoms of the d_9-TMS ether[5] of DHEA were also retained in the $[M - 56]\cdot^+$ ion.

High resolution mass measurement, carried out on the spectrum of the TMS ether of DHEA, showed that the particle eliminated had the composition C_3H_4O (found for ion of nominal *m/e* 304, 304.2198; calcd for $C_{19}H_{32}OSi$, 304.2222). The oxygen atom must, therefore, originate from the 3 position, and it seems likely that the $[M - 56]\cdot^+$ ions of these steroids are formed by a mechanism similar to that proposed for the formation of the $[M - 129]^+$ ion, but with initial transfer of the TMS group. This may proceed *via* a double (silyl and conventional) McLafferty-type rearrangement, as in Scheme II. Because of the relatively large separation

SCHEME II



of C-3 and C-6, the silyl rearrangement is presumed to take place in a stepwise manner.

It should be noted that the TMS ethers of the saturated steroid 3β-hydroxy-5α-androstan-17-one and its 16,16-d_2 analog give rise, respectively, to ions $[M - 56]\cdot^+$ and $[M - 58]\cdot^+$, indicating that such ions are formed by D-ring cleavage as illustrated in Scheme I.[6]

(1) G. von Unruh and G. Spiteller, *Tetrahedron*, **26**, 3289 (1970), and references cited therein.

(2) L. Tökés, R. T. LaLonde, and C. Djerassi, *J. Org. Chem.*, **32**, 1012 (1967).

(3) These deuterated analogs were prepared by *in transitu* labeling during GC-MS: G. M. Anthony and C. J. W. Brooks, *Chem. Commun.*, 200 (1970).

(4) A. M. Lawson, F. A. J. M. Leemans, and J. A. McCloskey, *Steroids*, **14**, 603 (1969).

(5) J. A. McCloskey, R. N. Stillwell, and A. M. Lawson, *Anal. Chem.*, **40**, 233 (1968).

(6) This work was supported by grants from the Medical Research Council (to C. J. W. B.), Science Research Council (B/SR/2398 to C. J. W. B. and G. Eglinton), NIH (GM-13901), and the Robert A. Welch Foundation (Q-125).

An Unexpected Conformational Preference in a Sugar Derivative

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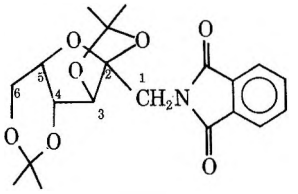
This paper presents a suggestion for the conformation of 1-phthalimido-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (**1**) derived from nmr studies.

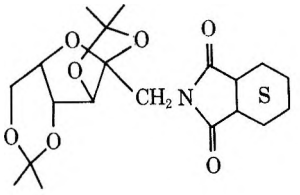


1

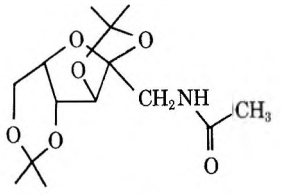
Specifically, the C_2–O bond of the isopropylidene ring is predominantly transcoplanar with the C_1–N bond in the favored rotamer.

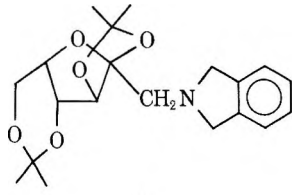
Phthalimide **1** was prepared from 1-*O*-*p*-toluenesulfonyl-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose. Chemical proof for the structure was obtained by conversion to the corresponding known primary amine.[2]

The nmr spectrum of phthalimide **1** reveals one methyl group resonating at unusually high field (Table I, **1** *vs.* **2**–**4**). Furthermore, the position of this methyl



3





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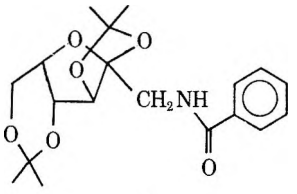


5

peak of **1** in DMSO-d_6 solution does not change upon 32-fold dilution, but moved downfield from δ 0.67 at 27° to 0.77 at 100° while no change occurred for other methyl bands. Thus, one methyl group is shielded intramolecularly by the phthalimide moiety. Shielding by an anisotropic benzene ring is well documented[3] and this effect has been used to determine stereochemistry and conformation[4] of aromatic compounds.

(1) University of Arizona, Tucson, Arizona.

(2) K. Tokuyama, *Bull. Chem. Soc. Jap.*, **37**, 1133 (1964). This amine was also prepared by reduction of the azide obtained from sodium azide and the same tosylate.

(3) J. A. Pople, *J. Chem. Phys.*, **24**, 1111 (1956); C. E. Johnson, Jr., and F. A. Bovey, *ibid.*, **29**, 1012 (1958).

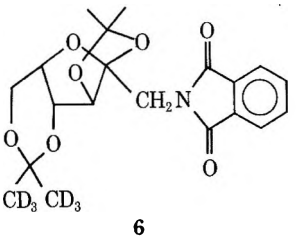
(4) J. F. Sebastian and M. Ti, *J. Org. Chem.*, **35**, 2644 (1970); N. Pravdić and D. Keglević, *Carbohyd. Res.*, **12**, 193 (1970).

TABLE I

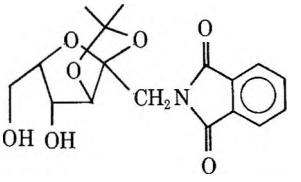
NMR CHEMICAL SHIFTS

Compd	Solvent	δ, Methyl groups			
1	DMSO-d_6	0.65	1.21	1.29	1.41
	CD_3OD	0.67	1.28	1.32	1.44
	Acetone-d_6	0.72	1.25	1.35	1.41
	$CDCl_3$	0.82	1.29	1.33	1.48
	C_6D_6	0.82	0.92	1.20	1.38
	C_6D_5N	0.91	1.29	1.31	1.51
2	$CDCl_3$	1.27	1.35	1.39	1.44
3	$CDCl_3$	1.35	1.40	1.43	1.46
4	DMSO-d_6	1.25	1.34	1.39	1.42
	$CDCl_3$	1.38	1.43	1.43	1.50
5	DMSO-d_6	1.06	1.19	1.32	1.36
	$CDCl_3$	1.03	1.38	1.42	1.50
6	DMSO-d_6		1.20		1.38
	Acetone-d_6		1.25		1.41
	C_6D_6			1.17	1.37
	C_6D_5N		1.27		1.48

When a catalytic amount of perchloric acid was added to a solution of **1** in acetone-d_6 and the nmr spectrum was measured at various times, the high-field methyl peak as well as one other methyl band disappeared rapidly, and the nmr and mass spectra of the deuterated compound are consistent with its formulation as 1-phthalimido-1-deoxy-2,3-mono-*O*-isopropylidene-4,6-mono-*O*-hexadeuterioisopropylidene-α-L-sorbofuranose (**6**).



6



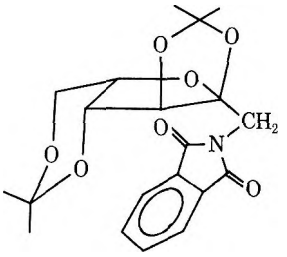
7

That exchange occurred in the 4,6 position was confirmed by selective acid-catalyzed hydrolysis of **6** to give a monoisopropylidene derivative **7** free of deuterium and identical with that obtained by partial hydrolysis of **1**. The nmr spectrum of **7** in DMSO-d_6 displays a doublet and a triplet which disappear on addition of deuterium oxide. This confirms the presence[5] of a primary and a secondary alcohol, as in structure **7**.

Consideration of molecular models of **1** reveals that only one methyl group in the 4,6-isopropylidene bridge can be shielded by the aromatic ring of the phthalimide moiety. This shielding may be achieved in the conformation depicted below. The reason for the importance of this conformation merits comment.

The most impressive conformational changes in phthalimide **1** are brought about by ring flip of the 1,3-dioxane ring and rotation about the C_1–C_2 and C_1–N

(5) D. E. Greer and M. M. Mocek, *J. Chem. Educ.*, **40**, 358 (1963).



single bonds. The 1,3-dioxane ring in the conformation shown above is in the energetically more favorable chair form.[6] Of the three staggered conformations about C_1–C_2, only the one shown should result in shielding[3,4,7] of a methyl group of the 4,6-isopropylidene group. To achieve the amount of shielding observed, phthalimide **1** must spend a considerable portion of its time in the conformation shown above. Dreiding molecular models reveal that the center of the methyl group is approximately 4 Å from the center of the benzene ring, and from this is predicted[3] a shielding of 0.8 ppm. The experimental values (0.5 to 0.6 ppm, compound **1** *vs.* 2, **3**, and **4** in Table I) were in good agreement. The other conformers might be destabilized by steric or dipolar interactions of the carbonyl groups or the conformer shown might be stabilized by some interaction. Since none of the methyl groups in isoindoline **4** resonate at high field, the first explanation may not apply. Although it is possible that the nitrogen is tetrahedral in **4** (sp^3 hybridized) but trigonal[8] in **1** (sp^2), the methylene protons of **4** are magnetically equivalent, suggesting trigonal hybridization. Thus, an intriguing possibility is that some interaction stabilizes the conformation shown. The oxygens of the 1,3-dioxane ring are very close to the carbonyl carbons of the phthalimide moiety. This may result in favorable intramolecular interaction, *e.g.*, dipolar interaction. A similar explanation was offered to explain an unusual conformational preference in substituted aziridines.[3] Such an interaction is not possible with isoindoline **4**, and this may account for the lack of substantial shielding of a methyl group in this compound.

Interestingly, one methyl group in benzamide **5** appears to absorb at slightly higher field than expected. Perhaps, effects similar to that proposed for phthalimide **1** are operative here, but hydrogen bonding, which is possible in benzamide **5** but not in phthalimide **1**, is likely to be of much importance.[9]

Experimental Section

Melting points were taken with a Thomas-Hoover capillary melting point apparatus and are not corrected. The ir spectra were recorded on a Perkin-Elmer 621 spectrophotometer, the uv spectra on a Cary 15 spectrometer, the nmr spectra on a Varian HA-100 spectrometer, and the mass spectra on a CEC 21-110 spectrometer.

1-Phthalimido-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (1).—1-*O*-*p*-Toluenesulfonyl-2,3:4,5-di-*O*-isopropylidene-α-L-sorbofuranose[10] (1.64 g, 4.00 mmol) and potassium phthalimide (0.833 g, 4.50 mmol) in *N*,*N*-dimethylformamide (35 ml) were heated at reflux for 48 hr[11] and cooled, the solvent was removed *in vacuo*, and the residue was diluted with water (30 ml) and extracted with six 50-ml portions of ether. The ethereal extract was dried (anhydrous Na_2SO_4), filtered, concentrated to dryness, chromatographed on silica gel, and recrystallized from ether–pentane to give 0.683 g (43%) of crystalline phthalimide **1**: mp 148–150°, mp of analytical sample 152.5–153°; $[\alpha]^{25}D$ −21.7° (*c* 0.96, $CHCl_3$); ir (KBr) 2990, 2910, 1770, 1720, 1400 cm^{-1}; uv max (C_2H_5OH) 219.5 mμ (ε 41,300), 233 (12,500), 241.5 (9150), 293.5 (1780).

Anal. Calcd for $C_{20}H_{23}NO_7$: C, 61.69; H, 5.95; N, 3.60. Found: C, 61.44; H, 5.88; N, 3.68.

Hyrazinolysis.[12]—A solution of **1** (712 mg, 1.83 mmol), 85% hydrazine hydrate (1.4 ml), and 95% ethanol (5.5 ml) was heated at reflux for 2 hr and cooled. A solution of sodium hydroxide (600 mg) in water (3.5 ml) was added, and the reaction mixture was extracted with four 20-ml portions of ether. The ethereal extract was washed with four 2-ml portions of water, dried (anhydrous K_2CO_3), concentrated to dryness, and chromatographed on silica gel to give 206 mg (43%) of a solid which was identical with authentic 1-amino-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose[2] by mixture melting point, tlc, ir, and nmr spectra.

Hexahydrophthalimide 2 was prepared according to general procedure[13] as colorless prisms: mp 52–54° from pentane; nmr ($CDCl_3$) δ 1.30–2.00 (m, 8, 4 CH_2), 2.97 (m, 2, CHCH), 4.00 (s, 5, CH + 2 CH_2), 4.24, 4.60 (s, 2, 2 CH).

Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.52; H, 7.47; N, 3.58.

Acetamide 3.—To a cooled solution of 1-amino-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (207 mg, 0.800 mmol) in pyridine (1.25 ml) was added acetic anhydride (1.50 ml). The solution was stirred at room temperature for 24 hr, concentrated to dryness, and crystallized from ether to give crystalline acetamide **3** (220 mg, 91%): mp 146–148°; $[\alpha]^{25}D$ −62.2° (*c* 2.27, C_2H_5OH); mass spectrum *m/e* 301; ir ($CHCl_3$) 3445, 2995, 1660, 1508, 1380 cm^{-1}; nmr ($CDCl_3$) δ 1.97 (s, 3, CH_3CO), 6.09 (broad, 1, NH).

Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69. Found: C, 56.08; H, 7.83.

Isoindoline 4 was prepared according to general procedure[14] as a colorless oil: nmr ($CDCl_3$) δ 3.22 (s, 2, CH_2N), 4.00–4.13 (m, 3, CH + CH_2), 4.15 (s, 4, CH_2NCH_2), 4.28 (d, 1, J = 2.5 Hz, CH), 4.47 (s, 1, CH).

Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.39; H, 7.60; N, 3.87.

Benzamide 5.—To a solution of 1-amino-1-deoxy-2,3:4,6-di-*O*-isopropylidene-α-L-sorbofuranose (129 mg, 0.50 mmol) in pyridine (0.2 ml) at 0° was added dropwise with stirring a solution of benzoyl chloride (81.3 mg, 0.58 mmol) in pyridine (0.4 ml) and the mixture was allowed to warm to room temperature during 2 hr. After removal of pyridine by evaporation under reduced pressure, aqueous copper sulfate and chloroform were added. The chloroform layer was washed with aqueous copper sulfate and water, dried (anhydrous Na_2SO_4), concentrated to dryness (205 mg), and chromatographed on silica gel plates. Elution with 9:1 (v/v) chloroform–methanol gave an oil: yield 184 mg; ir ($CHCl_3$) 3455, 1670 cm^{-1}; nmr ($CDCl_3$) δ 3.70–4.20 (m, 5, CH + 2 CH_2), 4.25 (d, 1, J = 2 Hz, CH), 4.49 (s, 1, CH), 6.53 (broad, 1, NH), 7.43 (m, 3, aromatic), 7.89 (m, 2, aromatic).

Phthalimide 6 from 1 by Ketone Exchange.—To phthalimide **1** (40 mg) in acetone-d_6 (0.4 ml) was added perchloric acid (71–72%, 0.5 ml) and the nmr spectra were taken after 20 min, 3.7 hr, and 24 hr.

(6) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **90**, 3444 (1968).

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Time	δ, Methyl groups			
0 min	0.72	1.25	1.35	1.41
20 min	0.71[a]	1.22	1.32[a]	1.40
3.7 hr		1.21		1.41
24 hr		1.22		1.40

[a] Peak height is *ca.* 20% that of sample before addition of $HClO_4$.

The above sample was poured into water and extracted with chloroform. The extracts were dried (anhydrous Na_2SO_4), concentrated, and recrystallized from ether to give **6**: mp 149–152°; nmr (acetone-d_6) δ 3.70–4.50 (m, 6), 4.76 (s, 1), 7.88 (s, 4); mass spectrum *m/e* 395.

1-Phthalimido-1-deoxy-2,3-*O*-isopropylidene-α-L-sorbofuranose (7) by Hydrolysis of 6.—A solution of 6 (46 mg, 0.12 mmol), glacial acetic acid (1.0 ml), and water (0.5 ml) was stirred at room temperature for 86 hr. Pyridine was then added and the solution was concentrated to dryness and extracted with ether. The extract was dried (anhydrous Na_2SO_4), filtered, and concentrated to dryness to give **7** as an oil which was crystallized from benzene to give 23 mg (55%) of **7**, mp and mmp with later sample 175–178°, ir and nmr spectra identical within experimental error to data below.

By Hydrolysis of 1.—Phthalimide **1** (500 mg, 1.29 mmol), hydrolyzed and worked up in the same way as **6**, afforded from benzene crystals of **7**: mp 178–181°; $[\alpha]^{25}D$ −4.5° (*c* 1.05, C_2H_5OH); ir ($CHCl_3$) 3455, 1777, 1720, 1714, 1425, 1398 cm^{-1}; uv max (C_2H_5OH) 220.5 mμ (ε 46,000), 234 (14,100 infl), 242 (10,000), 293.5 (2200); nmr (DMSO-d_6) δ 1.10, 1.36 (s, 6, 2 CH_3), 3.40–4.20 (m, 5, CH + CH_2), 4.46 (s, 1, CH), 4.44 (t, 1, *J* = 6 Hz, exchanged by D_2O addition, CH_2OH), 5.01 (d, 1, *J* = 4.5 Hz, exchanged by D_2O addition, CHO**H**), 7.85 (s, 4, aromatic).

Anal. Calcd for $C_{17}H_{19}NO_7$: C, 58.45; H, 5.48; N, 4.01. Found: C, 58.62; H, 5.47; N, 4.03.

Registry No.—**1**, 35170-82-2; **2**, 35170-83-3; **3**, 35170-84-4; **4**, 35192-04-2; **5**, 35170-85-5; **6**, 35170-86-6; **7**, 35170-87-7.

Acknowledgment.—We thank Dr. E. P. Oliveto and Dr. P. Rosen for encouragement and helpful discussions, and Mr. S. Kwoh and Mr. A. Sheffron for assistance in preparing some of the compounds. We also thank Mr. S. Traiman, Dr. V. Toome, and Dr. W. Benz for the ir, uv, and mass spectra, respectively, and Dr. F. Scheidl for optical rotation data and microanalyses.

Preferential Cleavage of an Aromatic Methylenedioxy Group in the Presence of Methoxyls with Boron Trichloride

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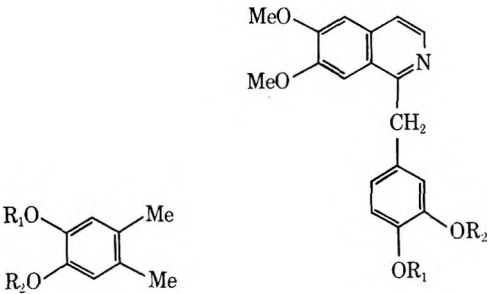
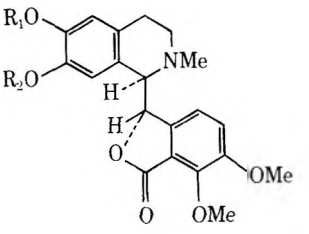
In connection with our studies on the transformation of phthalideisoquinolines into rheadans,[1] the methylenedioxy dimethoxy-substituted alkaloid (−)-β-hydrastine (**3a**) was deetherified with boron tribromide to the tetraphenol and methylated to the tetramethoxy phthalide (−)-cordrastine II[2] (**3c**). We now report a novel and more facile synthesis of **3c** based on the preferential O-demethylenation of **3a** with boron trichloride[3] followed by methylation of the resulting diphenol **3b**.





3a–c

a, $R_1 + R_2 = -CH_2-$
b, $R_1 = R_2 = H$
c, $R_1 = R_2 = Me$

The type and extent of deetherification of model compounds treated with boron trichloride in methylene chloride was influenced by the ratio of substrate to reagent as well as the reaction temperature and time. By proper selection of conditions, cleavage of a methylenedioxy group in preference to aromatic methoxyls could be achieved. For example, treatment of 4,5-methylenedioxy-*o*-xylene (**1a**)[4] at room temperature with either 1 or 2 equiv of boron trichloride for 64 and 3 hr, respectively, gave 4,5-dimethylcatechol (**1b**)[5] in 80% yield while cleavage of 4,5-dimethoxy-*o*-xylene (**1c**)[5] required either higher temperatures or longer reaction times to effect ether cleavage. Similarly, while both the methylenedioxy-substituted isoquinoline **2a**[6] and its methoxy analog papaverine (**2c**) were converted by treatment with 2 molar equiv of the reagent for 5 hr at room temperature into a mixture of phenolic materials, only **2a** was cleanly cleaved at 4° to yield 78% 3′,4′-O-demethylpapaverine (**2b**)[7] while **2c** was recovered unchanged.

To further illustrate the synthetic applicability of preferential *O*-demethylenation, commercially available (−)-β-hydrastine (**3a**) was treated with 2 mol of boron trichloride in methylene chloride at room temperature for 6 hr to afford 81% the diphenol **3b**. Reaction of **3b** with diazomethane provided the tetra-

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(2) S. Teitel, J. O'Brien, and A. Brossi, *J. Org. Chem.*, **37**, 1879 (1972).

(3) Boron trichloride has been used in the selective scission of cyclic acetals [T. G. Bonner and N. M. Saville, *J. Chem. Soc.*, 2851 (1960)] and in the preferential O-demethylenation of certain podophyllotoxins [E. Schreier, *Helv. Chim. Acta*, **47**, 1529 (1964); H. MacLean and B. F. MacDonald, *Can. J. Chem.*, **47**, 457 (1969)]. Its selective action parallels that of aluminum bromide in nitrobenzene [E. Mosettig and A. Burger, *J. Amer. Chem. Soc.*, **52**, 2988 (1930)].

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(7) A. Brossi and S. Teitel, *J. Org. Chem.*, **35**, 1684 (1970).

methoxy phthalide isoquinoline (−)-cordrastine II[2] (3c). In contrast, boron tribromide under similar reaction conditions was not selective and cleaved 3a to give mainly the corresponding tetraphenol.[2] This may be related to the stronger nucleophilic character of the bromide ion.

The above transformations demonstrate that boron trichloride can be used to selectively cleave a methylenedioxy group in methoxy-substituted aromatic compounds.

Experimental Section[8]

4,5-Dimethylcatechol (1b).—To 378 mg (2.5 mmol) of 4,5-methylenedioxy-*o*-xylene[4] (1a) dissolved in 70 ml of methylene chloride was added at room temperature 5 ml of a methylene chloride solution containing 585 mg (5 mmol) of boron trichloride. The solution was stored at ambient temperature for 3 hr; 5 ml of methanol was added and evaporated. The residue was crystallized from a mixture of benzene and petroleum ether to give 300 mg (80%) of 1b, mp 89–91°, identical in mixture melting point and tlc with authentic 4,5-dimethylcatechol.[5] Under these reaction conditions 4,5-dimethoxy-*o*-xylene[5] (1c) was recovered unchanged.

6,7-Dimethoxy-1-(3,4-dihydroxybenzyl)isoquinoline Hydrochloride (2b HCl).—To a solution of 323 mg (1 mmol) of 6,7-dimethoxy-1-(3,4-methylenedioxybenzyl)isoquinoline[6] (2a) in 15 ml of methylene chloride at 4° was added 7.1 ml of a methylene chloride solution containing 234 mg (2 mmol) of boron trichloride. The solution was stored at 4° for 5 hr; 5 ml of methanol was added and evaporated. The residue was dissolved in 30 ml of water and rendered neutral with saturated sodium bicarbonate; the resulting precipitate was collected and dissolved in ethanolic hydrogen chloride. The solution was evaporated and the residue crystallized from ethanol to give 275 mg (78%) of 2b HCl, mp 232–233°, identical in mixture melting point, tlc, and nmr with authentic 2b HCl.[7] Under these reaction conditions, papaverine (2c) was recovered unchanged.

(+)-1(*R*)-[6,7-Dimethoxy-3(*S*)-phthalidyl]-6,7-dihydroxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3b).—To a solution of 6 g (14.3 mmol) of (−)-β-hydrastine hydrochloride (3a HCl) in 350 ml of methylene chloride at room temperature was added a solution of 3.34 g (28.6 mmol) of boron trichloride in 50 ml of methylene chloride. The resulting turbid mixture was stirred at room temperature for 6 hr; 50 ml of methanol was added over 10 min and then evaporated. The residue was dissolved in 150 ml of 1 *N* hydrochloric acid, washed with chloroform, heated for 20 min at 95°, cooled, and then neutralized with saturated sodium bicarbonate. The resulting precipitate was collected, washed with water, dried, and crystallized from chloroform to give 4.3 g (81%) of 3b: mp 199–200°; nmr δ 2.45 (s, 3, NCH_3), 1.90–3.20 (m, 4, CH_2CH_2), 3.83, 3.86 (2 s, 6, 2 OCH_3), 3.94 (d, 1, J = 4 Hz, CHN), 5.54 (d, 1, J = 4 Hz, CHO), 6.35, 7.23 (2 d, 2, J_{ortho} = 8 Hz, aromatic), 6.35, 6.45 (2 s, 2, aromatic); uv max 218 nm (ε 29,000) (infl), 235 (12,500) (infl), 293 (6400), 313 (4500); $[\alpha]^{25}D$ +218° (*c* 1, 1 *N* HCl); ORD (*c* 0.371, MeOH) $[\phi]_{600}$ +10°, $[\phi]_{589}$ +12°, $[\phi]_{331}$ −4250° (tr), $[\phi]_{315}$ 0, $[\phi]_{295}$ +6000° (tr), $[\phi]_{232}$ +40,000° (pk), $[\phi]_{227}$ 0, $[\phi]_{209}$ −232,000° (tr); CD (*c* 0.01 *M*, MeOH) $[\theta]_{360}$ 0, $[\theta]_{315}$ −8400, $[\theta]_{294}$ −5100, $[\theta]_{278}$ −6000, $[\theta]_{255}$ 0, $[\theta]_{220}$ +106,000, $[\theta]_{210}$ 0, $[\theta]_{204}$ −145,000.

Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.43; H, 5.64; N, 3.77.

(−)-1(*R*)-[6,7-Dimethoxy-3(*S*)-phthalidyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline Hydrobromide [(−)-Cordrastine II HBr] (3c HBr).—A mixture of 1 g (2.67 mmol) of 3b in 20 ml of methanol was treated with an excess of diazomethane in ether; volatiles were removed at 40° in a stream of nitrogen; the residue was suspended in water, extracted with ethyl acetate and evaporated. The residue was dissolved in ethanolic hydrogen bromide, evaporated, and crystallized from ethanol to give 1.1 g (86%) of 3c HBr, mp 212–213°, $[\alpha]^{25}D$ + 188° (*c* 1, MeOH), identical in mixture melting point, nmr, and optical rotation with (−)-cordrastine II hydrobromide previously described.[2]

Registry No.—3b, 35337-18-9; 3c HBr, 34417-89-5; boron trichloride, 10294-34-5.

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(8) Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Nmr spectra were obtained in DMSO-d_6 on a Varian Ha-100 instrument. Uv spectra were measured in ethanol with a Cary recording spectrophotometer Model 14M and optical rotations with a Perkin-Elmer instrument. Rotatory dispersion curves were determined at 23° with a Durrum–Jasco spectrophotometer Model 5 using 1-cm, 0.1-cm, or 0.1-mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. Reported yields are of isolated products homogeneous to tlc.

Studies on the Reaction of Phenylmagnesium Bromide with Acetonitrile[1]

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Phenylmagnesium bromide is reported to react with acetonitrile to give poor yields of acetophenone except in cases where an excess of the latter reagent is employed.[3,4] It has been proposed that the acetonitrile molecule undergoes tautomerization and, in this form, can be thought of as a "pseudo-acid" which, when treated with the Grignard reagent, gives rise to considerable amounts of benzene.[5]

$$C_6H_5MgBr + CH_3C{\equiv}N \longrightarrow$$
$$C_6H_6 + BrMgCH_2CN \rightleftharpoons CH_2{=}C{=}NMgBr$$

The idea of hydrogen abstraction by the Grignard reagent is supported by the fact that benzonitrile, which has no active hydrogen atom, generally gives good yields of ketone with the Grignard reagent. Propionitrile, which has a less labile hydrogen than acetonitrile, is reported to give a good yield of ketone.[6] Pivalonitrile and trifluoroacetonitrile also give excellent yields of *tert*-butyl phenyl ketone and α,α,α-trifluoroacetophenone, as are shown in Table I.

We became interested in a more detailed study of the reaction of acetonitrile with the Grignard reagent since the low yield of acetophenone suggests that a much greater "active" hydrogen effect is present than when propionitrile is used.

The first attempts were directed toward establishing the true source of benzene produced in the reaction of acetonitrile and phenylmagnesium bromide. The technique of isotopic labeling was used for this purpose. Trideuterioacetonitrile was substituted for acetonitrile, and mass spectrographic analysis of the benzene produced in the reaction with phenylmagnesium bromide

(1) This work was partially supported by a grant from the Committee on Institutional Studies and Research, Murray State University, Murray, Kentucky.

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(3) C. R. Hauser and W. J. Humphlett, *J. Org. Chem.*, **15**, 359 (1950).

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(6) C. R. Hauser, W. J. Humphlett, and M. J. Weiss, *J. Amer. Chem. Soc.*, **70**, 426 (1948).

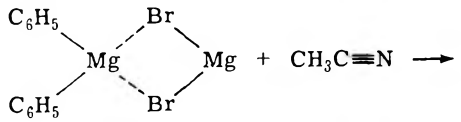
TABLE I
KETONES PREPARED FROM REACTION OF GRIGNARD REAGENT WITH NITRILES

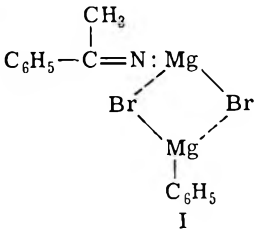
Nitrile	Grignard reagent	Ketone	% yield[a]	Reported yield[b]
Acetonitrile	Phenylmagnesium bromide	Acetophenone	42 (68)[c]	37–45 (70)[d]
Acetonitrile	3,5-Dibromophenylmagnesium bromide	3,5-Dibromoacetophenone	1 (52)[e]	
Acetonitrile	*n*-Pentylmagnesium bromide	2-Heptanone	44[c]	14
Acetonitrile	Benzylmagnesium chloride	Methylbenzyl ketone	34[c]	16
Acetonitrile	*n*-Octylmagnesium bromide	2-Decanone	49[c]	
Propionitrile	Phenylmagnesium bromide	Propiophenone	94	80–91
Pivalonitrile	Phenylmagnesium bromide	Pivalophenone	90	72
Trifluoroacetonitrile	Phenylmagnesium bromide	α,α,α-Trifluoroacetophenone	82	
Trideuterioacetonitrile	Phenylmagnesium bromide	α,α,α-Trideuterioacetophenone	65	

[a] Yield based on product isolated. Diethyl ether used as solvent except where noted. [b] M. S. Karasch and O. Reinmuth, "Grignard Reactions of Non-Metallic Substances," Prentice-Hall, New York, N. Y., 1954, p 793. [c] Benzene used as solvent. [d] Higher yield of 70% obtained when Grignard reagent used in large excess. [e] Benzene used as solvent and trimethyl orthoacetate used instead of acetonitrile.

showed 46.8% monodeuteriobenzene. This indicated that 53.2% benzene was being derived from a source other than the "active" hydrogen atoms of acetonitrile. A significant isotope effect was observed because an increase in ketone yield from 42% to 65% was found.

If one assumes that the Grignard reagent is dimeric in ether solution, a complex such as I, in all probability,





I

would be formed. Hydrolysis of I should also be a source of benzene. In the first hydrolysis experiment, deuterium oxide was added to react with unreacted Grignard reagent in the complex, followed by addition of hydrochloric acid to complete the hydrolysis. Analysis of the benzene produced gave only 2.4% monodeuteriobenzene. This observation was attributed to the fact that I is ether insoluble and forms a "ball-shaped" conglomerate, allowing only the outer surface to come in contact with the D_2O.

In order that unreacted phenylmagnesium bromide in I be permitted to react completely with a labeled compound such as D_2O, complete hydrolysis would be essential. For this purpose, deuterium chloride in deuterium oxide was used as a means for hydrolysis of I. Mass spectrometric analysis of the benzene fraction gave 51.8% monodeuteriobenzene.

It is of interest to note that a change in solvent from ether to benzene gives an increase in yield from 42% to ~70% acetophenone.

Experimental Section[7]

General Procedure for Synthesis of Ketones.—The appropriate Grignard reagent was prepared from reaction of the halide (0.1 mol) with magnesium (0.1 g-atom) in anhydrous diethyl ether (100 ml). Precautions were taken to exclude moisture from the reaction flasks. In some cases, benzene was added dropwise to the freshly prepared Grignard reagent, and the ether removed by distillation prior to addition of the nitrile. The nitrile (0.1 mol) was added dropwise over a period of approximately 15 min. Most of the reactions are quite exothermic. After continuous stirring and refluxing for 2 hr, the mixture was hydrolyzed with hydrochloric acid and ice. Extraction with ether or benzene, followed by vacuum distillation, gave the ketone.

Labeling Experiments.—Substitution of trideuteriacetonitrile for acetonitrile yielded benzene (25 g, 32%) containing 46.8% monodeuteriobenzene. Mass spectrometric analysis of the resulting ketone showed no deuterium atoms in the $C_6H_5CO^+$ and $C_6H_5^+$ ions, but that the labeling is limited to the methyl group. Overall, 80.5% of the methyl hydrogens are deuterium atoms, which is very close to the theoretical, 83%.

Benzene (26 g, 33%) obtained as a product from reaction of acetonitrile and phenylmagnesium bromide followed by attempted hydrolysis with D_2O showed only 2.4% labeling. Benzene (25 g, 32%) obtained from the same reactants, but followed by hydrolysis with 20% DCl in D_2O, showed 51.8% labeling.

Registry No.—Phenylmagnesium bromide, 100-58-3; acetonitrile, 75-05-8; acetophenone, 98-86-2; 3,5-dibromoacetophenone, 14401-73-1; 2-heptanone, 110-43-0; methyl benzyl ketone, 103-79-7; 2-decanone, 693-54-9; propiophenone, 93-55-0; pivalophenone, 938-16-9; α,α,α-trifluoroacetophenone, 434-45-7; α,α,α-trideuterioacetophenone, 17537-31-4.

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(7) Isotopic compositions of the benzene and acetophenone samples obtained from the labeling reactions were measured at reduced ionizing voltage and 70 eV, respectively, on a Consolidated 21-102/103c mass spectrometer. All deuterium labeled compounds were obtained from Diaprep, Inc., Atlanta, Georgia, and had 99.5% minimum isotopic purities.

2*H*-1,2,3-Triazoles from the Ethyl Nitrocinnamates[1]

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The facile synthesis of 2*H*-1,2,3-triazoles by the addition of azide ion to activated acetylenes (eq 1) is not

(1) Abstracted from the Ph.D. thesis of Y. T., 1972.

TABLE I

THE REACTIONS OF THREE ETHYL NITROCINNAMATES WITH SODIUM AZIDE[a]

Ethyl nitrocinnamate	Solvent[b] (additive)	Temp, °C	Time, hr	Triazole[c] yield,[i] % (I)	Azo[d] yield,[i] % (II)	Recovered[g] cinnamate, % (III)
Para	DMF	75	5	29	Trace	54
Para	DMF	120	2	64	4.7	5.8
Para	DMAC	120	2	55	3.6	
Para	DMSO	120	2	62	4.5	
Meta	DMSO	120	2	57	*e*	39
Meta	DMAC	120	14	48	*e*	
Meta	DMSO	150	2	52	*e*	
Ortho	DMF	120	2	13	*f*	
Para	($C_6H_5NO_2$)	90–110	3.5	52		25
Para	(m-$C_6H_4(NO_2)_2$)	120	2	0		59
Para	(p-$(CH_3)_2NC_6H_4NO$)	110	1	31		37
Para	(Dry air)[h]	120	2	23		58
Para	(SeO_2)	120	1	50		34

[a] The reactions were generally carried out on a 1-g scale under nitrogen, except as indicated. [b] DMF, dimethylformamide; DMAC, dimethylacetamide; DMSO, dimethyl sulfoxide. Where no additive is indicated none was used. The standard solvent with additives was DMF (not indicated). When 1-chloro-2,4-dinitrobenzene or sulfur powder were the additives (1–2 hr at 120°), colored gums were obtained. [c] Nitrophenyl-5-carboethoxy-1,2,3-triazole. [d] Ethyl p,p'-azocinnamate. Traces of azoxy compound were detected in mass spectrum. [e] Unknown brown gummy mixture. [f] Unknown red gummy mixture. [g] A blank means that recovery of material either was not attempted or was not successful. [h] Dry air was continuously bubbled through the reaction mixture. [i] Yields are based on purified compounds.

$$RC{\equiv}CR' \xrightarrow[2.\ H_3O^+]{1.\ NaN_3,\ DMF} \underset{\mathbf{T}}{\text{1,2,3-triazole}} \qquad (1)$$

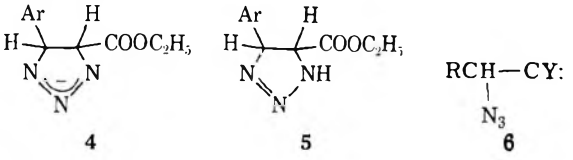
yet well known.[2,3] Having developed process 1 in great detail,[1] we believed that activated alkenes might also have synthetic possibilities. Although styrene[2] and ethyl maleate, quinone, and tetracyanoethylene did not give isolable products, the three ethyl nitrocinnamates (**1**) led, unexpectedly, to 1,2,3-triazoles (**2**), and in one case, also to ethyl azocinnamate (*p*-**3**).

The results of the investigation of process 2 are given in Table I. Among the aprotic solvents, DMF, DMAC, and DMSO, none showed any marked advantage. Our usual reaction temperatures were 100–150°, but temperatures above 150° led to decreased yields of **2**. Note that, if the reaction proceeded according to eq 2,

$$\underset{\mathbf{1}\ (o,\ m,\ p)}{O_2NC_6H_4CH{=}CHCOOC_2H_5} \xrightarrow[2.\ H_3O^+]{1.\ NaN_3,\ DMF} \underset{\mathbf{2}\ (o,\ m,\ p)}{\text{4-(o-nitrophenyl)-5-carboethoxy-1,2,3-triazole}} + \underset{p\text{-}\mathbf{3}}{(=NC_6H_4CH{=}CHCOOC_2H_5)_2} \qquad (2)$$

the stoichiometry (6 **1** → 4 **2**) set 66.7% as the theoretical maximum possible yield for **2**. Although this limit was approached for the meta and para isomers, the ortho yield did not get close, presumably because competing processes intervened (Table I).

As a working hypothesis, we considered that azide ion adds to **1** to give an open or closed anion (**4**), or triazoline (**5**). Now, triazolines may be oxidized,[4] may eliminate 5-H and 4-X to form triazoles, or may shed nitrogen and form aziridines, but they do not usually react with oxygen or the nitro function under our reaction conditions.[4,5] The fact that we were able to isolate **2** and *p*-**3** indicates that a redox process occurred, involving the transfer of hydride from **4**, **5**, or a



related species to some acceptor; it seems probable but is by no means certain yet that the oxidant is the nitro group (**1**) and/or other possible nitrogen precursors (hydroxylamino, nitroso, and azoxy)[6] to *p*-**3**. Nevertheless, our efforts to understand the detailed course of reaction 2 and to increase the yield of triazole by facilitating the oxidation of the intermediates with additives were negative or inconclusive (Table I). Potential oxidants such as air and dinitrobenzene turned out to be inhibitors and led to decreased yields of *p*-**2**.

A number of syntheses of triazoles from activated alkenes are on record. In one group of these, *e.g.*, from 5-nitro-2-oxopyrimidine,[7] 1,2-dicyanoethylene,[8] 1,4-dicyanobutadiene,[8] β,β'-dicyanostyrene,[8] and possibly β-nitrostyrene,[8] *there is a net displacement of X* from RCH=CR′X and the resulting triazole is the one formally derived from RC≡CR′, according to eq 1. Following azide addition to the double bond, the timing of the departure of X^-, ring closure, and proton transfer from carbon to nitrogen is unclear,[7,8] but in at least two possibly related cases a stable intermediate, *i.e.*, 2-

(2) A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR*, **158**, 408 (1964).

(3) F. P. Woerner and H. Reimlinger, *Chem. Ber.*, **103**, 1908 (1970).

(4) G. Caronna and S. Palazzo, *Gazz. Chim. Ital.*, **82**, 292 (1952).

(5) (a) P. Scheiner in "Selective Organic Transformations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, p 327; P. Scheiner, *Tetrahedron*, **24**, 2757 (1968); (b) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965).

(6) P. Buck, *Angew. Chem., Int. Ed. Engl.*, **8**, 120 (1969).

(7) H. U. Blank, I. Wemper, and J. J. Fox, *J. Org. Chem.*, **35**, 1131 (1970).

(8) (a) N. S. Zefirov and N. K. Chapovskaya, *Zh. Org. Khim.*, **6**, 2596 (1970); (b) N. S. Zefirov, N. K. Chapovskaya, and V. V. Kolesnikov, *Chem. Commun.*, 1001 (1971).

tosylvinyl azide or 2-benzoylvinyl azide, forms and slowly rearranges to T in the presence of base (N_3^-) in aprotic solvent.[9]

In a second group of syntheses, X may or may not be lost in the reaction, but here *a redox process or some other deep-seated changes* may occur: three β-nitrostyrenes yield 4-aryltriazoles and *sym*-triarylbenzenes;[8] β-cyanostyrene yields 4-phenyltriazole and 4-cyano-5-phenyltriazole;[8] three β-aroylethylene sulfonates yield corresponding 4-aroyltriazoles and phenylacylmethionic acids [p-$XC_6C_4COCH_2CH(SO_3^-)_2$];[10] three nitrocinnamates yield 4-(nitrophenyl), 5-carboethoxytriazole (eq 2). In his work, Zefirov, *et al.*, has pointed out that neither alkynes nor vinyl azides are necessary intermediates in these reactions; they suggest **4**, **5**, or the carbene **6** as possible precursors of the triazole.[8] However, even superficial consideration of these four examples discloses probable differences in the stoichiometry of the processes, in the nature of the coproducts, and in their detailed mechanisms. The formation of 4-cyano-5-phenyltriazole and the nitrophenyl-5-carboethoxytriazoles clearly require a hydride transfer; in the remaining reactions the cyano and sulfonate groups appear to be exchanged in "disproportionations." What does appear to connect all of the examples of this group and what does not seem to have been identified and emphasized previously is that redox processes are occurring. Admittedly, critical mechanistic information about them is still lacking. Since there would be obvious advantages in going to triazole directly from an alkene rather than from an alkyne made from the same alkene, there are practical and theoretical incentives for unravelling the mechanism(s) of these syntheses.

Experimental Section

Syntheses of Nitrophenyl-5-carboethoxy-1,2,3-triazoles from Nitrocinnamates.—The following preparative method was general, but the details of separation of components apply specifically to the para ester rather than to the ortho and meta compounds, for which the coproducts of the derived triazole were not identified. A summary of this work is given in Table I.

To a stirred suspension of sodium azide in an aprotic solvent,[11] blanketed by a stream of dry N_2, was added dropwise a solution of ethyl 4-nitrocinnamate in the same solvent at 75–150° over 30 min. The solution was kept at this temperature for 2–14 hr, when it turned green-brown, and then evaporated to dryness at *ca.* 60° under reduced pressure (2–3 mm). The residue was taken up in 50% aqueous methanol. Materials insoluble in the aqueous methanol were filtered off, washed with water, redissolved, and reprecipitated from acetone–water; these may consist of ethyl nitrocinnamate, ethyl azocinnamate, and possibly ethyl azoxycinnamate. Further separation was attempted by column chromatography on alumina with chloroform and chloroform–acetone as eluting solvents. Unreacted ethyl nitrocinnamate appeared in the first eluates. When present, the azo compound appeared next (trace amounts of azoxy compound mixed in with the azo compound were sometimes detected by mass spectroscopy, parent peak m/e 394). The aqueous solution, from which the mixture of the azo compound and the unchanged reactant were separated, was neutralized with 10% hydrochloric acid. An orange solid gradually precipitated. This was filtered off, washed with water, dried under reduced pressure, and reprecipitated from ethanol–water. The light orange solid was further purified by chromatography on silica gel with benzene, ether, and methanol as eluents, and identified as 4-nitrophenyl-5-carboethoxytriazole.

Ethyl p,p'-Azocinnamate (p-3).—This compound had mp 150–153° dec; nmr ($CDCl_3$) τ 8.65 (t, J = 7.3 Hz, 6 H), 5.69 (q, J = 7.3 Hz, 4 H), 3.51 (d, J = 16.2 Hz, 2 H), 2.27 (d, J = 16.2 Hz, 2 H), 2.32 (d, J = 8.7 Hz, 4 H), 2.05 (d, J = 8.7 Hz, 4 H); ir (Nujol) 1704, 1630 cm^{-1}; uv (ethanol) λ_{max} 366 nm (ε 52,300); mass spectrum m/e 378 (P^+), 333, 203, 181, 175, 147.

Anal. Calcd for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86. Found: C, 69.89; H, 5.82.

4-(p-Nitrophenyl)-5-carboethoxy-1,2,3-triazole.—This material had mp 170–171°; nmr (CD_3COCD_3) τ 8.66 (t, J = 7.1 Hz, 3 H), 5.60 (q, J = 7.1 Hz, 2 H), 1.72 (s and m, 4 H); ir (KBr) 3120, 1720, 1605, 1525 cm^{-1}; uv (ethanol) λ_{max} 290 nm (ε 12,400).

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.90. Found: C, 50.52; H, 4.09.

4-(m-Nitrophenyl)-5-carboethoxy-1,2,3-triazole.—This compound had mp 105–106°; nmr (acetone) τ 8.57 (t, J = 7.2 Hz, 3 H), 5.48 (q, J = 7.2 Hz, 2 H), 2.34 (m, 1 H), 1.71 (m, 2 H), 1.10 (t, J = 1.8 Hz, 1 H); ir (KBr) 3100, 1725, 1540 cm^{-1}; uv (ethanol) λ 249 nm (ε 16,700).

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.90. Found: C, 49.83; H, 3.90. In this reaction, the azo compound was presumed to be a coproduct.

4-(o-Nitrophenyl)-5-carboethoxy-1,2,3-triazole.—This light red triazole had mp 27–41°; nmr ($CDCl_3$) τ 8.82 (t, J = 7.1 Hz, 3 H), 5.72 (q, J = 7.1 Hz, 2 H), 2.33 (m, 3 H), 1.90 (m, 1 H); ir (liquid) 3160, 1715, 1520, 1440 cm^{-1}.

Anal. Calcd for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.90. Found: C, 50.14; H, 3.78.

Registry No.—p-2, 35307-27-8; m-2, 35378-21-3; o-2, 35307-28-9; p-3, 35340-31-9.

(9) (a) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **33**, 985 (1968); (b) S. Maiorana, *Ann. Chim. (Rome)*, **56**, 1531 (1960); (c) G. L'abbé and A. Hassner, *Angew. Chem., Int. Ed. Engl.*, **10**, 98 (1971).

(10) A. N. Nesmeyanov and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR*, **166**, 1362 (1966).

(11) *E.g.*, DMF, DMAC, or DMSO.

Nuclear Magnetic Resonance and Infrared Studies on the Tautomerism of 1-Ethyl-3-(3′-dimethylaminopropyl)-carbodiimide[1a]

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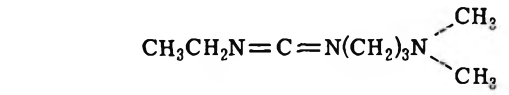
Chemotherapy trials performed during the past year have demonstrated that 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide (**1**), when administered as a saline solution of its hydrochloride salt, exerts a carcinostatic effect on transplanted tumors in mice.[2] Sheehan, *et al.*,[3] have suggested from ir studies that protonation of the tertiary amine of the carbodiimide **1** may lead to the formation of the tautomeric, reduced pyrimidines 2-ethylamino-3,3-dimethyl-3,4,5,6-tetrahydropyrimidine chloride (**4**) and/or 2-ethylimino-3,3-dimethylper-

(1) (a) This research was supported by U. S. Atomic Energy Commission Contract W-7405-eng-48 with the Lawrence Berkeley Laboratory. (b) Supported by a postdoctoral fellowship from the Bay Area Heart Research Committee, 1969–1971, and fellowship no. 1-FO2-CA-52469 from the National Cancer Institute 1971–1972.

(2) R. Fawwaz and T. Tenforde, *Proc. Amer. Ass. Cancer Res.*, **13**, 36 (1972).

(3) J. C. Sheehan, P. A. Cruickshank, and G. L. Boshart, *J. Org. Chem.*, **26**, 2525 (1961).

hydropyrimidine chloride (**5**). Titration data have established that the pK_a of compound **1** is ~10.75.



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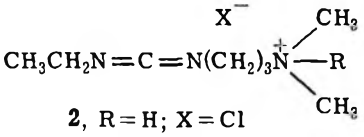
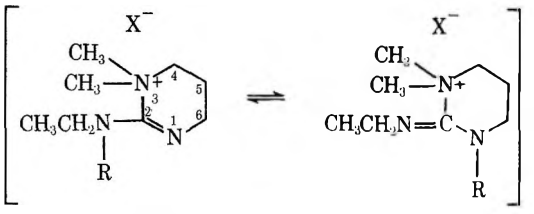


2, R = H; X = Cl
3, R = CH_3; X = I



4, R = H; X = Cl
6, R = CH_3; X = I

5, R = H; X = Cl
7, R = CH_3; X = I

Consequently, **1** exists largely as the protonated species in aqueous solution at physiological pH. We therefore have undertaken spectroscopic studies to confirm the existence of structures **4** and/or **5**, and to quantitate the relative percentages of isomeric species **2**, **4**, and **5** present in water at neutral pH. Information of this nature may prove to be of value both in understanding the mechanism of drug action against tumors and in the synthesis of new potentially tautomeric carbodiimides.

When examined in aqueous solution or as a crystalline dispersion in Nujol, the hydrochloride salt of **1** exhibits a weak absorption at 2128 cm^{-1} corresponding to the fundamental antisymmetric -N=C=N- stretching mode.[4] A strong band occurs at 1702 cm^{-1}, characteristic of the -N=C stretching mode present in structures **4** and **5**.[5] Ir spectra of the methiodide derivative of **1** in water and Nujol show a strong carbodiimide band at 2128 cm^{-1}, with no absorption at 1702 cm^{-1}. These observations are consistent with the anticipated N-methylation structure **3**, and indicate that reaction of **1** with methyl iodide does not produce isomeric structures **6** and/or **7**. Ir spectra of the free carbodiimide base, either in neat phase or in chloroform or unbuffered aqueous solution, are consistent with the open-chain structure **1**.

Since the methiodide derivative of **1** must exist exclusively in the carbodiimide form **3**, the extinction coefficient for the -N=C=N- band at 2128 cm^{-1} could be measured and was found to be 1.67×10^6 cm^2/mol in water. Assuming the same extinction coefficient for the 2128-cm^{-1} band observed in the aqueous solution ir spectrum of the hydrochloride salt of **1**, it was calculated that 7.4% of this compound exists as the open-chain carbodiimide hydrochloride **2**. Spectra were recorded in solutions buffered over the pH range of 6 to 9, and no significant variation was noted in the strength of the carbodiimide absorbance. Outside this pH range, carbodiimide hydrolysis prevented accurate measurements.

(4) G. D. Meakins and R. W. Moss, *J. Chem. Soc. (London)*, 993 (1957).
(5) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y., 1963, pp 265-267.

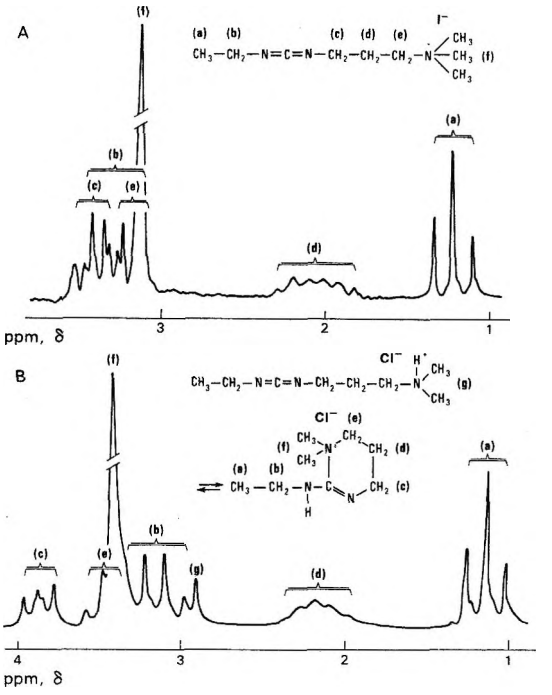


Figure 1.—Nmr spectra at 60 MHz in deuterium oxide of (A) 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide methiodide and (B) the hydrochloride salt of 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide. Both spectra were recorded with sodium 4,4-dimethyl-4-silapentanesulfonate (SDSS) as an internal reference standard (SDSS, 0.0 ppm).

In an effort to confirm and to extend the structural information obtained from ir data, nmr spectra of **1**, its hydrochloride salt, and its methiodide derivative **3** were recorded in deuterium oxide. In the spectrum of the methiodide derivative **3** (Figure 1A, Table I),

TABLE I
60-MHz CHEMICAL SHIFT AND COUPLING CONSTANT DATA[a]

Protons[b]	δ in ppm (J in Hz)		
	1	3	HCl salt of 1
a	1.21 (t, 7)	1.22 (t, 7)	1.16 (t, 7)
b	3.26 (q, 7)	3.31 (q, 7)	3.17 (q, 7)
c	3.27 (t, 6.5)	3.44 (t, 6.5)	3.86 (t, 7)
d	1.7 (m)	2.1 (m)	2.2 (m)
e	2.28 (t, 7)	3.20 (t, 7)	3.48 (t, 6.5)
f	2.21 (s)	3.16 (s)	3.41 (s)
g			2.92 (s)

[a] Spectra were recorded in deuterium oxide with sodium 4,4-dimethyl-4-silapentanesulfonate (SDSS) as an internal reference standard (SDSS, 0.0 ppm). [b] Proton designations are the same as in Figure 1.

the two partially resolved triplets centered at δ 3.20 and 3.44 ppm can be assigned to the c and e methylene proton resonances since all other signals can be unambiguously assigned. The difference in δ values for the f proton signals of the free base **1** and the methiodide derivative **3** ($\Delta_{1\rightarrow3}\delta_f$, Table I) is 0.95 ppm. Assuming a similar downfield shift of the e proton resonance for species **3** relative to **1**, the triplet at δ 3.20 ppm ($\Delta_{1\rightarrow3}\delta_e$ = 0.92 ppm) must be assigned to the signal for protons e. Consequently, the δ 3.44 ppm signal is associated with the c methylene protons.

The nmr spectrum of the hydrochloride salt of **1** in deuterium oxide (Figure 1B, Table I) indicates the presence of one major and one minor species. The

weak singlet appearing at δ 2.92 ppm has been assigned to the resonance of the *N*,*N*-dimethyl protons of the open-chain hydrochloride salt, structure **2**. The intensity of this signal is ~8% as great as that of the major *gem*-dimethyl proton signal at δ 3.41 ppm and is consistent with the percentage of **2** calculated from ir spectral data. The upfield shift of this signal relative to the NCH_3 signals for the quaternary compounds considered here can be explained by localization of the positive charge predominantly on the proton bonded to the tertiary nitrogen.[6] As a result of this charge distribution, the deshielding of the NCH_3 protons is less for species **2** than for the quaternary compounds.

Identification of the major component present in the hydrochloride salt of **1** can be made by comparison of chemical shift data for this compound and the free carbodiimide base **1** (Figure 1B, Table I). In the spectrum of the hydrochloride salt of **1**, the partially obscured triplet centered at δ 3.48 ppm can be assigned to the signal for the e protons since $\Delta_{1\rightarrow 1HCl}\delta_f = \Delta_{1\rightarrow 1HCl}\delta_e = 1.20$ ppm. The low field triplet at δ 3.86 ppm can then be assigned to the c proton signal. A comparison of the spectra of **1** and the hydrochloride salt of **1** also shows that $\Delta_{1\rightarrow 1HCl}\delta_b = -0.09$ ppm and $\Delta_{1\rightarrow 1HCl}\delta_c = 0.59$ ppm. Using these relative chemical shift data, we have assigned **4** as the predominant species present in the hydrochloride salt of **1** for the following reasons. First, the deshielding effect of N-1 in structure **4** is expected to be greater than that of the carbodiimino nitrogen of **1**, resulting in a downfield shift for the c proton signal.[7] Second, the deshielding effect of the amino nitrogen of **4** is expected to be less than that of the carbodiimino nitrogen of **1**, resulting in an upfield shift for the b proton signal. In the case of structure **5**, one would predict the signal for the b protons to occur downfield, and the c proton signal upfield, relative to the corresponding signals for compound **1**.

Nmr spectra were also recorded for the free carbodiimide base **1** in neat phase and as a solution in chloroform. In both cases, the observed chemical shifts and coupling constants were consistent with an open chain carbodiimide structure.

In summary, the ir and nmr studies presented here demonstrate that the hydrochloride salt of **1** in water at neutral pH exists as a mixture of two isomeric forms: 7.4% as **2** and 92.6% as **4**. The methiodide derivative **3** and the free base **1** exist only as open-chain carbodiimide structures.

Experimental Section[8]

The hydrochloride salt of 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide (**1**) with uncorrected mp 109–110° (lit.[3] mp 114–115°) was purchased from the Ott Chemical Co. (Muskegon, Mich.). The derivative 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide methiodide (**3**) with uncorrected mp 90–93° (lit.[3] mp 106.5–107.5°) was prepared from freshly distilled carbodiimide base **1** and methyl iodide.[3] Structure **3** and the hydrochloride salt of **1** in 50% methanol–50% acetone move on silica gel as single bands with R_f values of 0.65 and 0.71, respectively. Only trace amounts of impurities are present. The spectra of these compounds in water and as Nujol mulls demonstrate the absence of urea bands in the 1530–1680-cm^{-1} range. As determined from the absorbance at 2128 cm^{-1}, the hydrolysis of these compounds in water at neutral pH follows first-order kinetics. At 37°, the $t_{1/2}$ for hydrolysis of the hydrochloride salt of **1** is 60 hr, and for hydrolysis of **3** it is 26 hr.

Registry No.—**1**, 1892-57-5; **2**, 25952-53-8; **3**, 22572-40-3.

(6) J. M. George, L. B. Kier, and J. R. Hoyland, *Mol. Pharmacol.*, **7**, 328 (1971).

(7) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon, Oxford, England, 1969, pp 80, 81.

(8) Melting points were measured on a Thomas-Hoover apparatus. Ir spectra were recorded on a Perkin-Elmer Model 421 spectrometer. Spectra of solutions were obtained using matched 0.018-mm CaF_2 cells. Because of the weak absorbance of the hydrochloride salt of **1** at 2128 cm^{-1}, measurements at this frequency in aqueous solution were made by recording the transmittance at 5× scale expansion. Nmr spectra were recorded at ambient temperature on a Varian A-60A spectrometer.

A Facile Synthesis of 4-Substituted 3a,4,5,9b-Tetrahydrobenz[*e*]isoindolines

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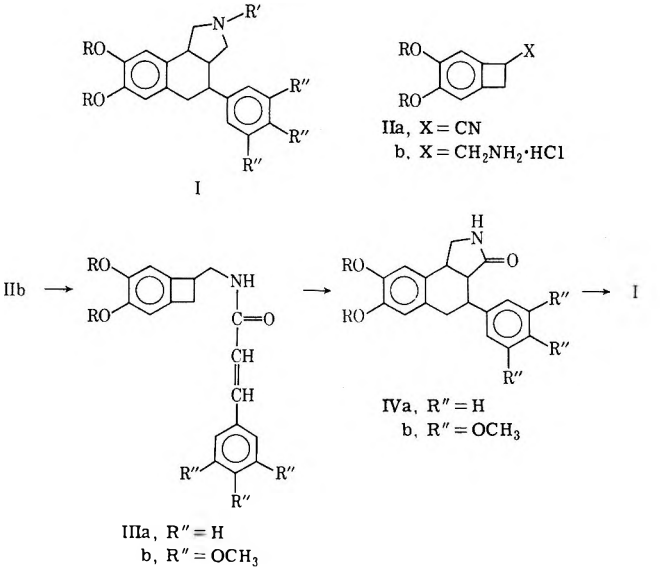
As part of our general structure–activity study of biologically active compounds,[1] synthesis of a series of 4-aryl-substituted 7,8-dialkoxy-3a,4,5,9b-tetrahydrobenz[*e*]isoindolines (I) was needed. Compounds of this type may be prepared by an Oppolzer reaction.[2] Although this route has been studied, certain required unsaturated amines may not be readily accessible and thus preclude its becoming a practical route. An alternate route has therefore been proposed. This involves direct reduction of the nitrile IIa to the amine IIb, treatment of the latter with the acid chloride of an appropriate α,β-unsaturated acid, and thermal cyclization of the resulting amide III to the α-lactam IV. The desired product I can be obtained from IV.



Since α,β-unsaturated acids are readily available and each of the aforementioned steps are convenient, high yield conversions, our method provides a useful route to compounds of this type. As an example, synthesis of 7,8-dimethoxy-2-ethyl-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]isoindoline (I, R = CH_3; R′ = C_2H_5; R″ =

(1) K. Y. Zee-Cheng and C. C. Cheng, *J. Pharm. Sci.*, **59**, 1630 (1970).

(2) W. Oppolzer, *J. Amer. Chem. Soc.*, **93**, 3833 (1971).

H) is described as follows. Treatment of 2-bromo-4,5-dimethoxyphenylpropionitrile, prepared from 3,4-dimethoxycinnamonitrile, with potassium in liquid ammonia gave a 74% yield of 1-cyano-4,5-dimethoxybenzocyclobutene[3] (IIa, R = CH_3), mp 83–84° Reduction of IIa (R = CH_3) with diborane in tetrahydrofuran[4] afforded an 85% yield of the amine IIb (R = CH_3), the hydrochloride of which melted at 201–203°. The amide IIIa (R = CH_3), mp 138–138.5°, was prepared from the amine IIb (R = CH_3) and cinnamoyl chloride in pyridine in 92% yield. A toluene solution of the amide IIIa (R = CH_3) heated at 200° for 47 hr resulted in 63% yield of the lactam IVa (R = CH_3), mp 249–250°. (Analysis of the toluene mother liquor by tlc showed at least five spots; these by-products were not studied at the present time.) The ir spectrum of the unsaturated amide IIIa (R = CH_3) showed a carbonyl stretching absorption at 1650 and a double-bond stretching absorption at 1620 cm^{-1}; the rearranged isomeric product IVa (R = CH_3) showed a carbonyl absorption at 1695 cm^{-1}, consistent with the γ-lactam assignment. No vinyl protons appeared in the pmr of IVa (R = CH_3). Regrettably, the methine and methylene proton signals did not provide enough information for stereochemical assignments.

The mass spectra of compounds IIIa (R = CH_3) and IVa (R = CH_3) showed that the molecular ion has the same mass in both cases [*m/e* 323 (M^+)]; yet the stability of the ionized molecules differ greatly. The molecular ion of IIIa (R = CH_3) has a measured relative intensity of 30.4%; the base peak had a *m/e* of 176. In contrast, compound IVa (R = CH_3) gave a more stable molecular ion with relative intensity of 81.3%.

Treatment of IVa (R = CH_3) with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, Vitride) in refluxing benzene gave the amine I (R = CH_3; R′ = H; R″ = H), isolated as the hydrochloride salt, in 89% yield. The pentamethoxy I (R = CH_3; R′ = H; R″ = OCH_3) was prepared in a similar manner from IIb and trimethoxycinnamoyl chloride.

The *N*-acetyl amine derivative, I (R = CH_3; R′ = $COCH_3$; R″ = H), which was prepared from I (R = CH_3; R′ = H; R″ = H) with a mixture of acetic anhydride and pyridine in 78% yield, was also reduced with Red-Al in refluxing benzene to furnish 7,8-dimethoxy-2-ethyl-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]-isoindoline (I, R = CH_3; R′ = C_2H_5; R″ = H).

Experimental Section

All melting points were taken on a Thomas–Hoover melting point apparatus. The pmr spectra were determined on Varian A-60 and Varian HA-100 D spectrometers. The mass spectra data were obtained with a Varian Mat CH-4B mass spectrometer. Infrared spectra were taken on a Perkin-Elmer 337 Infracord. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer.

2-Bromo-4,5-dimethoxyphenylpropionitrile.—A solution of 100 g of 3,4-dimethoxycinnamonitrile (mixture of cis and trans, Aldrich) in 450 ml of tetrahydrofuran was hydrogenated under 2.8 kg/cm^2 of H_2 for 48 hr with 1.5 g of 5% Pd/C. Filtration of the reaction mixture and removal of solvent yielded 96 g of syrupy 3,4-dimethoxyphenylpropionitrile. This was dissolved in 300 ml of acetic acid. The solution was cooled to 18° and to it was slowly added, with stirring, a solution of 85 g of Br_2 in 50 ml of acetic acid over 1 hr. The mixture was stirred for an additional 1.5 hr, then poured onto a mixture of 51 g of potassium acetate, 250 ml of water, and 300 g of ice. Crude 2-bromo-4,5-dimethoxyphenylpropionitrile separated as crystals. Recrystallization twice from methanol–water gave 63.2 g (48% yield) of product, mp 76–78°. An analytical sample was prepared by an additional recrystallization from methanol, mp 75–76°, ir (Nujol) ν_{max} 2230 cm^{-1} (C≡N, w).

Anal. Calcd for $C_{11}H_{12}BrNO_2$: C, 48.91; H, 4.48; N, 5.19. Found: C, 49.17; H, 4.50; N, 5.28.

1-Cyano-4,5-dimethoxybenzocyclobutene (IIa, R = CH_3).—A 5-l. three-necked flask equipped as reported by Bunnett and Skorez[5] was flame-dried and flushed with dry helium. The flask was half-filled with anhydrous liquid ammonia; then small pieces (<50 mg) of potassium were added until the intense blue color of the solution persisted for several minutes. A small crystal of ferric nitrate was added followed by portionwise addition of freshly cut potassium (18.7 g). After the color of the blue solution changed to dull brown, 32.3 g of 3-(2-bromo-4,5-dimethoxy)phenylpropionitrile was rapidly added in one portion. The reaction mixture was stirred for 6 min and 41 g of ammonium nitrate was added to neutralize the basic mixture. Ammonia was allowed to evaporate and the residue was treated with a mixture of 150 ml of $CHCl_3$ and 150 ml of H_2O. The aqueous portion was extracted three times with $CHCl_3$ (500 ml) and the combined $CHCl_3$ solution was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was concentrated to a viscous oil and eluted with chloroform through a 50-mm (i.d.) column containing acid-washed alumina (300 g, Fisher, Brockman activity I). The product was isolated as a white powder from the initially eluted component. It was triturated with hexane to give 16.8 g (74.4% yield) of IIa, mp 83–84°. An analytical sample was obtained by recrystallization from ethanol, mp 83–84°, ir (Nujol) ν_{max} 2220 cm^{-1} (C≡N).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.78; H, 5.55; N, 7.27.

1-Aminomethyl-4,5-dimethoxybenzocyclobutene Hydrochloride (IIb, R = CH_3).—A solution of 27 g of IIa in 150 ml of 1 *M* BH_3 in tetrahydrofuran was stirred under helium at room temperature for 3 hr. Absolute EtOH (19 ml) was then cautiously added. After 15 min, 39 g of 21% ethanolic HCl was added and the resulting suspension was stirred overnight. The desired product was isolated as a white powder (28 g, 85% yield), mp 196–198°. An analytical sample was prepared by recrystallization from 2-propanol, mp 201–203°, ir (Nujol) ν_{max} 3125 and 2575 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}NO_2 \cdot HCl$: C, 57.52; H, 7.02; N, 6.10. Found: C, 57.78; H, 7.15; N, 5.92.

***N*-[(4,5-Dimethoxybenzocyclobuten-1-yl)methyl]cinnamamide (IIIa, R = CH_3).**—A mixture of 4.05 g of IIb and 3.30 g of cinnamoyl chloride in 18 ml of dry pyridine was heated on a steam bath for 1 hr. The resulting solution was allowed to stand at room temperature for 2 hr and poured, with stirring, into a mixture of ice and water (200 ml) and left overnight. The resulting solid product was collected by filtration, washed with water, and recrystallized from EtOH–H_2O to give 5.23 g (92% yield) of off-white solid, mp 133–134°. Recrystallization from ethyl acetate gave analytically pure IIIa (R = CH_3) as white needles: mp 138–138.5°; ir (Nujol) ν_{max} 3320, 3275, 1650, 1620, 1320 cm^{-1}; mass spectrum *m/e* 324 ($M^+ + 1$, 6.2%), 323 (M^+, 30.4%), 177 (46.8%), 176 (100%), 163 (46.8%).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.27; H, 6.55; N, 4.33. Found: C, 74.31; H, 6.64; N, 4.23.

***N*-[(4,5-Dimethoxybenzocyclobuten-1-yl)methyl]-3,4,5-trimethoxycinnamamide (IIIb, R = CH_3).**—This compound was prepared in a similar manner from 4.41 g of IIb, 5.60 g of 3,4,5-trimethoxycinnamoyl chloride and 25 ml of pyridine. Recrystallization from a mixture of EtOH and H_2O gave 5.83 g of product, mp 152–153°. An analytical sample was prepared by recrystallization from ethyl acetate: mp 152–153°; ir (Nujol) ν_{max} 3370, 1675, 1640, 1575 cm^{-1}; uv (EtOH) λ_{max} 230 nm (log ϵ 4.48), 295 (4.43); mass spectrum *m/e* 413 (M^+).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 67.05; H, 6.88; N, 3.48.

7,8-Dimethoxy-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]isoindolin-3-one (IVa, R = CH_3).—A solution of 15.0 g of IIIa (R = CH_3) in 730 ml of toluene was heated at 195–200° for 47 hr. The product, which separated from the cooled reaction

(3) I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970).

(4) $LiAlH_4$ or Raney nickel reduction of an analogous nitrile to the corresponding amine was reported. *Cf.* Belgian Patent 635,901 (1964); *Chem. Abstr.*, **62**, 3987 (1965).

(5) J. F. Bunnett and J. A. Skorez, *J. Org. Chem.*, **27**, 3836 (1962).

mixture, was collected by filtration and washed with ether to give 9.5 g (63% yield) of a light yellow solid, mp 244–246°. Recrystallization from $CHCl_3$–MeOH yielded 8.5 g of analytically pure white crystals: mp 249–250°; ir (Nujol) 3190 (NH), 1695 cm^{-1} (C=O, γ-lactam); uv (EtOH) λ_{max} 230 nm (log ε 4.00), 285 (3.76); nmr ($CDCl_3$–TMS) δ 7.24 (5 P, s, Ar H), 6.66 (1 P, s, Ar H), 6.52 (1 P, s, Ar H), 6.11 (1 P, NH), 3.86 (3 P, s, Ar OCH_3), 3.82 (3 P, s, Ar OCH_3), 3.80–2.00 (7 P, m, methine and methylene hydrogens); mass spectrum *m/e* 324 (M^+ + 1, 20.3%), 323 (M^+, 81.3%), 279 (24.2%), 266 (20.3%), 232 (46.0%), 193 (34.0%), 192 (24.2%), 189 (25.0%), 176 (34.4%), 161 (40.5%), 131 (81.3%).

Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.36; H, 6.34; N, 4.42.

7,8-Dimethoxy-4-(3,4,5-trimethoxyphenyl)-3a,4,5,9b-tetrahydrobenz[*e*]isoindolin-3-one (IVb, R = CH_3).—A solution of 4.25 g of IIIb in 250 ml of toluene was heated at 210–225° for 48 hr. The product was collected in a similar manner as described for IVa (R = CH_3) and dried at 120° *in vacuo* to give 2.19 g of white crystals, mp 223–225°. An analytical sample was prepared by recrystallization from toluene: mp 225–227°; ir (Nujol) 3220, 1695, 1590, 1130 cm^{-1}; uv (EtOH) λ_{max} 282 nm (log ε 3.83); mass spectrum *m/e* 413 (M^+).

Anal. Calcd for $C_{23}H_{27}NO_6$: C, 66.81; H, 6.58; N, 3.39. Found: C, 66.79; H, 6.45; N, 3.31.

7,8-Dimethoxy-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]isoindoline Hydrochloride (I HCl, R = CH_3; R′ = H; R″ = H).—A boiling solution of 8.1 g of IVa (R = CH_3) in 350 ml of dry benzene was rapidly cooled and the resulting fine suspension was treated with 25 ml of Red-Al. The mixture was refluxed for 2.5 hr, cooled, and to it was cautiously added 200 g of 10% aqueous NaOH. The separated aqueous layer was extracted with 100 ml of benzene. The combined benzene extracts were washed with saturated aqueous NaCl solution, filtered, and distilled to remove most of the benzene. Anhydrous Et_2O (100 ml) was added. The mixture was stirred in an ice bath while 8 g of 21% ethanolic HCl in 100 ml of anhydrous Et_2O was added dropwise. The solid was collected by filtration, washed with Et_2O and dried to give 7.7 g (89% yield) of white powder. An analytical sample was obtained by precipitation from a methanolic solution with Et_2O: mp 285° dec; ir (Nujol) ν_{max} 2700, 2400 cm^{-1}; nmr ($CDCl_3$–TMS) δ 7.24 (5 P, s, Ar H), 6.62 (1 P, s, Ar H), 6.46 (1 P, s, Ar H), 3.83 (6 P, s, Ar OCH_3), 3.80–2.00 (9 P, m).

Anal. Calcd for $C_{20}H_{23}NO_2 \cdot HCl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.28; H, 7.06; N, 3.83.

7,8-Dimethoxy-4-(3,4,5-trimethoxyphenyl)-3a,4,5,9b-tetrahydrobenz[*e*]isoindoline Hydrochloride (I HCl, R = CH_3; R′ = H; R″ = OCH_3).—This compound was prepared in a similar manner from 2.06 g of IVb and 170 ml of benzene. The product, 2.02 g (93% yield), was collected as a white powder, mp 261–262°. An analytical sample was prepared by precipitation from a methanolic solution with Et_2O: mp 261–262°; ir (Nujol) 3400, 2700, 2400, 1590, 1130 cm^{-1}; uv (EtOH) λ_{max} 282 nm (log ε 3.66); mass spectrum *m/e* 399 (M^+ − HCl).

Anal. Calcd for $C_{23}H_{29}NO_5 \cdot HCl$: C, 63.37; H, 6.94; N, 3.21. Found: C, 63.49; H, 7.05; N, 3.14.

2-Acetyl-7,8-dimethoxy-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]-isoindoline (I, R = CH_3; R′ = $COCH_3$; R″ = H).—A mixture of 2.28 of I HCl (R = CH_3; R′ = H, R″ = H), 10 ml of Ac_2O, and 10 ml of pyridine was stirred at room temperature for 16 hr. After the usual work-up the residue was recrystallized from a mixture of EtOAc and heptane to give 1.8 g (78% yield) of product, mp 178–180°. An additional recrystallization from EtOAc yielded an analytically pure sample: mp 181–182°; ir (Nujol) ν_{max} 1630 cm^{-1} (C=O); mass spectrum *m/e* 352 (M^+ + 1, 24.9%), 351 (M^+, 100%), 292 (10.2%), 279 (55.0%), 265 (20.0%).

Anal. Calcd for $C_{22}H_{25}NO_3 \cdot {}^1/_4H_2O$: C, 74.23; H, 7.22; N, 3.94. Found: C, 74.40; H, 7.40; N, 3.96.

7,8-Dimethoxy-2-ethyl-4-phenyl-3a,4,5,9b-tetrahydrobenz[*e*]-isoindoline Hydrochloride (I HCl; R = CH_3; R′ = C_2H_5; R″ = H).—To a solution of 1.70 g of the aforementioned acetamide in 100 ml of dry benzene was added 4 ml of Red-Al. The mixture was refluxed for 1 hr and cooled. To the mixture was cautiously added, with stirring, 100 ml of 10% aqueous NaOH solution. The benzene layer was separated, washed with 100 ml of saturated aqueous NaCl solution, dried (Na_2SO_4), and filtered. The filtrate was evaporated *in vacuo* and the residual syrup diluted with 200 ml of anhydrous Et_2O. To this was added 5 ml of 20% ethanolic HCl and the precipitated white powder was collected by filtration to give 1.69 g (94% yield) of product, mp 278–280°. An analytically pure sample was prepared by dissolving the product in methanol and reprecipitation with ether, mp 279–280°, ir (Nujol) ν_{max} 2440 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}NO_2 \cdot HCl$: C, 70.66; H, 7.55; N, 3.75. Found: C, 70.63; H, 7.62; N, 3.59.

Registry No.—I (R = CH_3; R′ = $COCH_3$; R″ = H), 35202-50-7; I HCl (R = CH_3; R′ = H; R″ = H), 35202-51-8; I HCl (R = CH_3; R′ = H; R″ = OCH_3), 35202-52-9; I HCl (R = CH_3; R′ = C_2H_5; R″ = H), 35202-53-0; IIa (R = CH_3), 35202-54-1; IIb (R = CH_3), 35202-55-2; IIIa (R = CH_3), 35202-56-3; IIIb (R = CH_3), 35202-57-4; IVa (R = CH_3), 35202-58-5; IVb (R = CH_3), 35202-59-6; 2-bromo-4,5-dimethoxyphenylpropionitrile, 35249-62-8.

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Syntheses of the Dihydronepetalactones

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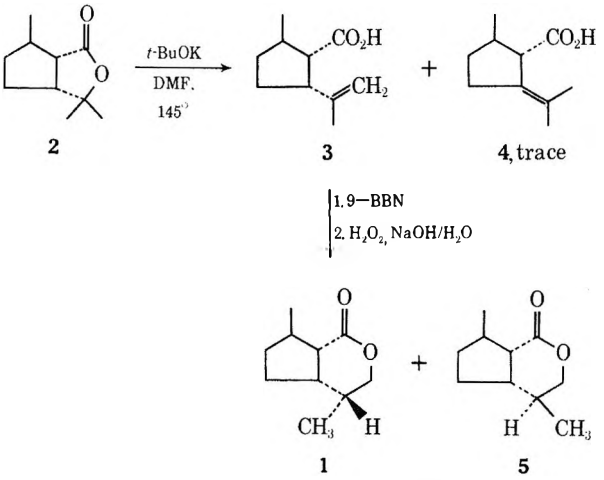
During a study of the base-catalyzed cyclization of methyl 6,7-epoxycitronellate it was discovered that alkoxides act on lactones to produce unsaturated carboxylic acids.[1] Herein we describe the use of the lactone elimination reaction in a highly stereoselective synthesis of dihydronepetalactone (**1**) and *cis,cis*-



dihydronepetalactone (**10**). Dihydronepetalactone (**1**), the enantiomer of a major constituent of matatabi-

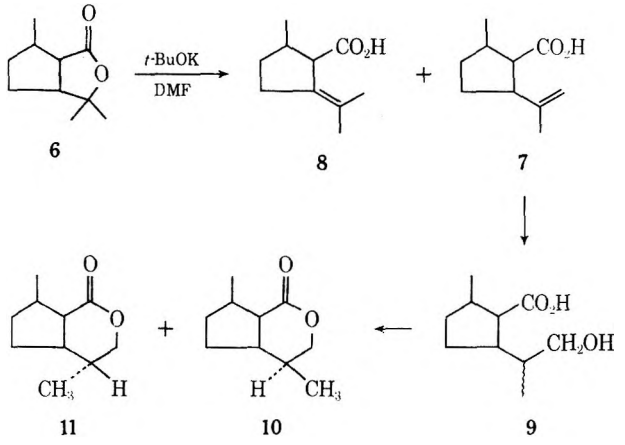
(1) J. Wolinsky, P. Hull, and E. J. Eustace, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., spring, 1971. Details of this work will be described in a forthcoming publication.

lactone[2] and a trace ingredient in catnip oil,[2] is more attractive to cats[3] than nepetalactone or epinepetalactone.[4]

The reaction of potassium *tert*-butoxide with *cis,trans*-pulegandide (2)[5] in dry DMF to yield *cis,trans*-2-isopropenyl-5-methyl-1-cyclopentanecarboxylic acid (3) was best conducted at 145° for 4–5 hr using a 1.05:1.00 ratio of base to lactone. The presence of water seemed to increase the proportion of pulegenic acid (4) in the product. Unlike pulegenic acid (4), acid 3 readily converts to lactone 2 and care must be taken to avoid elevated temperature in the reaction work-up. The crude acid 3 was generally obtained in ~90% yield and was used immediately in the next step.

Hydroboration of acid 3 with 9-BBN[6] gave a 46% yield (based on lactone 2) of a mixture of dihydronepetalactone (1) and isodihydronepetalactone (5) in a 7:1 ratio.

Heating *cis,cis*-pulegandide (6)[7] with potassium *tert*-butoxide in DMF gave a mixture of unsaturated acid 7 and *cis*-pulegenic acid (8) in a ratio of 2.6:1.0.

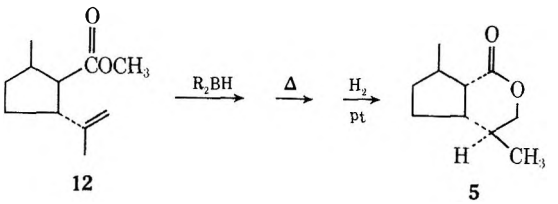


6 8 7 11 10 9

The crude acid was hydroborated with 9-BBN, but in this instance a mixture of hydroxy acids 9 was isolated. Heating 9 at 175° for 1 hr gave a mixture of *cis,cis*-dihydronepetalactone (10) and *cis,cis*-isodihydronepetalactone (11) in a 5:1 ratio.

The configurations of 10 and 11 were assigned on the basis of ir and nmr spectral comparison with 1 and 5. The ir spectra of 1 and 10 were nearly identical, while the spectra of 5 and 11 were very similar. The nmr signals for the CH_2O protons in these compounds were characteristic of the AB portion of an ABX pattern. In the case of 1 and 10 coupling constants J_{AX} and J_{BX} were small while in lactones 5 and 11 J_{AX} and J_{BX} were large.[8]

It is of interest to point out that stereoselective routes to dihydronepetalactone (1) and isodihydronepetalactone (5) are now available. Hydroboration of 3 affords dihydronepetalactone (1), whereas hydroboration of 12, followed by catalytic hydrogenation gives isodihydronepetalactone (5)[9] as the major product.



12 5

cis,cis-Isodihydronepetalactone (11) proved to be identical with a minor product isolated from the hydroboration of 12.[9]

Experimental Section[10]

***cis,trans*-2-Isopropenyl-5-methyl-1-cyclopentanecarboxylic Acid (3).**—To a stirred slurry of 3.5 g (31.2 mmol) of potassium *tert*-butoxide in 20 ml of anhydrous DMF at 120°, under a nitrogen atmosphere, was rapidly added 5.0 g (29.8 mmol) of *cis,trans*-pulegandide (2). The deep red solution was heated at 145° for 4 hr, cooled, and poured onto ice. The mixture was extracted with ether; the ether was dried and removed to leave 650 mg of lactone 2.

The aqueous phase was acidified with dilute hydrochloric acid and extracted with ether. The ether solution was washed with water and dried ($MgSO_4$), and the ether was removed under diminished pressure to give 4.2 g of crude acid: ir 5.83, 6.05, and 11.13 μ; nmr (CCl_4) 1.09 (d, 3, CH_3), 1.76 (s, 3, $CH_3C{=}C$), 4.78 (s, 2, $C{=}CH_2$), and 11.20 ppm (s, 1, CO_2H). Nmr analysis indicated that acid 3 was contaminated with 2% lactone 2 and ~10% *trans*-pulegenic acid (4).

An ether solution of crude 3 was treated with an ether solution of diazomethane and a pure sample of methyl *cis,trans*-2-isopropenyl-5-methyl-1-cyclopentanecarboxylate (13) was isolated by glpc: ir (CCl_4) 5.74, 11.22 μ; nmr (CCl_4) 1.05 (d, 3, J = 6 Hz, CH_3), 1.72 (s, 3, $CH_3C{=}C$), 3.52 (s, 3, OCH_3), and 4.67 ppm (s, 2, $C{=}CH_2$).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.32; H, 10.00.

Dihydronepetalactone (1).—To 44 ml of 0.57 M solution (25 mmol) of 9-BBN in THF[6] at 0° was added 4.2 g (~25 mmol) of crude acid 3 in 10 ml of dry THF. A total of 24 mmol of hydrogen gas was evolved. An additional 44 ml of 9-BBN solution was then added and the solution was stirred at ambient temperature for 6 hr. The solution was cooled to 0° and 30 ml of 3 N potassium hydroxide solution was added rapidly, followed by the slow addition (30 min) of 30 ml of 30% hydrogen peroxide. The solution was allowed to warm to ambient temperature and was stirred for 18 hr. The reaction mixture was poured onto ice and extracted with ether. The aqueous solution was acidified with dilute hydrochloric acid and allowed to stir at ambient temperature for 1 hr before it was extracted with ether. The ether solution was washed with water, dried ($MgSO_4$), and distilled to give 2.27 g (45% based on 2) of liquid, bp 107–110° (1 mm). Glpc analysis indicated the liquid was comprised of 82% dihydronepetalactone (1), 11% isodihydronepetalactone (5), and 7% lactone 2. Pure samples of each lactone were isolated by preparative glpc and each showed ir, nmr, and vpc retention times identical with those of authentic samples.[2]

***cis,cis*-2-Isopropenyl-5-methyl-1-cyclopentanecarboxylic Acid (7).**—A mixture of 2.4 g (21.4 mmol) of potassium *tert*-butoxide and 3.5 g (20.8 mmol) of *cis,cis*-pulegandide (6) in 25 ml of anhydrous DMF was heated at 145° for 4.5 hr. The usual work-up gave 420 mg of 6 in the neutral fraction and 2.70 g of oil in the acidic fraction: ir 5.86, 6.08, and 11.17 μ; nmr (CCl_4) 1.06 (d, 3, CH_3), 1.78 (s, 3, $CH_3C{=}C$), 4.77 (s, 2, $C{=}CH_2$), and 11.17 ppm (s, 1, CO_2H). Nmr analysis indicated that acid 7 was con-

(2) T. Sakan, J. Wolinsky, *et al.*, *Tetrahedron Lett.*, 4097 (1965).
(3) J. Wolinsky and D. L. Nelson, unpublished results.
(4) R. B. Bates and C. W. Sigel, *Experientia*, **19**, 565 (1963).
(5) J. Wolinsky, H. Wolf, and T. Gibson, *J. Org. Chem.*, **28**, 274 (1963).
(6) H. C. Brown and E. F. Knight, *J. Amer. Chem. Soc.*, **90**, 5281 (1968).
(7) J. Wolinsky, T. Gibson, D. Chan, and H. Wolf, *Tetrahedron*, **21**, 1247 (1965).
(8) See K. Sisido, K. Inomata, T. Kageyema, and K. Utimoto, *J. Org. Chem.*, **33**, 3149 (1968), for a discussion of the nmr spectra of the iridolactones.
(9) J. Wolinsky and D. Nelson, *Tetrahedron*, **25**, 3767 (1969).
(10) All boiling and melting points are uncorrected. Infrared spectra were measured with a Perkin–Elmer Infracord. Nuclear magnetic resonance spectra were determined at 60 MHz with a Varian Associates A-60 spectrometer. Optical rotations were measured with a Zeiss polarimeter. Mass spectra were recorded on a Hitachi RMU-6A spectrometer employing an ionization energy of 70 eV, an inlet temperature of *ca.* 185°, and a source temperature of 160°. Microanalyses were performed by Dr. C. S. Yeh and associates.

taminated with ~28% *cis*-pulegenic acid. A pure sample of **7** proved difficult to obtain because of its conversion to lactone **6**.

Methyl *cis,cis*-2-isopropenyl-5-methyl-1-cyclopentanecarboxylate (**14**), prepared by treatment of acid **7** with diazomethane and purified by glpc, showed ir absorption at 5.75, 6.07, and 11.18 μ; nmr (CCl_4) 0.97 (d, 3, CH_3), 1.72 (s, 3, $CH_3C{=}C$), 2.85–3.05 (m, 1, $CHCO_2Me$), 3.48 (s, 3, OCH_3), and 4.71 (s, 2, $C{=}CH_2$).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.50; H, 10.22.

cis,cis-Dihydronepetalactone (**10**) and *cis cis*-Isodihydronepetalactone (**11**).—A solution of crude **7** in THF was added to 28 ml of 0.57 *M* 9-BBN under a nitrogen atmosphere. A total of 0.90 equiv of hydrogen gas was evolved. An additional 24 ml of 9-BBN solution was added and the solution was stirred at ambient temperature for 13 hr. The reaction was worked up in the usual manner and the basic aqueous solution was acidified and allowed to stir overnight. Extraction with ether afforded 2.65 g of liquid whose ir spectrum showed the presence of a hydroxy acid and only a small amount of lactone. The liquid was heated at 175° for 1 hr, and some acidic material was removed by dissolving the oil in ether and washing with sodium bicarbonate solution. The ether was removed and glpc (20% Carbowax 20M column at 195°) indicated the presence of two major components and three minor components (2%) which were not investigated further. The major component were isolated by glpc.

cis,cis-Isodihydronepetalactone (**11**) (15–20% of the mixture) showed a retention time of 68 min; $[\alpha]^{28}D$ −92.4° (*c* 4.30, $CHCl_3$); ir (CCl_4) 5.70 μ; nmr 0.92 (d, 3, *J* = 6 Hz, CH_3), 1.12 (d, 3, *J* = 5.5 Hz, CH_3), 3.69 and 4.28 (m, 2, J_{AB} = 11.5 Hz, J_{AX} = 6.5 Hz, J_{BX} = 7.5 Hz, $CHCH_2O$); mass spectrum *m/e* (rel intensity) 168 (7), 113 (37), 110 (46), 95 (44), 82 (33), 81 (92), 69 (47), 67 (56), 55 (40), 41 (100), and 39 (74).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.62; H, 9.76.

cis,cis-Dihydronepetalactone (**10**) (75–80% of the mixture) showed a retention time of 82 min; $[\alpha]^{28}D$ −15.6° (*c* 11.0, $CHCl_3$); ir (CCl_4) 5.74 μ; nmr 0.90 (d, 3, *J* = 6.5 Hz, CH_3), 0.92 (d, 3, *J* = 7 Hz, CH_3), 3.0 (m, 1, J_{AX} = 10 Hz, J_{BX} = 8.5 Hz, CHCO), and 3.95 ppm (m, 2, J_{AB} = 7 Hz, J_{BX} = 8.5 Hz, CHCO), and 3.95 ppm (m, 2, J_{AB} = 7 Hz, J_{AX} = 1.5 Hz, J_{BX} = 0, $CHCH_2O$); mass spectrum *m/e* (rel intensity) 168 (5), 113 (55), 81 (38), 67 (45), 55 (30), 53 (28), 41 (100), and 39 (83).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.66; H, 9.69.

Registry No.—**1**, 35337-11-2; **3**, 35337-12-3; **7**, 35337-13-4; **10**, 35337-14-5; **11**, 35337-15-6; **13**, 35337-16-7; **14**, 35337-17-8.

2,4,9-Trioxaadamantanes from Isobutylene and Pivaloyl Halides

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Contribution No. 1914 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

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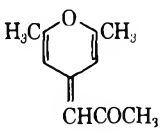
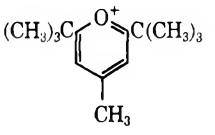
The Friedel–Crafts acylation of olefins has been one of the more thoroughly studied reactions.[1] Monoacylation is known to give chloro ketones and α,β- and β,γ-unsaturated ketones, whereas diacylation forms pyrilium salts. One type of triacylation is known in which formation of the pyrane **1** from 3 mol of acetyl chloride and 1 mol of isobutylene in the presence of aluminum chloride involves each of the terminal carbon atoms of isobutylene.[2] However, acylation of isobutylene with pivaloyl chloride in the presence of aluminum chloride has only been reported to give $(CH_3)_3CCOCH{=}C(CH_3)_2$[3] and a pyrilium salt (**2**) when stannic chloride is used.[4]

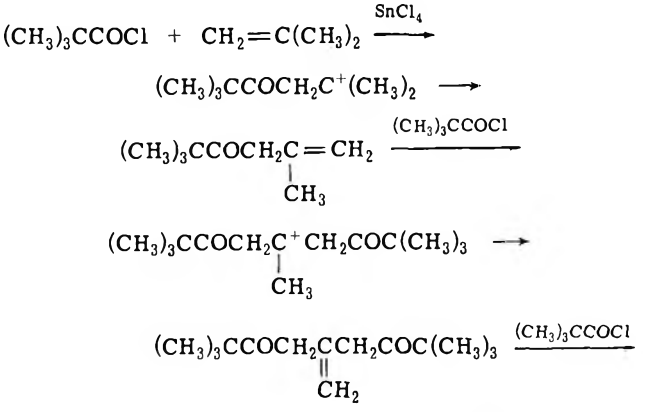


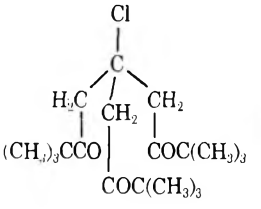
1



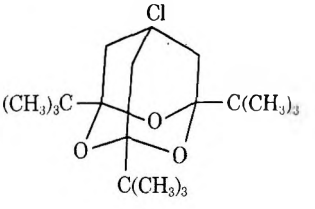
2

A new type of triacylation product has now been found in the reaction of pivaloyl halides with isobutylene. Simply by adding less than 0.1 molar equiv of stannic chloride to a liquid mixture of isobutylene and pivaloyl chloride at −15°, a 32–35% yield of 7-chloro-1,3,5-tri-*tert*-butyl-2,4,9-trioxaadamantane (**4**) can be filtered off. Another 6% can be obtained from the filtrate. The compound presumably arises through the intermediate formation of triketone **3** by a reaction sequence of the following type.





3



4

That a tricarbonyl compound of the structure $R'C(CH_2COR)_3$ will cyclize to a 2,4,9-trioxaadamantane was established by Stetter and Dohr,[5] who ozonized trimethallylcarbinol. The triketone was not isolated but spontaneously formed the 7-hydroxytrioxaadamantane, which they converted to 7-chloro-1,3,5-trimethyl-2,4,9-trioxaadamantane. Only one other synthesis for 2,4,9-trioxaadamantanes, that of Stetter and Stark,[6] has been reported. This route involved the preparation of $HC(CH_2COCHN_2)_3$ and conversion with hydrogen chloride or bromide to $HC(CH_2COCH_2X)_3$, which cyclized.

The ir spectrum of 7-chloro-1,3,5-tri-*tert*-butyl-2,4,9-trioxaadamantane (**4**) was taken at 155, 165, and 183° but gave no indication of reversion to the carbonyl form. The chlorine atom, as in the Stetter and Dohr compound, was unaffected by refluxing al-

(1) C. D. Nenitzescu and A. T. Balaban in "Friedel–Crafts and Related Reactions," Vol. III, Part 2, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, pp 1033–1152.

(2) A. T. Balaban, P. T. Frangopol, A. R. Katritzky, and C. D. Nenitzescu, *J. Chem. Soc.*, 3889 (1962).

(3) M. E. Grundy, W. H. Hsü, and E. Rothstein, *ibid.*, 4136 (1952).

(4) A. T. Balaban and C. D. Nenitzescu, *Justus Liebigs Ann. Chem.*, **625**, 74 (1959).

(5) H. Stetter and M. Dohr, *Chem. Ber.*, **86**, 589 (1953).

(6) H. Stetter and H. Stark, *ibid.*, **92**, 732 (1959).

coholic potassium hydroxide, in accord with its bridgehead position. Nmr ($CDCl_3$) showed singlets at 0.99 and 2.16 ppm in a 9:2 ratio.

Use of pivaloyl bromide and stannic bromide gave the bromo analog in 28% yield. With chloropivaloyl chloride and stannic chloride a 0.5% yield of 7-chloro-1,3,5-tris(2-chloro-1,1-dimethylethyl)-2,4,9-trioxaadamantane was obtained.

Experimental Section

7-Chloro-1,3,5-tri-*tert*-butyl-2,4,9-trioxaadamantane.—Pivaloyl chloride (80 g, 0.66 mol) was placed in a 500-ml, three-necked flask equipped with magnetic stirrer, Dry Ice condenser, thermometer, and inlet tube. The flask was cooled to −30° and 50 g (0.9 mol) of liquid isobutylene was introduced. The inlet tube was replaced with a small dropping funnel and anhydrous stannic chloride (7 ml, 16 g, 0.06 mol) was added dropwise during 45 min while the temperature was maintained at *ca.* −15° by cooling with Dry Ice–acetone. The cooling bath was removed and the mixture was allowed to stand for 1 hr. The crystals of the trioxaadamantane were filtered off and rinsed with methanol. The original filtrate was kept separate from the methanol rinse. The yield at this point was 24 g (32%): mp 161–162° after recrystallization from acetone; ir 2976, 2882 (CH), 1389, 1359 (gem CH_3 groups), 1175–1050 cm^{-1} (multiple strong bands for C–O–C–O–C), no evidence of C=O, C=C, OH.

Anal. Calcd for $C_{19}H_{33}ClO_3$: C, 66.16; H, 9.64; Cl, 10.28; mol wt, 345. Found: C, 66.21; H, 9.78; Cl, 10.14; mol wt, 339 (cryoscopic in benzene).

After standing for a day, the original filtrate from the crystals was distilled to give 21.3 g (23%) of 2,2,5-trimethyl-4-hexen-3-one:[3] bp 67–68° (24 mm); $n^{25}D$ 1.4437; nmr (neat) 0.75 [s, $(CH_3)_3C$], 1.52 and 1.72 [unsharp doublets, $=C(CH_3)_2$], 5.98 ppm (broad peak, =CH). The pot residue yielded 4.7 g (6%) more of the trioxaadamantane. In a run in which the liquid product was distilled immediately, HCl had not split out and 5-chloro-2,2,5-trimethyl-3-hexanone, $(CH_3)_3CCOCH_2CCl(CH_3)_2$, distilled out: bp 71–72° (12 mm); $n^{25}D$ 1.4367; nmr (neat) 0.97 [s, $C(CH_3)_3$], 1.53 [s, $ClC(CH_3)_2$], 2.92 ppm (s, CH_2), no =CH peak. On standing overnight, the chloro ketone turned dark and evolved HCl. External tetramethylsilane was used as nmr reference for all compounds.

The reaction between pivaloyl chloride and isobutylene was tried in the stoichiometric ratio of 3:1, without solvent and with hexane as a solvent, but the yields of the trioxaadamantane filtered off were only 11 and 9%, respectively. When a mole ratio of 1:1 was used, without solvent, the yield filtered off was 35%.

7-Bromo-1,3,5-tri-*tert*-butyl-2,4,9-trioxaadamantane.—The reaction was carried out as for the chloro compound using 25 g (0.15 mol) of pivaloyl bromide,[7] 8 g (0.14 mol) of isobutylene, and 4 g (0.009 mol) of stannic bromide.[8] The mixture did not become noticeably exothermic at −15°, but when the cooling bath was removed the temperature eventually rose to 33° and crystals separated. The cooled mixture was filtered and the crystals were rinsed with methanol to give 5.4 g (28%) of the trioxaadamantane. Recrystallization from acetone left 4.6 g: mp 166°; ir 2967, 2882 (CH), 1393, 1376 (*gem*-CH_3 groups), 1175–1050 cm^{-1} (multiple bands for C–O–C–O–C); nmr ($CDCl_3$) 0.99 [s, $(CH_3)_3C$], 2.38 ppm (CH_2).

Anal. Calcd for $C_{19}H_{33}BrO_3$: C, 58.60; H, 8.54; Br, 20.52. Found: C, 58.84; H, 8.41; Br, 20.21.

7-Chloro-1,3,5-tris(2-chloro-1,1-dimethylethyl)-2,4,9-trioxaadamantane.—Dropwise addition of stannic chloride (5 ml, 11.3 g, 0.043 mol) to 100 g (0.65 mol) of chloropivaloyl chloride[9] and 50 g (0.9 mol) of isobutylene at −15° produced an exothermic reaction and a viscous polymer layer separated. The mixture was allowed to stand for 16 hr. A few crystals in the liquid phase were filtered off. The polymer layer was extracted with hot acetone to yield a few more crystals. The yield of the trioxaadamantane was 0.5 g (0.5%): mp 156–157° from acetone; ir 2994, 2890 (CH), 1374, 1359 (*gem*-CH_3 groups), 1182, 1121, 1038 cm^{-1} (C–O–C–O–C); nmr ($CDCl_3$) 1.14 [s, $C(CH_3)_2$], 2.32 (s, ring CH_2), 3.67 ppm (s, CH_2Cl).

Anal. Calcd for $C_{19}H_{30}Cl_4O_3$: C, 51.01; H, 6.76; Cl, 31.71. Found: C, 51.07; H, 6.80; Cl, 31.57.

Passing isobutylene into a mixture of chloropivaloyl chloride and stannic chloride gave a similar result.

Registry No.—**4**, 35336-97-1; 2,2,5-trimethyl-4-hexen-3-one, 14705-30-7; 5-chloro-2,2,5-trimethyl-3-hexanone, 35336-99-3; 7-bromo-1,3,5-tri-*tert*-butyl-2,4,9-trioxaadamantane, 35337-00-9; 7-chloro-1,3,5-tris(2-chloro-1,1-dimethylethyl)-2,4,9-trioxaadamantane, 35337-01-0; isobutylene, 115-11-7.

(7) Y. Yamase, *Bull. Chem. Soc. Jap.*, **34**, 480 (1961).
(8) Research Organic/Inorganic Chemical Corp., Sun Valley, Calif.
(9) F. Neidel and U. Kretzschmar, *Justus Liebigs Ann. Chem.*, **688**, 61 (1965).

Mononitration of Perylene. Preparation and Structure Proof of the 1 and 3 Isomers

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The limitations of the published method[1] for the preparation of 3-nitroperylene have recently been pointed out, and an improved procedure was disclosed employing attack by nitrite ion on the perylene radical cation.[2] These limitations have also led us to search for a better method of preparing this nitro compound. We wish to report a simple procedure that not only affords 3-nitroperylene in good yield, but also gives the previously unknown 1 isomer. Formation of the latter is of interest, since the only other example of substitution at position 1 occurred during the reaction of perylene with alkyllithium reagents.[3-5]

When perylene is nitrated in dioxane with dilute nitric acid, a mixture containing two mononitroperylenes is obtained. This mixture is readily separated by column chromatography into a rather insoluble, higher melting (210–212°) isomer (56%) and a lower melting (170–171°) isomer (24%). The higher melting isomer is identical with the compound obtained by the procedure of Dewar and Mole.[1] They proposed, but did not prove, that this compound was 3-nitroperylene (**1a**).

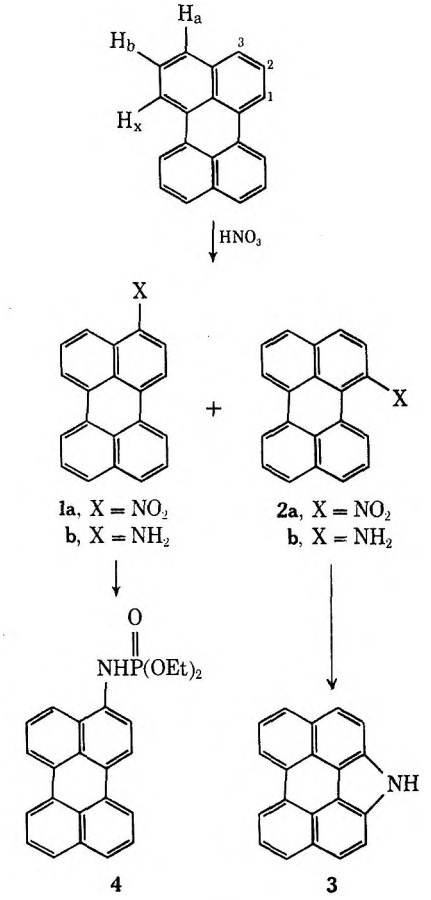
In order to make an unequivocal assignment of structure, the behavior of each isomer toward triethyl phosphite was examined. Only 1-nitroperylene should readily cyclize[6] to an amine. The 3 isomer should give tar,[6] or possibly a phosphoramidate, as observed with 4-dimethylaminonitrosobenzene.[7]

The lower melting isomer (170–171°) gave a good yield (82%) of amine **3** when heated with triethyl phosphite. The higher melting isomer gave a phosphorus-containing compound which is assigned structure **4**, based on its analysis ane spectral properties (Experimental Section). Thus the lower melting isomer is 1-

(1) M. J. S. Dewar and T. Mole, *J. Chem. Soc.*, 1441 (1956).
(2) C. V. Ristagno and H. J. Shine, *J. Amer. Chem. Soc.*, **93**, 1811 (1971).
(3) H. E. Zieger and J. E. Rosenkranz, *J. Org. Chem.*, **29**, 2469 (1964).
(4) H. E. Zieger and E. M. Laski, *Tetrahedron Lett.*, 3801 (1966).
(5) H. E. Zieger, *J. Org. Chem.*, **31**, 2977 (1966).
(6) J. I. G. Cadogan, *et al.*, *J. Chem. Soc.*, 4831 (1965).
(7) P. J. Bunyan and J. I. G. Cadogan, *ibid.*, 42 (1963).

TABLE I
NMR SPECTRA

Compd	Multiplicity	Area	Peak positions or range, τ	J, Hz	Assignment
Perylene (CS_2)	m	4	1.7–1.9		H_x
	m	8	2.3–2.8		$H_a + H_b$
3-Nitroperylene,	m	5	1.7–2.2		H_x
1a (DMSO-d_6)	m	6	2.4–2.8		$H_a + H_b$
3-Aminoperylene,	m	5	1.7–2.1		H_x
1b (DMSO-d_6)	m	5	2.4–2.8		$H_a + H_b$
	d	1	3.08	8.0	Proton adjacent to NH_2
			3.22		
	s	2	4.40		NH_2
1-Nitroperylene,	m	2	1.8–2.0		H_x
2a ($DCCl_3$)	m	9	2.3–2.8		$H_a + H_b$
1-Aminoperylene,	m	3	1.6–2.1		H_x
2b ($DCCl_3$)	m	7	2.4–2.8		$H_a + H_b$
	d	1	3.12	8.0	Proton adjacent to NH_2
			3.25		
	s	2	5.64		NH_2



nitroperylene (2a) and the higher melting isomer is 3-nitroperylene (1a), as originally suggested.[1]

The nmr spectra of the two mononitroperylenes and the corresponding amines (Table I) also support the proposed structures. The spectrum of perylene[8] is an ABX pattern, and consists of a low-field group of peaks (τ 1.7–1.9) for the four H_x atoms and a high-field group (τ 2.3–2.8) for the eight $H_a + H_b$ atoms. Both mononitroperylenes have these same two groups of peaks. The higher melting isomer (1a) has five protons in the H_x group instead of four, and six in the $H_a + H_b$ group instead of seven. This shift of one proton from the $H_a + H_b$ group to the H_x group is attributed to the peri interaction characteristic of 1-substituted naphthalenes;[9] proton 4 being deshielded by the presence of the 3-nitro substituent. The corresponding amine (1b) also has five protons in the H_x group, as expected.

The lower melting isomer (2a) has two protons in the H_x group instead of three and nine in the $H_a + H_b$ group instead of eight. Thus, one proton in the H_x group is shielded. This shift is attributed to the influence of the anisotropy of the nitro group on the proton at position 12. When the nitro group is reduced to the amino substituent (2a → 2b), the shielding effect is removed and there are three protons in the H_x group.

Experimental Section[10]

Nitration of Perylene.—To a hot solution of 10 g (0.04 mol) of perylene in 120 ml of dioxane was added a mixture of 45 ml of water and 30 ml of nitric acid (d = 1.5). The resulting solution was heated on a steam bath for 1 hr, cooled, and poured into 2 l. of water. The solid was collected, washed, dried, dissolved in 130 ml of chlorobenzene, and chromatographed on 500 g of Florisil. Benzene eluted 0.1 g of perylene, followed by 2.8 g (24%) of brick-red 1-nitroperylene (2a). Methylene chloride eluted 6.6 g (56%) of similarly colored 3-nitroperylene (1a), mp 210–212°, which did not depress the melting point of a sample prepared by the method of Dewar and Mole.[1] 1-Nitroperylene was recrystallized from benzene (soluble)–ethanol: mp 170–171°; uv λ_{max} (ETOH) 255 nm (log ϵ 4.45), 393 (3.93), and 437 (4.08).

Anal. Calcd for $C_{20}H_{11}NO_2$: C, 80.8; H, 3.7; N, 4.7. Found: C, 80.7; H, 3.9; N, 4.7.

Treatment of 1-Nitroperylene with Triethyl Phosphite.—A mixture of 0.50 g (0.0017 mol) of 1-nitroperylene (2a) and 5 ml of triethyl phosphite was heated at reflux under nitrogen for 2 hr. Upon cooling to room temperature, the yellow-brown amine 3 crystallized: yield 0.36 g (82%); mp 360° dec; ir 3400 cm^{-1} (NH); nmr (DMSO-d_6) τ 5.35 (s, 1, NH) and 1.22–2.33 (m, 10, aromatic).

Anal. Calcd for $C_{20}H_{11}N$: C, 90.5; H, 4.2; N, 5.3. Found: C, 90.2; H, 4.4; N, 5.1.

Treatment of 3-Nitroperylene with Triethyl Phosphite.—A mixture of 1.0 g (0.0034 mol) of 3-nitroperylene (1a) and 10 ml of triethyl phosphite was heated at reflux under nitrogen for 1 hr, cooled, and chromatographed on Florisil. After removal of small amounts of material with benzene and methylene chloride, the phosphoramidate 4 was eluted with ethanol and recrystallized from chlorobenzene: yield 0.70 g (51%); mp 225° dec (depends upon rate of heating); nmr (DMSO-d_6) τ 1.7–2.0 (m, 5, aromatic)

(8) N. Jonathan, S. Gordon, and B. P. Dailey, *J. Chem. Phys.*, **36**, 2443 (1962).

(9) V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(10) The nmr spectra were measured on a Varian Associates Model A-60 spectrometer and the uv spectrum on a Perkin-Elmer Model 202 spectrometer. All melting points are uncorrected.

2.4–2.8 (m, 7, aromatic and NH, one proton exchangeable with D_2O), 5.7–6.2 (pair of overlapping quartets, 4, methylene coupled to phosphorus), 8.77 (t, 6, methyl).

Anal. Calcd for $C_{24}H_{23}NO_3P$: C, 71.5; H, 5.5; N, 3.5; P, 7.7. Found: C, 71.6; H, 5.5; N, 3.5; P, 7.9.

1-Aminoperylene (2b).—Reduction of 1-nitroperylene (**2a**) was performed as described[1] for 3-nitroperylene, except that 1,2-dimethoxyethane proved to be a better solvent. A solution was prepared by heating 1.0 g (0.0034 mol) of 1-nitroperylene in 50 ml of 1,2-dimethoxyethane. About 100 mg of 10% palladium on charcoal was added, followed by 2 ml of 64% hydrazine. After the mixture had been heated for 3 min, the catalyst was removed and the solvent was distilled to leave a yellow solid. Recrystallization from a mixture of benzene (soluble) and ethanol gave 0.75 g (83%) of amine **2b**, mp 195–197°.

Anal. Calcd for $C_{20}H_{13}N$: C, 89.9; H, 4.9; N, 5.2. Found: C, 89.5; H, 4.5; N, 5.0.

The 3-amino compound[1] **1b** was prepared in better yield by using this solvent in place of ethanol.

Registry No.—**1a**, 20589-63-3; **1b**, 20492-13-1; **2a**, 35337-20-3; **2b**, 35337-21-4; **3**, 35337-22-5; **4**, 35337-23-6; perylene, 198-55-0.

Thallium in Organic Synthesis. XXXV. Oxidation of Cyclohexanones to Adipoins Using Thallium(III) Nitrate[1,2]

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Received December 22, 1971

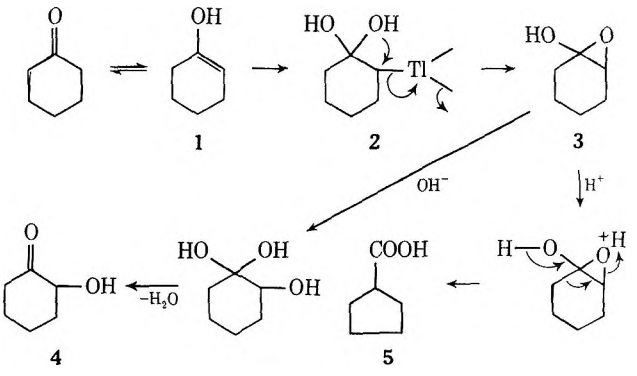
There are only four reports describing the reactions of cyclohexanones with thallium(III) salts. Oxidation with thallium(III) acetate in hot acetic acid has been found to result in α-acetoxylation in low yield,[3,4] but conflicting claims have been made as to the products formed using thallium(III) perchlorate in aqueous acidic media. Littler reported that cyclohexanone was converted first into adipoin and then into cyclohexane-1,2-dione.[5] In a later study, however, Wiberg and Koch found that the major product was cyclopentanecarboxylic acid (75%), and that only 3% of adipoin was obtained. They also showed that adipoin did not serve as the precursor for the ring-contracted product.[6] In view of this apparent duality in reaction pathway we have investigated the reaction of cyclohexanone with thallium(III) nitrate (TTN).[7]

Oxidation of cyclohexanone with TTN in acetic acid at room temperature proceeded rapidly, and precipitation of thallium(I) nitrate was complete in a few minutes. Filtration and neutralization of the filtrate with aqueous sodium bicarbonate solution followed by extraction with ether gave adipoin in 84% yield. This result at first sight confirmed Littler's claim; closer investigation of the reaction, however, revealed that the nature of the product formed on oxidation was temperature dependent. Thus, if oxidation was performed at room temperature, the thallium(I) nitrate was removed by filtration, and the filtrate was heated above about 40° for a few minutes, no adipoin was obtained. The sole product isolated, again in 84% yield, was cyclopentanecarboxylic acid.

That there were indeed two different reaction pathways was readily proved as follows. Oxidation of cyclohexanone was carried out as described above. The filtrate obtained after removal of the thallium(I) nitrate was divided into two equal portions. One of these was treated with aqueous sodium bicarbonate and gave adipoin (**4**). The other was heated for a few minutes and gave cyclopentanecarboxylic acid (**5**). Each product was uncontaminated by the other, thus indicating the intermediacy of a common precursor. Moreover, this precursor cannot be an organothallium derivative, as thallium(I) nitrate had been recovered in almost quantitative yield. It would therefore appear from the above results that both Littler and Wiberg and Koch may have been correct with respect to the products they isolated. There is little doubt, however, that the mechanism postulated by Wiberg for formation of the cyclopentanecarboxylic acid is incorrect, as it involved the intermediacy of an organothallium derivative.

We suggest that the mechanisms of these transformations are best represented as shown in Scheme I, and

SCHEME I



that the common precursor to **4** and to **5** is the epoxy enol **3**. Oxythallation of enols (*cf.* **1** → **2**) is a known process,[8] while Kruse and Bednarski have recently shown that epoxides may be prepared by oxidation of olefins with thallium(III) acetate.[9] Not unexpectedly, all attempts to isolate **3** from the reaction mixture were unsuccessful. One noteworthy feature of the mechanism shown in Scheme I is that water is involved as nucleophile in the oxythallation step; this must be the

(1) Part XXXIV: A. McKillop, O. H. Oldenziel, B. P. Swann, E. C. Taylor, and R. L. Robey, *J. Amer. Chem. Soc.*, in press.

(2) We gratefully acknowledge partial financial support of this work by Eli Lilly and Company, the CIBA Pharmaceutical Company, and G. D. Searle and Company.

(3) H.-J. Kabbe, *Justus Liebigs Ann. Chem.*, **656**, 204 (1962).

(4) S. Uemura, T. Nakano, and K. Ichikawa, *J. Chem. Soc. Jap.*, **88**, 1111 (1967).

(5) J. S. Littler, *J. Chem. Soc.*, 827 (1962).

(6) K. B. Wiberg and W. Koch, *Tetrahedron Lett.*, 1779 (1966); we have confirmed this result.

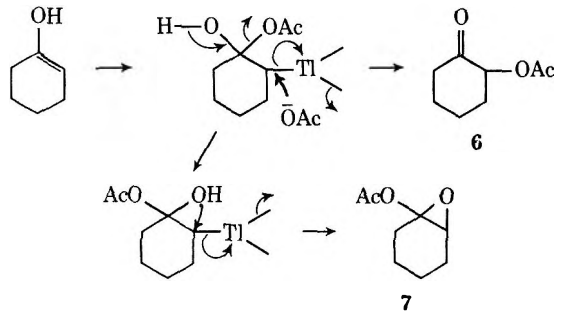
(7) A. McKillop, J. D. Hunt, E. C. Taylor, and F. Kienzle, *ibid.*, 5275 (1970).

(8) A. McKillop, B. P. Swann, and E. C. Taylor, *J. Amer. Chem. Soc.*, **93**, 4919 (1971).

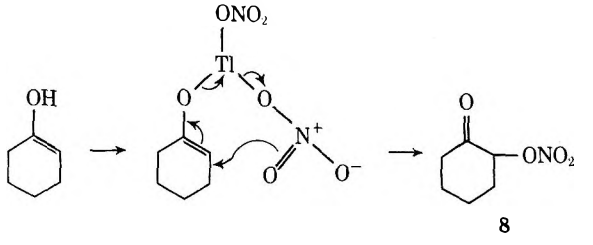
(9) W. Kruse and T. M. Bednarski, *J. Org. Chem.*, **36**, 1154 (1971).

water of crystallization of TTN.[10] The mechanisms outlined in Scheme I are also consistent with the observations that neither 2-acetoxycyclohexanone (**6**),[11] 1-acetoxycyclohexene oxide (**7**),[12] nor 2-oxocyclohexyl nitrate (**8**)[13] is the immediate precursor to **4** and **5**. Plausible mechanisms can be postulated both for formation of these intermediates (Schemes II and III)

SCHEME II



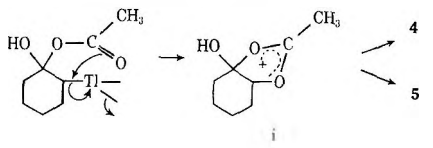
SCHEME III



and for their subsequent conversion into **4** and **5**. Each of these compounds was therefore prepared independently and subjected to the isolation procedures used in the oxidation reaction. Both 2-acetoxycyclohexanone and 2-oxocyclohexyl nitrate were recovered virtually unchanged from both aqueous sodium bicarbonate solution and hot acetic acid.[14] Treatment of 1-acetoxycyclohexene oxide with aqueous sodium bicarbonate solution resulted in quantitative hydrolysis to adipoin, but all attempts to induce ring contraction of **7** to cyclopentanecarboxylic acid were unsuccessful.

Examination of the reactions of a wide variety of ketones with TTN in acetic acid revealed a remarkable specificity with respect to ketone structure. Thus, oxidation of 4-methyl- and 4-*tert*-butylcyclohexanone gave the corresponding adipoins in 98 and 97% yield, respectively. On the other hand, complex mixtures of products were obtained with 2- and 3-substituted cyclohexanones, with 5-, 7- and 12-membered cycloalkanones, and with aliphatic ketones.

(10) TTN is a trihydrate, and participation of the water of crystallization in oxythallation has been noted previously: A. McKillop, J. D. Hunt, R. D. Naylor, and E. C. Taylor, *J. Amer. Chem. Soc.*, **93**, 4918 (1971). It has been suggested by a referee that the nucleophile could alternatively be acetic acid rather than water. This would lead to the acetoxonium ion (i) which could serve as the precursor to **4** and **5**.



(11) G. W. K. Cavill and D. H. Solomon, *J. Chem. Soc.*, 4426 (1955).

(12) M. Mousseron and R. Jacquier, *Bull Soc. Chim. Fr.*, 698 (1950).

(13) J. E. Franz, J. F. Herber, and W. S. Knowles, *J. Org. Chem.*, **30**, 1488 (1965).

(14) 2-Oxocyclohexyl nitrate hydrolyzed to the extent of about 10% on treatment with aqueous sodium bicarbonate solution.

Experimental Section[15]

Preparation of Adipoin.—TTN (18 g, 0.04 mol) was added to a solution of 4 g (0.04 mol) of cyclohexanone in 40 ml of acetic acid. Thallium(I) nitrate precipitated almost immediately. The inorganic salt was removed by filtration, the filtrate was neutralized with sodium bicarbonate, and the solution was allowed to stand overnight. It was then extracted with chloroform, and the extracts were washed with 2 *N* sulfuric acid and water and dried (Na_2SO_4). Evaporation of the solvent gave a colorless liquid which slowly solidified on standing. Crystallization of the solid from ethanol gave 3.83 g (84%) of adipoin dimer[16] as beautiful, colorless needles, mp 112.5–113.5° (lit.[17] mp 113°), identical in all respects with a genuine sample prepared by hydrolysis of 2-chlorocyclohexanone.[17]

4-Methyl-2-hydroxycyclohexanone dimer was obtained in 98% yield in exactly the same way from 4-methylcyclohexanone as colorless needles from ethanol, mp 163°.

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.46; H, 9.54.

4-*tert*-Butyl-2-hydroxycyclohexanone dimer was prepared similarly in 97% yield from 4-*tert*-butylcyclohexanone as colorless needles from ethanol, mp 116–118°.

Anal. Calcd for $C_{20}H_{36}O_4$: C, 70.55; H, 10.66. Found: C, 70.33; H, 10.45.

Ring Contraction of Cyclohexanone to Cyclopentanecarboxylic Acid.—Oxidation of cyclohexanone was conducted as described above, and the filtrate obtained after removal of the thallium(I) nitrate was heated gently under reflux for 30 min. Most of the acetic acid was then removed by distillation under reduced pressure, and the residue was neutralized with a solution of sodium bicarbonate. The resulting solution was washed with ether, reacidified with concentrated hydrochloric acid, and extracted with chloroform and the extracts were dried (Na_2SO_4). Removal of the solvent left a pale yellow liquid which on distillation gave 3.84 g (84%) of pure cyclopentanecarboxylic acid, bp 83–85° (5 mm) [lit.[18] bp 102° (14 mm)]. Identity of the acid was confirmed by conversion to the methyl ester and subsequent comparison of ir, nmr, and glpc data with those of a genuine sample.

Registry No.—TTN, 13746-98-0; 4-methyl-2-hydroxycyclohexanone dimer, 35326-28-4; 4-*tert*-butyl-2-hydroxycyclohexanone dimer, 35326-29-5.

(15) Melting points were determined using a Kofler hot-stage microscope melting point apparatus and are uncorrected. Where appropriate, identity of compounds was confirmed by comparison of ir spectra, determined on a Perkin-Elmer Model 257 grating infrared spectrophotometer using the normal Nujol mull or liquid film techniques.

(16) Dimerization of acyloins to 1,4-dioxanes is a general phenomenon: R. Jacquier, *Bull. Soc. Chim. Fr.*, 83 (1950). The acyloins may be regenerated from the dimers by treatment with dilute acid.

(17) P. D. Bartlett and G. F. Woods, *J. Amer. Chem. Soc.*, **62**, 2933 (1940).

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See Editorial, *J. Org. Chem.*, **37**, No. 19, 4A (1972).

A Novel β-Alkylation of Pyridine and Quinoline 1-Oxides[1]

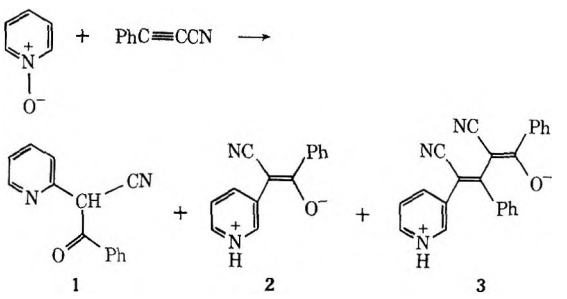
Summary: Pyridine and quinoline 1-oxide react with phenylpropiolonitrile to give a rearranged 3-alkylated derivative as the main product (whose structure has been confirmed spectroscopically, by degradation, synthesis, and, in the case of the pyridine derivative, by single-crystal X-ray analysis) together with minor amounts of the expected 2-alkylation product.

Sir: As a possible extension of the intramolecular nucleophilic substitutions leading to the direct acylamination of heteroaromatic *N*-oxides[2] we have studied the reaction of pyridine 1-oxide with phenylpropiolonitrile in boiling ethylene chloride.

The expected product (**1**) of intramolecular substitution at the α position was obtained in very low yield [mp 156–157°; ν (KBr) 2190 (C≡N), 1630 cm^{-1} (C=O); identical with an authentic sample prepared from pyridine 1-oxide, benzoylacetonitrile, and acetic anhydride]. The main product, isomeric with **1** and obtained in up to 56% yield, was a yellow solid, mp 238–239°. It exhibited bands at 2600–2340 (>NH$^+$), 2190 (C≡N), and 2120 cm^{-1} (w, br) and only a very weak broad band at 1640 cm^{-1}. Its nmr spectrum in CF_3CO_2H indicated the presence of two pyridine α protons [δ 9.44 (d, $J_{2,4}$ = 1 Hz, H_2), 8.59 (d, $J_{5,6}$ = 3 Hz, H_5)], a pyridine β proton [δ 8.07 (d d, $J_{4,5}$ = 4, $J_{5,6}$ = 3 Hz, H_5], and a γ proton [δ 8.92 (d t, H_4)] in addition to the phenyl protons and one proton which underwent H–D exchange. These data are consistent with structure **2** for this product, which was confirmed by its hydrolysis with dilute HCl to 3-pyridylacetic acid and benzoic acid, and by its synthesis from 3-pyridylacetonitrile and ethyl benzoate with NaOEt/EtOH.

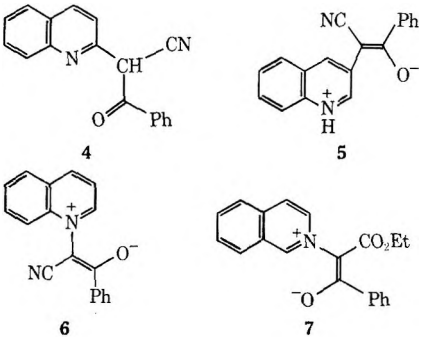
In view of the structure (**7**) of the adduct from isoquinoline 2-oxide and ethyl phenylpropiolate[3] (*vide infra*), the structure of **2** was also established by single-crystal X-ray analysis ($C_{14}H_{10}N_2O$): triclinic, $P\bar{1}$; a = 7.027 (6), b = 7.919 (6), c = 9.685 (7) Å; α = 90.75 (4), β = 95.28 (5), γ = 96.65 (5); ρ_{calcd} = 1.38 g cm^{-3} for Z = 2. Least-squares refinement gave R_1 (F) = 4.4% and R_2 (F) = 4.1% for 586 independent observed diffractometry data. The archistructure of **2** is depicted in Figure 1.

A third product, obtained in 6–17% yield, has been tentatively assigned structure **3** on the basis of its analysis, ir, and nmr spectrum (3-substituted pyridine, two Ph groups), and mass spectrum [*m/e* 349 (M$^+$), 105 (PhC≡O$^+$)].



1 2 3

Compounds **4** and **5** corresponding to **1** and **2** were obtained in 10 and 18% yields, respectively, from quinoline 1-oxide and phenylpropiolonitrile. Authentic **4** was synthesized from quinoline 1-oxide, benzoylacetonitrile, and acetic anhydride.[4] **5** had the expected nmr and mass spectra. From the complex residual reaction mixture a red solid (6.5%), mp 223–224°, was isolated by tlc and has been tentatively assigned structure **6** on the basis of its analysis and spectral properties: ν (KBr) 2170 cm^{-1} (C≡N) (no >NH$^+$); nmr ($CDCl_3$) δ 9.16 (1 H, d d, $J_{7,8}$ = 3, $J_{6,8}$ = 0.5 Hz, H_8), 8.68 (2 H, t, $J_{2,3}$ = $J_{3,4}$ = 4.5 Hz, H_2, H_4), 8.18–7.86 (4 H, m), 7.83 (2 H, t + q, $J_{2,3}$ = 4.5, $J_{7,8}$ = 3 Hz, H_3 and H_7), 7.45 (3 H, t, J = 1.5 Hz), no exchange with D_2O; mass spectrum *m/e* 272 (68) (M$^+$), 271 (86) (M$^+$ − 1), 105 (79) (PhC≡O$^+$), 77 (100) (Ph$^+$).



4 5 6 7

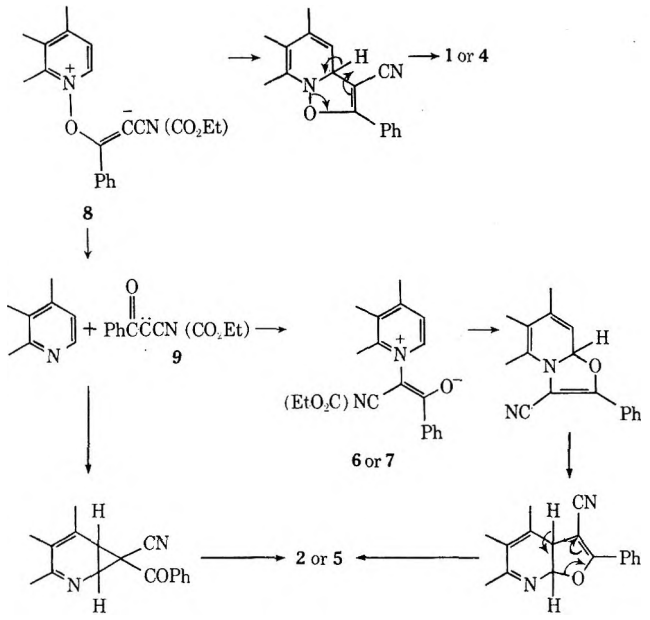
Huisgen, Seidl, and Wulff[3] reported the formation of the ylide **7** from isoquinoline 2-oxide and ethyl phenylpropiolate but no product of C-alkylation was found nor was a mechanism proposed for the formation of **7**. Our results and Huisgen's can be explained if the first step in the reaction is assumed to be the addition of the *N*-oxide to the triple bond to give **8**. This can either undergo intramolecular cyclization and ring opening to give **1** and **4** (alternatively these could arise by 1,3-dipolar addition) or heterolysis to give the pyridine and the highly electrophilic benzoylcyano- (or

(1) Detailed experimental procedures and X-ray crystallographic data will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-37-3383. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

(2) R. A. Abramovitch and G. M. Singer, *J. Amer. Chem. Soc.*, **91**, 5672 (1969); R. A. Abramovitch and R. B. Rogers, *Tetrahedron Lett.*, 1951 (1971).

(3) R. Huisgen, H. Seidl, and J. Wulff, *Chem. Ber.*, **102**, 915 (1969).

(4) M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (*Tokyo*), **11**, 415 (1963).



carbethoxy-) carbene (**9**) which, on recombination, would give **6** or **7**. Two routes can then be envisioned to **2** and **5**: (i) cyclization of the ylide followed by a 1,5-sigmatropic shift,[2] or (ii) addition of the carbene to C_2–C_3 of the pyridine ring followed by ring opening, in an analogous fashion to the formation of 3-benzenesulfonylaminopyridines from benzenesulfonylnitrene.[5] The mechanism of the reaction is now under investigation. A similar pathway may be followed in the formation of the products of the reaction of 1-alkoxycarbonyliminopyridinium ylides with dimethyl acetylenedicarboxylate.[6]

(5) R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).

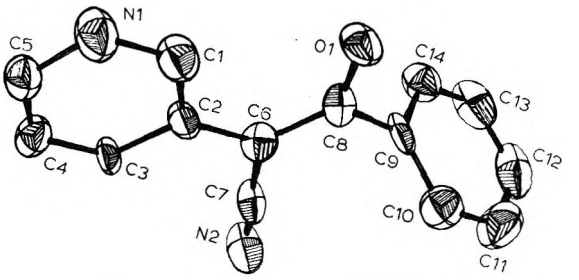


Figure 1.—Molecular structure of **2** with the thermal motions of the atoms represented by their 50% probability ellipsoids. Relevant bond distances follow: C6–C8, 1.424 (6); C6–C5, 1,450 (6); C6–C7, 1.426 (6); C8–C9, 1.485 (7); C8–O1, 1.265 (5); C7–N2, 1.161 (6) Å. The closest intermolecular approach is 2.609 (5) Å between N1 (H) and O1′. C2, C6, C7, C8, C9, and O1 are coplanar to within 0.03 Å; the plane thus constituted makes a dihedral angle of 81° with the plane of the phenyl group (C9, C10, C11, C12, C13, C14).

Acknowledgments.—This work was carried out with the support of an NIH grant (GM 16626) for which we are grateful.

(6) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **36**, 2979 (1971).

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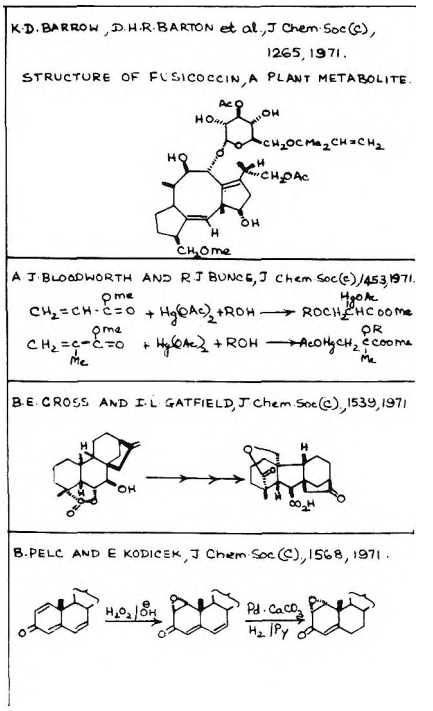

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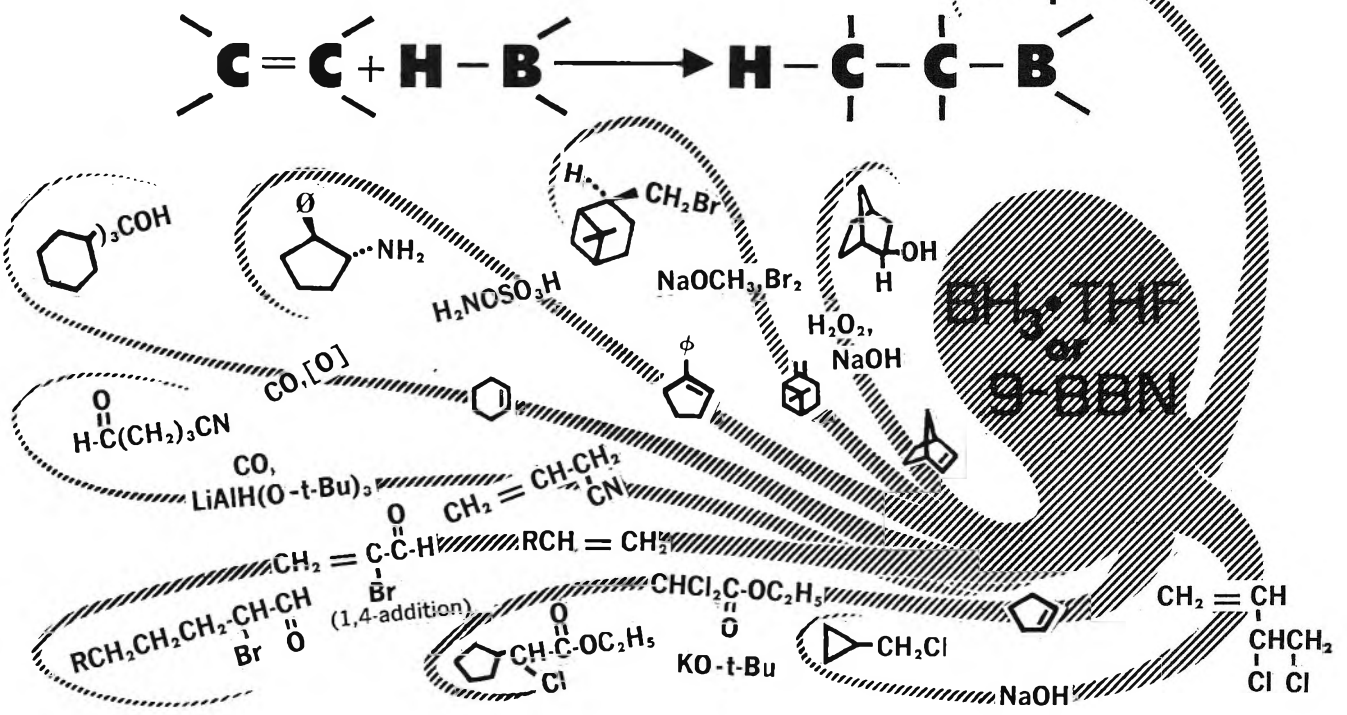

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