VOLUME 37 JULY 28, 1972 NUMBER 15 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

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

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

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JOCEAH 37(15) 2367-2522 (1972)

THE JOURNAL OF Organic Chemistry®

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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 15

JULY 28, 1972

Disulfur Monoxide. Reaction with Dienes

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Received December 29, 1971

Disulfur monoxide (S_2O) reacts with 2,3-disubstituted butadienes to form 4,5-disubstituted 3,6-dihydro-1,2-dithiin 1-oxides. The structure of 4,5-diphenyl-3,6-dihydro-1,2-dithiin 1-oxide (**3**) was established by independent synthesis. Reaction of *cis*- or *trans*-1,4-dibromo-2,3-diphenyl-2-butene (**5** or **4**) with sodium polysulfide in dimethylformamide gave a mixture of 4,5-diphenyl-3,6-dihydro-1,2-dithiin (**6**), 3,4-diphenylthiophene (**8**), and the cyclic tetrasulfide 6,7-diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin (**7**). Oxidation of **6** with hydrogen peroxide–formic acid gave **3**. Oxidation of **7** gave a monoxide formulated as 6,7-diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin 1-oxide (**9**).

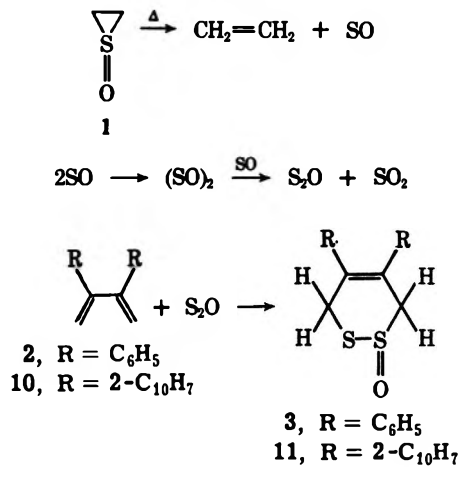
Reactions of sulfur dioxide with conjugated dienes to give five-membered ring sulfones are well known.[1] We have previously reported on the reactions of sulfur monoxide with conjugated dienes.[2] Interest in the reactions of the lower oxides of sulfur has prompted us to examine the reactions of disulfur monoxide (S_2O)[3] with substituted butadienes.

Saito[4] had shown that the sulfur monoxide (SO) generated by pyrolysis (580°, 0.02 mm) of thiirane oxide (**1**) had been converted almost entirely to S_2O (48%) and SO_2 (40%) on passage through a 30-cm tube. Since the only major contaminant was ethylene, we chose this method for the generation of disulfur monoxide. Evidence for the intermediacy of $(SO)_2$ in the conversion of sulfur monoxide to disulfur monoxide is provided by the mass spectrum[5] of thiirane oxide (**1**) [$(SO)_2$ *m/e* calcd 95.93396; found 95.9333; 0.048% of M^+ (*m/e* 76), the base peak].

Results

Disulfur monoxide generated by pyrolysis of thiirane oxide (**1**) reacted with 2,3-diphenylbutadiene (**2**) to give 4,5-diphenyl-3,6-dihydro-1,2-dithiin 1-oxide (**3**) (Scheme I). The structure of **3** was assigned from its analysis, from the presence of a very strong absorption band at 1064 cm^{-1} in its ir spectrum ($CHCl_3$), corresponding to an SO vibration frequency,[6] and from the presence of two overlapping AB quartets in its nmr spectrum. The structure of compound **3** was established by the independent synthesis outlined in Scheme II.

SCHEME I



The addition of 1 mol of bromine to 2,3-diphenylbutadiene (**2**) yielded *cis*- (**5**) and *trans*-1,4-dibromo-2,3-diphenyl-2-butene (**4**).[7] Reaction of the *cis*- (**5**) as well as the *trans*-1,4-dibromo-2,3-diphenyl-2-butene (**4**) with sodium disulfide in dimethylformamide gave

(1) (a) For a review of the early literature, see S. D. Turk and R. L. Cobb in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, pp 13–45. (b) W. L. Mock, *J. Amer. Chem. Soc.*, **88**, 2857 (1966). (c) S. D. McGregor and D. M. Lemal, *ibid.*, **88**, 2858 (1966).

(2) (a) R. M. Dodson and R. F. Sauers, *Chem. Commun.*, 1189 (1967); (b) R. M. Dodson and J. P. Nelson, *ibid.*, 1159 (1969).

(3) (a) For reviews of the synthesis of sulfur monoxide and disulfur monoxide, see P. W. Schenk and R. Steudel, "Inorganic Sulfur Chemistry," G. Nickless, Ed., Elsevier, London, 1968, p 366; P. W. Schenk and R. Steudel, *Angew. Chem., Int. Ed. Engl.*, **4**, 402 (1965). (b) For a more recent method for the generation of sulfur monoxide, see Y. L. Chow, J. N. S. Tam, and J. E. Blier, *J. Chem. Soc. D*, 1604 (1970).

(4) (a) S. Saito, *Tetrahedron Lett.*, 4961 (1968). (b) For alternate paths for the thermal decomposition of thiirane oxides, see J. E. Baldwin and G. Hofte, *J. Amer. Chem. Soc.*, **93**, 2810 (1971).

(5) J. P. Nelson, Ph.D. Thesis, University of Minnesota, Dec 1969; G. Liuti, S. Dondes, and P. Harteck, Abstract of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 40 T.

(6) S. Ghersetti and G. Modena [*Spectrochim. Acta*, **19**, 1809 (1963)] have reported a strong absorption band at 1075 cm^{-1} for $CH_3SS(O)CH_3$ in chloroform.

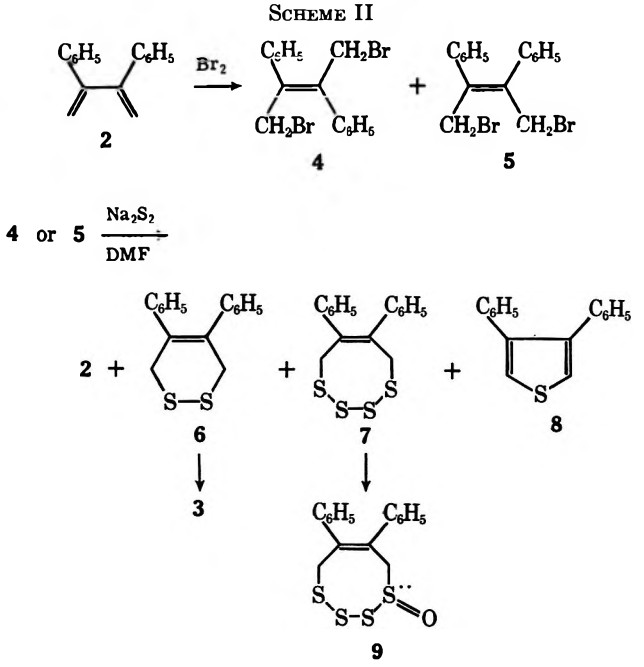
(7) C. F. H. Allen, C. G. Eliot, and H. Bell, *Can. J. Res.*, **17B**, 75 (1939).

TABLE I

1,4-Dibromo-1,4-diphenyl-2-butene	Composition of polysulfide	Temp, °C	Ratio of products: Disulfide	Tetrasulfide	3,4-Diphenylthiophene	2,3-Diphenylbutadiene	Total yield, %
cis-5	Na_2S_2	70[a]	1.0	Trace	2.4	Trace	70–80
trans-4	Na_2S_2	70[a]	1.0	Trace	1.7	0.19	70–80
trans-4	Na_2S_2	Room[b]	1.0	0.13	0.33	0.26	70–80
cis-5	Na_2S_4	70[c]	1.0	0.77	2.3		70–80
trans-4	Na_2S_4	70[a]	1.0	0.63	2.2		70–80
trans-4	Na_2S_4	50[b]	1.0	0.74	0.61		70–80
trans-4	Na_2S_4	Room[b]	1.0	0.67	0.73		5–10[d]
trans-4	Na_2S_6	50[b]	1.0	1.6	1.0		70–80
trans-4	Na_2S_8	50[b]	1.0	0.80	0.52		70–80

[a] These reactions were run using 16.4 mmol of the dibromide (4 or 5) and 19.7 mmol of the sodium polysulfide in 350 ml of dimethylformamide for 24 hr. [b] These reactions were run using 8.2 mmol of the dibromide (4 or 5) and 9.8 mmol of the sodium polysulfide in 175 ml of dimethylformamide for 24 hr. [c] This reaction was run using 5.5 mmol of the dibromide (5) and 6.6 mmol of the sodium polysulfide in 118 ml of dimethylformamide for 24 hr. [d] Polymeric materials were the predominant products.

SCHEME II



4,5-diphenyl-3,6-dihydro-1,2-dithiin (**6**) as one of the products (*vide infra*). The nmr spectrum of **6** showed a four-proton singlet at δ 3.33 for the methylene groups. This eliminated 3,4-diphenyl-1-sulfo-2,5-dihydrothiophene as a possible structure for **6**. Oxidation of **6** in chloroform solution with a hydrogen peroxide–formic acid mixture yielded **3** identical with **3** prepared above.

Disulfur monoxide (S_2O), generated by the pyrolysis of thiirane oxide (**1**), was also added to 2,3-di-2-naphthyl-1,3-butadiene (**10**) (Scheme I) to yield 4,5-di-2-naphthyl-3,6-dihydro-1,2-dithiin 1-oxide (**11**) which had spectral properties similar to those of **3**. Compound **11** could also be synthesized by the addition to **10** of disulfur monoxide generated by the reaction of cupric oxide and sulfur[8] at 300–350° at atmospheric pressure in a stream of helium. Attempts to add di-

$$CuO + 3S \xrightarrow{\Delta} CuS + S_2O$$

sulfur monoxide generated by this latter method to **2** gave detectable (nmr spectrum) but very low yields of **3**. Attempts to add disulfur monoxide generated from thiirane oxide to 1,3-pentadiene, 1,4-dichloro-1,3-butadiene, *trans,trans*-1,4-dimethyl-2,3-diphenylbutadiene, 1,3-di-*tert*-butylbutadiene, and 1,3-cyclopentadiene gave no detectable 3,6-dihydro-1,2-dithiin 1-oxides.

The 3,6-dihydro-1,2-dithiin 1-oxides (**3** and **11**) are unstable compounds. They decompose to diene on chromatography on silica gel or alumina, on drying *in vacuo* at 80°, and on being shaken in organic solvents with water. The compounds **3** and **11** are cyclic analogs of Allicin,[9] a bacteriostatic and fungistatic agent isolated from garlic. Compound **3** shows similar bacteriostatic and fungistatic properties.

The reaction of *cis*- (**5**) and *trans*-1,4-dibromo-2,3-diphenyl-2-butene (**4**)[10] with sodium polysulfide proved to be of considerable complexity. In addition to the 4,5-diphenyl-3,6-dihydro-1,2-dithiin (**6**) mentioned above, the following products were also obtained: 2,3-diphenylbutadiene (**2**), 6,7-diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin[11] (**7**), and 3,4-diphenylthiophene (**8**). The yield and composition of the product mixture, determined by analysis of the nmr spectrum of the crude product, depended on the temperature of the reaction and the ratio of sodium sulfide to sulfur used (Table I). The yield of the tetrasulfide **7** was maximized by polysulfide of the composition Na_2S_6 and a temperature of 50°. It should be noted that both *cis*- and *trans*-1,4-dibromo-2,3-diphenyl-2-butene (**5** or **4**, respectively) gave essentially the same mixture of **2**, **6**, **7**, and **8** when allowed to react under similar conditions. More 3,4-diphenylthiophene (**8**) was obtained from reactions run at 70° than from those run at lower temperature. Our failure to demonstrate the presence of any cyclic trisulfide is also of interest.

The structure of the 6,7-diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin (**7**) followed from its nmr spectrum, which showed a sharp singlet (δ 3.99) for the four methylene

(8) S. R. Satyanarayana and A. R. Vasudeva Murthy, *Proc. Indian Acad. Sci.*, **A59**, 263 (1964).

(9) C. J. Cavellito and J. H. Bailey, *J. Amer. Chem. Soc.*, **66**, 1950 (1944).

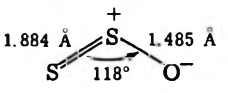
(10) Assignment of the stereochemistry of **5** and **4** is based on the direct comparison of the nmr spectra of **5** and **4** with the nmr spectra of the *cis*- and *trans*-α,α'-dimethylstilbene of established stereochemistry: Y. Nagai, O. Sumamura, and L. Ehara, *Bull. Chem. Soc. Jap.*, **35**, 244 (1962); O. Sumamura and H. Suzuki, *ibid.*, **27**, 231 (1954). *cis*-α,α'-Dimethylstilbene had mp 65.5–67.5° (lit. mp 67°); nmr ($CHCl_3$-*d*) δ 7.00 (s, $W_{1/2}$ = 2 Hz, 10.0, C_6H_5), 2.16 (s, 6.0, CH_3). *trans*-α,α'-Dimethylstilbene had mp 106–107° (lit. mp 107°); nmr ($CHCl_3$-*d*) δ 7.26 (s, $W_{1/2}$ = 1.5 Hz, 10.0, C_6H_5), 1.88 (s, 6.0, CH_3). In both series, the aliphatic protons of the cis isomer are deshielded and the aromatic protons of the cis isomer are shielded with respect to those of the trans isomer.

(11) H. Poisel and V. Schmidt [*Chem. Ber.*, **104**, 1714 (1971)] also obtained a cyclic tetrasulfide by the reaction of 3,6-dibromo-1,4-dimethylpiperazine-2,5-dione with sodium disulfide. For additional references to the formation of cyclic tetrasulfides see R. Rahman, S. Safe, and A. Taylor, *Quart. Rev., Chem. Soc.*, **24**, 208 (1970).

protons. Any branching in the sulfur portion of this cyclic compound should have resulted in two AB quartets for these protons in the nmr spectrum of **7**. When the nmr spectrum of **7** was taken at lower temperatures the singlet for methylene protons began to broaden and became quite broad ($W_{1/2}$ = 5.2 Hz) at −60°. This suggested a slow interconversion between different conformers of **7** at low temperatures, which became quite rapid at room temperature. Oxidation of **7** in methylene chloride solution with 1 molar equiv of *m*-chloroperbenzoic acid at −30° gave a monoxide (**9**), which showed two widely separated AB quartets in its nmr spectrum. This has been formulated as 6,7-diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin 1-oxide (**9**) in analogy with the oxidations of 1,5-dihydro-2,3,4-benzotrithiepin.[12] Attempted oxidation of **7** with 2 molar equiv of *m*-chloroperbenzoic acid gave sulfur, 3,4-diphenylthiophene (**8**), and another compound, which, because of its instability, has eluded characterization.

Discussion

Disulfur monoxide has been shown to have the following structural parameters.[13] From the dipole moment



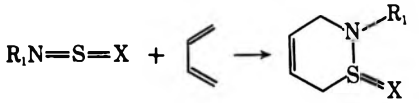
μ_{SSO} = 1.47 D
μ_{SO} = 1.58 D
μ_{SS} = 0.30 D

data it can be concluded that the bond order of the S–S bond would be close to 2.0.

Sulfur dioxide reacts with dienes to give five-membered ring sulfones in a concerted reaction.[1] Sulfur monoxide reacts with dienes to give five-membered ring sulfoxides. The latter reaction probably proceeds through a diradical intermediate.[2b,14] Phosphorus dihalides, phosphorus trihalides, and trialkyl phosphites also react with 1,3-dienes to give five-membered ring phosphorus containing heterocyclic compounds,[15] presumably *via* polar intermediates.[16]

In contrast, *N*-sulfinyl compounds react with 1,3-dienes to give six-membered ring compounds, 2-substituted 3,6-dihydro-1,2-thiazine 1-oxides, or 1-imines[17] (Scheme III). In the present work it has been shown that disulfur monoxide reacts similarly with 1,3-dienes to give six-membered ring products.

SCHEME III

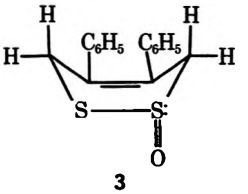


R_1 = C_6H_5, RC_6H_4, $C_6H_5SO_2$, or $RC_6H_4SO_2$

X = O or $NSO_2C_6H_5$

The reason for this difference in behavior of disulfur monoxide and *N*-sulfinyl compounds from sulfur dioxide and sulfur monoxide apparently lies in the availability, in the former compounds, of a double bond with a very low dipole moment (S=S or S=N) connected to an electron-withdrawing substituent. Orbitals on both atoms of this double bond are of such size and energy that overlap with orbitals on the diene is favorable. Hence, the S=S or S=N double bond is involved in the cycloaddition giving a six-membered ring. In sulfur dioxide and sulfur monoxide the high dipole moment of the S–O bond make it a poor dienophile. The orbitals on oxygen are small and of low (large negative) energy. This favors participation of nonbonding of antibonding electrons on sulfur in the cycloaddition and thus leads to five-membered rings.

Examination of a Dreiding model of compound **3** shows that the molecule prefers the boat conformation. In this conformation the double bond is predicted to have no effect on the coupling constants of the adjacent geminal protons, since the dihedral angle formed by one C–H bond and the plane of the double bond is about 120°, while the other C–H bond lies in the plane of the double bond.[18] The large observed geminal coupling constant ($J_{AB} = J_{A'B'}$ = 13.2 Hz) is consistent with predominance of that conformation possessing an axial sulfoxide[19] [13.7 Hz in 3,3,5,5-tetradeuteriothiane (ax) 1-oxide].[19] The geminal coupling constant adjacent to an equatorial sulfoxide has been found to be smaller [11.7 Hz in 3,3,5,5-tetradeuteriothiane (eq) 1-oxide].[19] The large separation of the chemical shifts of the geminal protons (δ ν_A 4.21, ν_B 3.68; $\nu_{A'}$ 4.44, $\nu_{B'}$ 3.68) also indicates the predominance of one conformer.[19b] However, with the information available, any direct assignment of the chemical shifts to the geminal protons would be speculative.



3

The distance between the axial protons in the boat conformation of **3** was estimated, from the Dreiding model, to be 2.6 Å. Since this is greater than twice the van der Waals radius of the hydrogen atom (2 × 1.2 Å), the steric interaction between these hydrogen atoms should not destabilize the boat conformation.

Experimental Section[20]

2,3-Diphenyl-2,3-butanediol.—Pinacolic reduction of acetophenone (95.50 g, 0.795 mol) in absolute ethanol (390 ml)–

(12) B. Milligan and J. M. Swan, *J. Chem. Soc.*, 2901 (1965).
(13) D. J. Meschi and R. J. Meyers, *J. Mol. Spectrosc.*, **3**, 409 (1959).
(14) R. A. Sikstrom, Ph.D. Thesis, University of Minnesota, Feb 1971.
(15) For a recent review of cycloaddition of trivalent phosphorus compounds see L. D. Quin in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, p 47.
(16) Y. Ogata and M. Yamashita, *J. Org. Chem.*, **36**, 2584 (1971).
(17) (a) For a recent review of the cycloaddition reactions of *N*-sulfinyl compounds see G. Kresge in, "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, p 453. (b) "Thionitrosobenzene" and phenylphosphinothioylidene also react with dienes to form six-membered ring compounds: P. Tavs, *Angew. Chem.*, **78**, 1057 (1966); S. Nakayama, M. Yoshifuji, R. Okazaki, and N. Inamoto, *J. Chem. Soc. D*, 1186 (1971). Mechanistically, the reactions of "thionitrosobenzene" resemble those of sulfur monoxide and apparently proceed *via* radical intermediates: R. M. Dodson and W. S. Li, unpublished results.
(18) M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85**, 1899 (1963).
(19) (a) B. J. Hutchinson, K. K. Anderson, and A. R. Katritzy, *ibid.*, **91**, 3839 (1969); (b) J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966); (c) A. B. Foster, T. D. Inch, M. H. Qadir, and J. M. Webber, *Chem. Commun.*, 1086 (1968); (d) see also R. M. Dodson, P. D. Hammen, and R. A. Davis, *J. Org. Chem.*, **36**, 2693 (1971); D. N. Harpp and J. G. Gleason, *ibid.*, **36**, 1314 (1971).
(20) All melting points were determined in capillary tubes on a calibrated Mel-temp melting point apparatus. Infrared spectra were determined on a Perkin-Elmer Model 257 spectrometer. Nuclear magnetic resonance spectra were taken on Varian Associates A-60 or T-60 spectrometers. All mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6D spectrometer by Mr. Adrian S. Swanson and his assistants. Anhydrous sodium sulfide was prepared by heating crystalline $Na_2S \cdot 9H_2O$ (Mallinkrodt Analytical Reagent) at 0.1 mm and 100° for 24 hr.

benzene (390 ml) solution with aluminum foil (Reynolds Wrap) (24.00 g, 0.890 g-atom) in the presence of a small amount of mercuric chloride (1.50 g, 5.5 mmol), according to the procedure of Newman,[21] gave a thick oil. This crude product was triturated with petroleum ether (bp 30–60°, 100 ml). The resulting white solid was collected on a Buchner funnel and washed with petroleum ether (25 ml), giving 2,3-diphenyl-2,3-butanediol isomers as a white solid (84.60 g, 88%), mp 74–85° (lit.[21] mp 100–123°, 54–59%, material obtained by distillation of crude product); ir (Nujol) 3300–3500 cm^{-1} (b s, OH); nmr (CCl_4) δ 7.15, 7.10 (9.9, 2-, 3-C_6H_5), 2.85 (b s, $W_{1/2}$ = 2 Hz), and 2.37 (b s, $W_{1/2}$ = 2 Hz) (2.0, 2-, 3-OH), 1.42, 1.37 (s, 6.1, 1-, 4-CH_3). The nmr spectrum indicates a 1:1 ratio of meso and dl isomers.

2,3-Diphenyl-1,3-butadiene (2).—2,3-Diphenylbutadiene has been prepared by Allen, Eliot, and Bell,[7] in 30% yield, by dehydration of 2,3-diphenyl-2,3-butanediol with acetyl bromide. Alder and Haydn[22] have prepared 2,3-diphenylbutadiene, in 80% yield, by dehydration of 2,3-diphenyl-2,3-butanediol with anhydrous potassium bisulfate at 150–170° (13 mm). We have found the latter method to be quite convenient for the preparation of 2,3-diphenylbutadiene, although, in our hands, the yield was only 35%.

2,3-Diphenyl-2,3-butanediol (50.00 g, 0.202 mol) was mixed with powdered, freshly fused potassium bisulfate (1.25 g, 9.2 mmol). The mixture was distilled at 13 mm by gradual heating with an oil bath to a final bath temperature of 210°. Heating had to be controlled very carefully between 160 and 180°. The product distilled between 145 and 170° (13 mm) and had a tendency to solidify in the condenser. The distillation took 2.5 hr. The distillate was cooled in a freezer (−15°). It was then slowly warmed to room temperature and filtered, giving 2,3-diphenylbutadiene (2) as a white, crystalline solid (10.40 g, 25%): mp 41–46°; nmr ($CHCl_3$-*d*) δ 7.03–7.47 (2-, 3-C_6H_5), ν_A 5.25, ν_B 5.47 (AB quartet, J_{AB} = 2 Hz, 1-, 4-CH_2).

The filtrate was dried (Drierite) in chloroform (80 ml) solution and then treated with bromine (11.10 g, 69.5 mmol) in chloroform (15 ml) at 0°. Removal of the solvent and trituration of the residue with acetone gave an off-white solid (10.4 g). Further trituration and crystallization of the residue from acetone gave *trans*-1,4-dibromo-2,3-diphenyl-2-butene (4) as a white, crystalline solid (8.80 g, 12%), mp 151.5–153° (lit.[7] mp 144–147°). The dibromide was converted to 2,3-diphenylbutadiene, mp 46–47° (lit.[7] mp 46–47°), with zinc in 90% yield according to the procedure of Allen, Eliot, and Bell.[7]

***cis*- and *trans*-1,4-Dibromo-2,3-diphenyl-2-butene (5 and 4).**—2,3-Diphenylbutadiene (13.00 g, 63.0 mmol) was dissolved in carbon tetrachloride (130 ml) and the solution was dried (Drierite). The solution was cooled in an ice bath and bromine (10.10 g, 63.2 mmol) in carbon tetrachloride (15 ml) was added drop by drop until the red color persisted (17.8 ml of bromine solution was needed). After 15 min the solvent was removed. The crude product was crystallized from acetone (*ca.* 130 ml) to give two crops of *trans*-1,4-dibromo-2,3-diphenyl-2-butene as white crystals (16.33 g, 71%): mp 151.5–153° (lit.[7] mp 144–147°); nmr ($CHCl_3$-*d*) δ 7.48 (s, 10.3, 2-, 3-C_6H_5), 4.05 (s, 3.7, 1-, 4-CH_2). The mother liquor was evaporated and the resulting greenish-white solid was dissolved in hot hexane. The solution was filtered from some greenish-black tarry material. When cooled, the solution deposited *cis*-1,4-dibromo-2,3-diphenyl-2-butene as a white, crystalline solid (2.75 g, 12%): mp 100.8–101.8°; nmr ($CHCl_3$-*d*) δ 7.13 (s, 10.1, 2-, 3-C_6H_5), 4.52 (s, 3.9, 1-, 4-CH_2).

Anal. Calcd for $C_{16}H_{14}Br_2$ (366.10): C, 52.49; H, 3.86. Found: C, 52.42; H, 3.80.

4,5-Diphenyl-3,6-dihydro-1,2-dithiin 1-Oxide (3).—A gas-phase pyrolysis apparatus was constructed which allowed passage of a gas through 30 cm of coiled Pyrex tubing (6 mm i.d.) which was itself heated in an Abderhalden-type chamber by refluxing solvent. With helium gas flowing through the chamber at the rate of 6 l./hr and heat being supplied by refluxing diphenyl ether (bp 259°), the gas exiting the chamber had a temperature of 250–259°. The residence time of the gas in the heated chamber under these conditions was estimated to be 2–3 sec. By the time the gas had traveled from the exit of the heated chamber to the reaction vessel itself (30 cm), it had cooled to slightly above room temperature.

Generation of Disulfur Monoxide from Thiirane Oxide.—Thiirane oxide (1) (1.00 g, 13.1 mmol) was placed in the vaporization chamber (a 125 ml, three-necked, round-bottom flask) and heated to 70° with an oil bath. Helium gas (6 l./hr) was passed over the surface of the thiirane 1-oxide and through the pyrolysis chamber, which was heated by refluxing diphenyl ether (bp 259°). The pyrolysis gases were passed through 30 cm of Pyrex tubing to the bottom of the reaction vessel (125 ml, three-necked, round-bottom flask, equipped with a water cooled condenser, a Drierite drying tube and a magnetic stirrer) into a stirred solution of 2,3-diphenyl-1,3-butadiene (2) (2.00 g, 9.7 mmol) in toluene (50 ml). This process was continued for 6 hr; during this time 0.30 g of thiirane oxide (1) had been evaporated. The toluene was then evaporated under reduced pressure at room temperature. Crystallization of the residue from carbon tetrachloride yielded 0.20 g (53% based on thiirane oxide consumed) of **3**: mp 126–127°; ir (KBr) 1490 (m, aromatic), 1440 (m), 1052 (vs, SO); ir ($CHCl_3$) 1064 cm^{-1} (SO); ir (CS_2) 1084 cm^{-1} (SO); nmr ($CHCl_3$-*d*) δ 7.18 (s, 10.3, 4-, 5-C_6H_5); two overlapping AB quartets: ν_A 4.21, ν_B 3.68 (J_{AB} = 13.2 Hz), $\nu_{A'}$ 4.44, $\nu_{B'}$ 3.68 ($J_{A'B'}$ = 13.2 Hz) (3-, 6-CH_2); mass spectrum molecular ion 286 (0.0023% of B), 284 (0.014% of B, M − 2), 270 (0.077% of B, M − O), 236 (0.001% of B, M − H_2SO, 3,4-diphenylthiophene), 206 (base peak, M − S_2O), 80 (94.6% of B, S_2O), 64 (27.0% of B, S_2), 48 (32.4% of B, SO).

Anal. Calcd for $C_{16}H_{14}OS_2$ (286.42): C, 67.10; H, 4.93; S, 22.39. Found: C, 66.63, 66.57; H, 4.87, 4.65; S, 21.88, 22.15.

Generation of Disulfur Monoxide from Cupric Oxide and Sulfur.—Cupric oxide (8.00 g, 0.10 mol) and sulfur (9.60 g, 0.30 g-atom) were powdered well, mixed with glass helices (8.00 g), and packed into a column (48 × 2.5 cm o.d.). This column was covered with asbestos sheet, wound with Nichrome wire (6.7 m, 22 ohms), and then fitted with a glass jacket (35.5 × 3.5 cm o.d.) placed 7.5 cm from the bottom of the column. The top of the column was connected through tygon tubing to a gas inlet tube leading to the bottom of a 100-ml, three-necked, round-bottomed flask fitted with a water condenser and a stopper. A solution of 2,3-diphenylbutadiene (1.00 g, 4.8 mmol) in toluene (50 ml) was placed in the flask. Pure and dry helium (dried with a Drierite tower) was passed at the rate of 200 ml/min through the system from the bottom of the packed column. The solution was stirred with a magnetic stirrer. The glass column was heated gradually by the heating coil starting with 30 V on the variac and increasing the voltage by 5 V every 30 min to a final voltage of 59 V. In a blank experiment 59 V was found to give a temperature of about 325° inside the column with the same helium flow. The gases from the top of the column were swept through the diene solution held at room temperature for 9 hr. The heating was stopped, and after the column had cooled to room temperature, the gas flow was stopped. The toluene solution was filtered to remove the small amount of suspended solids (sulfur?) and the filtrate was evaporated under vacuum at room temperature. The nmr spectrum ($CHCl_3$-*d*) of the residual pale yellowish-white solid (1.06 g) showed lines at 209, 222.5, 246, 259.75, and 273.5 Hz (downfield from tetramethylsilane) which corresponded to those of the adduct, 4,5-diphenyl-3,6-dihydro-1,2-dithiin 1-oxide (**3**). From the nmr spectrum the amount of the adduct was estimated to be about 3–4% of the residue. The rest was the unconverted diene **2**.

4,5-Diphenyl-3,6-dihydro-1,2-dithiin 1-Oxide (3) from 4,5-Diphenyl-3,6-dihydro-1,2-dithiin (6).—4,5-Diphenyl-3,6-dihydro-1,2-dithiin (0.100 g, 0.36 mmol) was dissolved in chloroform (5.0 ml) and the solution was cooled in an ice bath. Formic acid (0.4 ml) was added and the mixture was stirred to form an emulsion. Five drops of 30% hydrogen peroxide was added over a period of 5 min. The suspension was stirred for an additional 0.5 hr in an ice bath and then allowed to warm to room temperature over a period of 15 min. The reaction mixture was added to saturated sodium chloride solution (20 ml). The chloroform layer was separated. The aqueous layer was extracted twice with chloroform (15 ml). The combined chloroform layers were dried with Drierite for 1 hr. Removal of the solvent on a rotary evaporator left a pale yellowish-white solid (0.094 g). An nmr spectrum of this crude product showed the presence of the expected monosulfoxide, the starting disulfide, and a trace of 2,3-diphenylbutadiene. One crystallization from chloroform–petroleum ether (bp 60–70°) gave a pale yellowish-white solid, **3** (0.048 g, 45%), mp 126–127°, mmp 126–127° with the sample of **3** prepared by gas-phase pyrolysis of thiirane oxide. The ir and nmr spectra of the two samples were superimposable.

2,3-Di-2-naphthyl-2,3-butanediol.—β-Acetonaphthone (87.0 g, 0.515 mol) was dissolved in dry benzene (250 ml) and absolute

(21) M. S. Newman, *J. Org. Chem.*, **26**, 582 (1961).

(22) K. Alder and J. Haydn, *Justus Liebigs Ann. Chem.*, **570**, 201 (1950).

ethanol (250 ml). The resulting solution was heated to boiling, and aluminum foil (20.0 g, 0.740 g-atom) cut in small pieces (1 in.^{2}) was added to it at a rate that kept the mixture gently refluxing (*ca.* 1.5 hr). The reaction mixture was then heated under reflux for an additional 4 hr. It was cooled to 10°, and the complex was decomposed with cold, dilute hydrochloric acid. The suspension was extracted with benzene. The combined benzene extracts were washed with 5% hydrochloric acid, water, and 5% aqueous sodium bicarbonate and dried ($MgSO_4$). Evaporation of the solvent and trituration of the residue with petroleum ether afforded a white solid (70.0 g, 80%). Crystallization from benzene–petroleum ether gave 2,3-di-2-naphthyl-2,3-butanediol (65.0 g, 74%):[23] mp 179–182° (lit. mp 158–171°,[23a] 184°,[23b] 165–171°[23c]); ir (KBr) 3520 (ms), 3450 (bw, OH), 3035 (w, aromatic), 2960 (ms), 2925 (w, CH_3), 1620 (w), 1599 (ms), 1500 (ms, aromatic), 1370 (s), 1350 (ms), 1320 (ms, CH_3), 1150 (ms), 1110 (s), 1095 (vs, C–O), 895 (ms), 850 (s), 820 (s), 750 (vs, aromatic); nmr ($CHCl_3$-*d*) δ 8.00–7.20 (14.4, $C_{10}H_7$), 2.76, 2.36 (s, 2.0, 2, 3-OH), 1.64, 1.68 (s, 5.6, 1,4-CH_3). The two isomers are present in the ratio 1:2.3.

Anal. Calcd for $C_{24}H_{22}O_2$ (342.44): C, 84.18; H, 6.48. Found: C, 83.95; H, 6.26.

1,4-Dibromo-2,3-di-2-naphthyl-2-butene.—2,3-Di-2-naphthyl-2,3-butanediol (17.1 g, 0.05 mol) was mixed with β-naphthylamine (0.2 g), and acetyl chloride (freshly distilled and purified) (40 ml) was added. The reaction was vigorously exothermic, and the mixture started refluxing without further heating. When the vigor of the reaction had subsided, the mixture was heated under reflux for another 4 hr and then was cooled and added to ice–water. The aqueous suspension was extracted with benzene. The combined benzene layers were washed with water and 5% $NaHCO_3$ and dried ($MgSO_4$). The solvent was removed in a rotary evaporator, and the residue was dissolved in carbon tetrachloride (200 ml). Bromine (7.2 g, 0.045 mol) in dry carbon tetrachloride (90 ml) was added dropwise to the above solution, cooled in an ice–water bath. The solvent was removed under reduced pressure. Crystallization of the residue from acetone gave 11.5 g (49%) of 1,4-dibromo-2,3-di-2-naphthyl-2-butene: mp 205.5–206.5° dec; ir (KBr) 3030 (w), 3020 (w, aromatic), 2950 (w, CH_2), 1596 (ms), 1500 (ms, aromatic), 1426 (s), 1358 (s), 1200 (s), 1185 (s, CH_2), 1122 (ms), 1060 (w), 868 (s), 820 (s), 768 (ms), 748 (s), 740 (s), 730 (ms, aromatic); nmr ($CHCl_3$-*d*) δ 8.08–7.47 (14.0, $C_{10}H_7$), 4.28 (very small singlet), 4.20 (s, 4.0, 1,4-CH_2).

Anal. Calcd for $C_{24}H_{18}Br_2$ (466.22): C, 61.83; H, 3.89; Br, 34.28. Found: C, 16.90; H, 3.62; Br, 34.54.

2,3-Di-2-naphthyl-1,3-butadiene (10).—1,4-Dibromo-2,3-di-2-naphthyl-2-butene (9.3 g, 0.02 mol) was dissolved in acetone (250 ml) with stirring, and the resulting solution was heated to boiling. Zinc dust (3.8 g, 0.58 g-atom) was added at such a rate that gentle reflux was maintained. After the addition was completed (*ca.* 0.5 hr) the mixture was heated under reflux with stirring for another 2 hr and then was filtered while still hot. The filtrate was concentrated under reduced pressure and cooled. The resulting precipitate was collected on a Buchner funnel and dried under vacuum. Recrystallization from petroleum ether (bp 40–60°) gave 4.8 g (79%) of 2,3-di-2-naphthyl-1,3-butadiene: mp 143–144°; ir (KBr) 3025 (w), 1597 (ms), 1580 (s), 1500 (ms, aromatic), 1120 (ms), 905 (s), 893 (vs, $=CH_2$), 857 (s), 820 (vs), 765 (ms), 740 (vs, aromatic); nmr ($CHCl_3$-*d*) δ 7.93–7.23 (cm, 14.4, $C_{10}H_7$), 5.73, 5.45 (AB quartet, J_{AB} = 2 Hz, 4.0, 1,4-CH_2).

Anal. Calcd for $C_{24}H_{18}$ (306.41): C, 94.08; H, 5.92. Found: C, 93.82; H, 5.75.

4,5-Di-2-naphthyl-3,6-dihydro-1,2-dithiin 1-Oxide (11). A.—Disulfur monoxide, generated from cupric oxide and sulfur as described above, was passed in a stream of helium through a solution of 2,3-di-2-naphthylbutadiene (1.00 g, 3.3 mmol) in dry toluene (50 ml) in a 100-ml three-necked flask for 7 hr. The gas flow was stopped after the column cooled. The toluene solution was filtered on a Hirsch funnel to remove some suspended sulfur. The filtrate was evaporated in a rotary evaporator under reduced pressure without applying heat. The nmr spectrum of the residue showed the presence of unreacted diene and *ca.* 60% conversion of the diene to the desired adduct 11. The residue was dissolved in benzene, and petroleum ether (bp 30–60°) was added until the solution became cloudy. When cooled in the refrigerator, the solution deposited white, crystalline 4,5-di-2-naphthyl-3,6-dihydro-1,2-dithiin 1-oxide (11) (0.60 g, 48%): mp 138–139°; ir (KBr) 1595, 1500 (m, aromatic), 1060 (vs, S=O), 890 (m), 855 (s), 815 (s), 740 cm^{-1} (s, aromatic); nmr ($CHCl_3$-*d*) δ 8.00–7.10 (m, 14.15, $C_{10}H_7$), two overlapping AB quartets, ν_A 4.61, ν_B 3.79, J_{AB} = 13.4 Hz, $\nu_{A'}$ 4.37, ν_B 3.79, $J_{A'B'}$ = 13.4 Hz, 3,6-CH_2.

Anal. Calcd for $C_{24}H_{18}OS_2$ (386.54): C, 74.58; H, 4.69; S, 16.59. Found: C, 73.90, 73.94, 73.27, 73.62; H, 4.70, 4.68, 4.76, 4.78; S, 16.57.

B.—Disulfur monoxide was generated by the pyrolysis of thiirane oxide as described above. 2,3-Di-2-naphthylbutadiene (1.0 g, 3.26 mmol) was dissolved in toluene (50 ml) and the mixture of gases from the pyrolysis of thiirane oxide vapors was passed through this solution for 7 hr. The solvent was removed under reduced pressure at room temperature. The residue was dissolved in chloroform, and petroleum ether (bp 30–60°) was added until the solution became cloudy. On being cooled overnight, the solution deposited crystals of 11 (0.70 g, 56%), mp 138–139°. This material (11) was identical in all respects (mixture melting point and ir spectrum) with the sample described in A above.

Reaction of *trans*-1,4-Dibromo-2,3-diphenyl-2-butene with Sodium Tetrasulfide. 3,4-Diphenylthiophene (8), 4,5-Diphenyl-3,6-dihydro-1,2-dithiin (6), and 6,7-Diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin (7). A solution of *trans*-1,4-dibromo-2,3-diphenyl-2-butene (6.00 g, 16.4 mmol) in dimethylformamide (100 ml) was added slowly to the deep purple solution of anhydrous sodium sulfide (1.53 g, 19.7 mmol) and sulfur (1.89 g, 0.059 g-atom) in dimethylformamide (250 ml). The resulting mixture was stirred at 70° for 24 hr and then poured into water (700 ml) and ice (200 g). The aqueous suspension was saturated with sodium chloride and extracted with ether (3 × 200 ml, 2 × 150 ml). The combined ether extracts were washed with water (150 ml) and saturated sodium chloride solution (150 ml) and dried overnight (Drierite). Evaporation of the ether extracts under aspirator pressure left a red semisolid (4.5 g). Trituration of this residue with ether (2 × 20 ml) left a pale yellow solid residue (0.84 g). Trituration of this yellow residue with chloroform left a bright yellow solid (0.40 g), mp 119–120°, which was shown to be sulfur (mixture melting point). Evaporation of the chloroform triturates gave a very pale yellow solid (0.44 g, 1.32 mmol), mp 142–147°. A part of this solid was sublimed (100°, 0.1 mm). Crystallization of the white sublimate from chloroform–hexane gave 6,7-diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin (7) as white crystals: mp 151–152°; ir (KBr) 3040 (w), 3000 (w, aromatic), 2970 (w), 2900 (w, CH_2), 1597 (ms), 1570 (w), 1485 (s, aromatic), 1430 (vs, CH_2), 1220, 1205 (ms), 1073, 1023 (ms, aromatic), 930 (ms), 845 (ms), 775 (vs), 755 (vs), 740 (s), 700 (vs), 690 (vs, aromatic), 660 (ms); nmr ($CHCl_3$-*d*) δ 7.13 (s, 10.3, 6,7-C_6H_5), 4.09 (s, 3.7, 5,8-CH_2); nmr (CS_2) δ 7.07 (s), 3.99 (s). When the chloroform solution was cooled, the absorption band of the aromatic protons remained sharp while the absorption band of the methylenic protons broadened as shown (0°, $W_{1/2}$ = 0.70 Hz; −30°, $W_{1/2}$ = 1.3 Hz; −60°, $W_{1/2}$ = 5.2 Hz).

Anal. Calcd for $C_{16}H_{14}S_4$ (334.54): C, 57.45; H, 4.22; S, 38.34. Found: C, 57.52; H, 4.22; S, 38.72.

The ether triturate on evaporation gave a reddish yellow solid (3.41 g). This was chromatographed on silica gel. Elution with petroleum ether (bp 60–70°)–benzene (9:1) gave after some initial fractions containing sulfur, a pale yellow crystalline solid (1.71 g), mp 111–113°. Crystallization from ethanol–water gave 3,4-diphenylthiophene (8) as shiny white flakes (1.55 g, 6.56 mmol), mp 113–114° (lit.[24] mp 114°); nmr ($CHCl_3$-*d*) δ 7.32 (s) overlapping 7.24 (s).

Anal. Calcd for $C_{16}H_{12}S$ (236.34): C, 81.31; H, 5.12; S, 13.57. Found: C, 81.06; H, 5.13; S, 13.40.

Further elution with petroleum ether (bp 60–70°)–benzene (4:1) removed a pale yellow solid (0.99 g), which appeared to be a mixture of two compounds. Repeated extraction of this solid with hexane gave a white solid (0.20 g, 0.6 mmol; total 0.64 g, 1.91 mmol), mp 140–143°, which was shown to be identical with the 6,7-diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin isolated above (nmr spectrum).

The hexane extracts on evaporation gave 4,5-diphenyl-3,6-dihydro-1,2-dithiin (6), mp 89–93° (0.75 g, 2.77 mmol). Sublimation and crystallization of the sublimate from hexane gave analytically pure 4,5-diphenyl-3,6-dihydro-1,2-dithiin (6): mp

(23) (a) See ref 21; Newman reports a yield of 18%; (b) M. P. Balfe, J. Kenyon and C. E. Searle, *J. Chem. Soc.*, 380 (1951); (c) R. S. Davidson, P. F. Lambeth, F. A. Younis, and R. Wilson, *J. Chem. Soc. C*, 2203 (1969).

(24) O. Hinsberg, *Chem. Ber.*, **48**, 1611 (1915).

101–102°; ir (KBr) 3050 (w), 3035 (w), 3000 (w, aromatic), 2910 (w), 2865 (w, CH_2), 1600 (w), 1575 (w), 1489 (ms, aromatic), 1440 (ms), 1388 (ms, CH_2), 1245 (w), 1213 (w), 1160 (w), 1062 (w), 1027 (w, aromatic), 920 (w), 915 (w), 912 (w), 785 (ms), 780 (ms), 733 (ms), 718 (s), 686 (vs, aromatic); nmr ($CHCl_3$-*d*) δ 7.00 [s, 10.2, 4,5-(C_6H_5)], 3.33 (s, 3.8, 3,6-CH_2).

Anal. Calcd for $C_{16}H_{14}S_2$ (270.42): C, 71.07; H, 5.22. Found: C, 71.25; H, 5.29.

Further elution with ether gave an unidentified orange, pungent liquid (0.44 g) which was not identified.

6,7-Diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin is quite unstable towards heat. On sublimation, in addition to the white solid (**7**) isolated above, a yellow crusty solid was obtained. This was found to be a mixture of the tetrasulfide **7**, the disulfide **6**, 3,4-diphenylthiophene (**8**), and sulfur. Similar decomposition took place when **7** was heated in refluxing xylene.

The nmr spectrum of the initially isolated crude material in the above reaction showed the presence of all the compounds isolated above. Because of the clear separation of signals for methylenic protons in the tetrasulfide **7** from those in the disulfide **6**, calculation of the molar ratio of the three products was possible. The molar ratio tetrasulfide–disulfide–2,3-diphenylthiophene was calculated to be 1:1.6:3.5. This was almost identical with the ratio of the isolated products.

Reactions of *cis*- and *trans*-1,4-dibromo-1,4-diphenyl-2-butene with sodium polysulfide (Table I) were run using the conditions and method of analysis described above.

6,7-Diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin 1-Oxide (9).—6,7-Diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin (**7**) (0.91 g, 2.72 mmol) was dissolved in methylene chloride (36 ml) and cooled to −25 to −30°. A solution of *m*-chloroperbenzoic acid (0.55 g, 2.72 mmol) in 21 ml of methylene chloride was also cooled to −25 to −30° and was added drop by drop to the above solution with stirring over a period of 30 min. The resulting mixture was allowed to warm slowly to room temperature (1 hr) and gave a yellow solution. This was washed with 5% sodium bicarbonate solution (2 × 50 ml) and water (1 × 50 ml) and was dried overnight (Drierite). Evaporation of the methylene chloride solution gave a pale yellow solid, which on crystallization from carbon tetrachloride–hexane gave 0.34 g (0.96 mmol, 35%) of 6,7-diphenyl-5,8-dihydro-1,2,3,4-tetrathiocin 1-oxide (**9**): mp 135.3–137.3°; ir (KBr) 1060 cm^{-1} (S=O); nmr ($CHCl_3$-*d*) two overlapping AB quartets: ν_A 4.94, ν_B 3.62, J_{AB} = 14.3; $\nu_{A'}$ 5.32, $\nu_{B'}$ 4.49, $J_{A'B'}$ = 12.8; 7.13 (C_6H_5).

Anal. Calcd for $C_{16}H_{14}OS_4$ (350.54): C, 54.82; H, 4.02. Found: C, 54.80; H, 4.05.

Registry No.—**2**, 2548-47-2; **3**, 34826-14-7; **4**, 34804-71-2; **5**, 6363-17-3; **6**, 34804-73-4; **7**, 34804-74-5; **8**, 16939-13-2; **9**, 34804-76-7; **10**, 34804-77-8; **11**, 34792-39-7; disulfur monoxide, 20901-21-7; *meso*-2,3-diphenyl-2,3-butanediol, 4217-65-6; *dl*-2,3-diphenyl-2,3-butanediol, 22985-90-6; *meso*-2,3-di-2-naphthyl-2,3-butanediol, 24227-54-1; *dl*-2,3-di-2-naphthyl-2,3-butanediol, 24227-55-2; 1,4-dibromo-2,3-di-2-naphthyl-2-butene, 34804-80-3.

Acknowledgment.—Acknowledgment is made to the National Institutes of Health (Grant No. AM-12954) for support of this research.

Benzofurazan Oxide. Reaction with Sulfur Enolate Anions

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Received October 12, 1971

This paper reports a new synthesis of 2-substituted 1-hydroxy-3-oxobenzimidazoles, in fair yields, from the reaction of benzofurazan oxide and β-carbonyl sulfones. 2-Phenylthioacetophenone, however, gave the corresponding quinoxaline 1,4-dioxide.

The condensation of benzofurazan oxide (**1**) with enamines[3] and other enolate anions[4,5] to give substituted quinoxaline 1,4-dioxides has been reported and a mechanism for the reaction has been suggested. The condensation of benzofurazan oxide with primary and secondary aliphatic nitro compounds[6] in basic media to yield 1-hydroxy-3-oxobenzimidazole and 1,3-dioxobenzimidazole derivatives, respectively, has also been reported. In this paper we report a new synthetic route to 1-hydroxy-3-oxobenzimidazole (**4R**$_1$) and its 2-substituted derivatives from the reaction of β-keto sulfones **2** and α-sulfonyl carboxamides **3** with benzofurazan oxide in an alkaline medium (Scheme I). On the other hand, 2-phenylthioacetophenone reacted with benzofurazan oxide to give a compound similar to those described by Haddadin, *et al.*,[4] which was assigned the quinoxaline 1,4-dioxide structure (Scheme II). (The compounds obtained by the reaction of benzofurazan oxide with substituted 2-phenylthioacetophenone will be the subject of a subsequent paper.)

Synthesis.—β-Keto sulfones **2** and α-sulfonyl carboxamides **3** were synthesized by the direct reaction of sodium benzenesulfinate dihydrate with the corresponding α-halo ketones and α-halo amides, respectively.[7] 2-Phenylthioacetophenone (**7**) was prepared from 2-bromoacetophenone and sodium thiophenate in a Williamson type synthesis. The structures of all the starting materials were confirmed by ir and nmr spectroscopy.

The reaction of 2-benzenesulfonylacetophenone (**2R**$_1$) with benzofurazan oxide in 4% methanolic potassium hydroxide solution afforded 1-hydroxy-3-oxobenzimidazole (**4R**$_1$) in 90% yield. 2-Nitrobenzenesulfonanilide (**5**) and benzoic acid (**6**) were the major by-products that were isolated. The structure of **4R**$_1$ was established by its controlled reduction with carbon disulfide to 1-hydroxybenzimidazole (**11**), which is in tautomeric equilibrium with the 3-oxobenzimidazole **12**.[8] The melting point, ir, and nmr of **11** were identical with those of an authentic sample prepared by the reduction of *o*-nitroformanilide with ammonium sulfide.[9]

(1) Submitted in partial fulfillment of the doctoral degree requirements.

(2) Submitted in partial fulfillment toward the masters degree requirements.

(3) M. J. Haddadin and C. H. Issidoridis, *Tetrahedron Lett.*, 3253 (1965).

(4) M. J. Haddadin and C. H. Issidoridis, *J. Org. Chem.*, **31**, 4067 (1966).

(5) M. J. Haddadin, G. Agopian, and C. H. Issidorides, *ibid.*, **36**, 514 (1971).

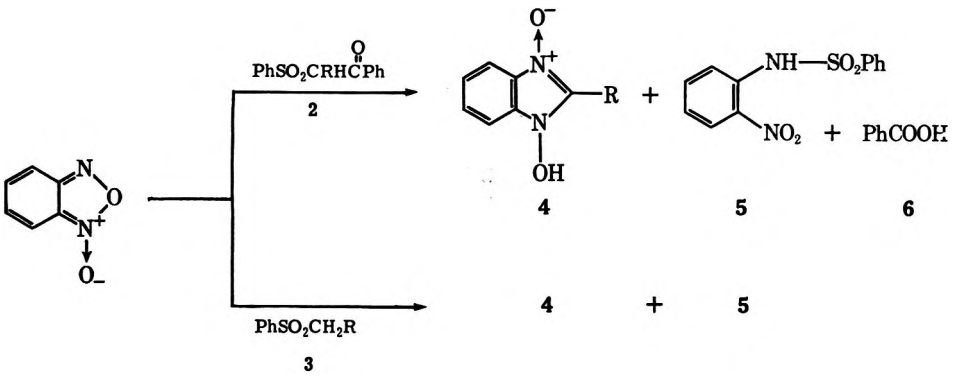
(6) (a) J. D. Johnston, M. Abu El-Haj, B. W. Doming, J. W. McFarland, C. H. Issidorides, and M. J. Haddadin, IUPAC Meeting in London, July 1968, Abstract H 4, 437; (b) 156th National Meeting, of the American Chemical Society, Atlantic City, N. J., Sept 1968; (c) M. J. Abu El-Haj, *J. Org. Chem.*, in press.

(7) C. M. Suter, "The Organic Chemistry of Sulfur," Wiley, Chapman and Hall, London, 1944, pp 658–762.

(8) S. Takahashi and H. Kano, *Chem. Pharm. Bull.*, **11**, 1375 (1963).

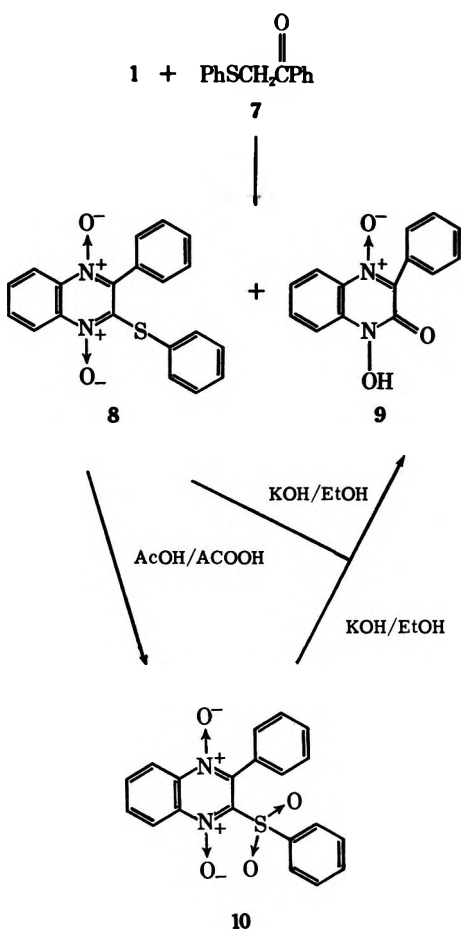
(9) S. von Niementowski, *Ber.*, **20**, 1874 (1887).

SCHEME I



2, R_1 = H; R_2 = CH_3; R_3 = Et; R_4 = Bu
3, R_5 = O=CNH_2; R_6 = O=CNHPh; R_7 = O=$CN(Et)_2$; R_8 = O=CN (i-Pr)$_2$; R_9 = morpholino carbonyl; R_{10} = O=$CNCH_3Ph$; R_{11} = O=COEt

SCHEME II



Its reduction with Raney Ni in alkaline solution gave benzimidazole **14** (Scheme III). No 2-benzenesulfonyl-3-phenylquinoxaline 1,4-dioxide (**10**) or 1-hydroxy-3-phenylquinoxalin-2-one 4-oxide (**9**), the product expected to result from **10** under the reaction conditions, were isolated or observed by separating the product on a Florisil chromatographic column or with tlc, and testing by ir spectroscopy.

2-Alkyl-2-benzenesulfonylacetophenones reacted with benzofurazan oxide in the same way to give the 2-alkyl derivatives of 1-hydroxy-3-oxobenzimidazole $4R_2$, R_3, R_4 in low yields. The structure of 1-hydroxy-2-methyl-3-oxobenzimidazole ($4R_2$) was proved by its independent synthesis from *o*-quinone dioxime and acetaldehyde as previously reported by Katritzky[10] and his coworkers.

2-Benzenesulfonylacetamides $3R_5$–R_{10} reacted with benzofurazan oxide in basic media to give 1-hydroxy-3-oxobenzimidazole-2-carboxamides $4R_5$–R_{10}, respectively. *o*-Nitrobenzenesulfonanilide was the only by-product that was isolated. Structural assignment of these compounds was based on their nmr spectra, elemental analyses, and their analogous ir spectra to that of the parent molecule (Table I).

Ethyl 2-benzenesulfonylacetate reacted with benzofurazan oxide in 4% methanolic potassium hydroxide solution to give 1-hydroxy-3-oxobenzimidazole-2-carboxylic acid ($4R_{11}$), which was isolated as a mixture of the acid and its potassium salt. Furthermore, the acid hydrolysis of 1-hydroxy-3-oxobenzimidazole-2-carboxamide ($4R_5$) gave an acid which was identical with $4R_{11}$.

2-Phenylthioacetophenone (**7**) was found to react with benzofurazan oxide in 1% methanolic potassium hydroxide solution to give 2-phenylthio-3-phenylquinoxaline 1,4-dioxide (**8**) and 1-hydroxy-3-phenylquinoxaline-2-one 4-oxide (**9**) with *o*-quinone dioxime, phenyl disulfide, and benzenethiol as by-products. No 1-hydroxy-3-oxobenzimidazole ($4R_1$) was detected. Treating **8** with methanolic potassium hydroxide converted it slowly to **9** with the liberation of benzenethiol. Oxidation of **8** gave 2-benzenesulfonyl-3-phenylquinoxaline 1,4-dioxide (**10**). The sulfone **10** reacted immediately with potassium hydroxide to give **9**. The structure of **8** was established by its ir spectrum, which displayed bands at 1340 (*N*-oxide), 750 (ortho-substituted phenyl), and 695 cm^{-1} (monosubstituted phenyl). The nmr spectrum showed singlets at δ 7.07 (5 H) and 7.30 ppm (5 H) and two multiplets centered at δ 7.69 (2 H) and 8.40 ppm (2 H). The two hydrogens at δ 8.40 ppm are consistent with the expected deshielding effect on the protons at positions 5 and 8. The ir spectrum of **9** displayed bands at 3460 (hydroxyl), 1608 (carbonyl), 1350 (*N*-oxide), and 760 cm^{-1} (ortho-substituted phenyl). Its nmr spectrum showed a multiplet centered at δ 7.88 ppm (8 H) and a doublet at δ 8.40

(10) A. J. Boulton, A. C. Gripper Gray, and A. R. Katritzky, *J. Chem. Soc. B*, 911 (1967).

SCHEME III

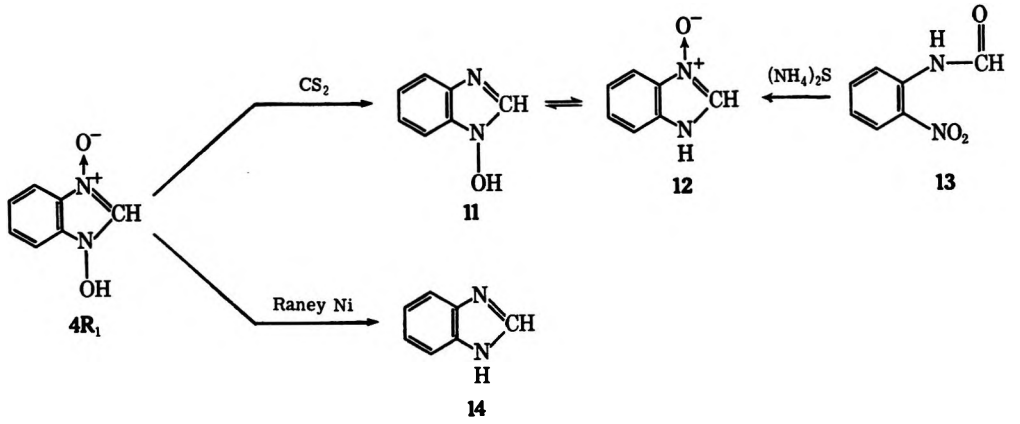


TABLE I

PHYSICAL CONSTANTS OF 1-HYDROXYBENZIMIDAZOLE 3-OXIDE DERIVATIVES (4)[a]

	R	Mp, °C	Yield, %	Nmr (CF_3COOH), ppm		J, Hz	Ir, cm^{-1}
R_1	H	224 dec	90	m 7.72	4 H		3085, 1340, 1255, 1217, 1145, 1065, 745, 640
				s 9.23	1 H		
R_2	CH_3	200–201 dec	35	s 2.91	3 H		3100, 1350, 1300, 1225, 1170, 1100, 1050,
				m 7.69	4 H		970, 870, 760, 740
R_3	Et	190–191 dec	28	t 1.58	3 H	7	1350, 1290, 1210, 1150, 1052, 855, 750
				q 3.48	2 H	7	
				m 7.70	4 H		
R_4	Bu	172–174 dec	24	t 1.05	3 H	5.5	3100, 1360, 1300, 1250, 1150, 1108, 1050,
				m 1.3–2.17	4 H		840, 740
				t 3.48	3 H	7.5	
				m 7.70	4 H		
R_5		218–220 dec	12	m 7.82	4 H		3280, 3130, 1685, 1608, 1480, 1340, 1300,
O=CNH_2				s 8.44	2 H		1215, 1165, 1100, 1015, 990, 860, 748,
							710, 680
R_6		218–219 dec	39	m 7.45	5 H		3270, 1687, 1605, 1561, 1352, 1320, 1302,
O=CNHPh				m 7.82	4 H		1257, 1210, 1112, 1022, 1000, 878, 742,
				s 10.08	1 H		720, 690
R_7		189–189.5 dec	57	t 1.41	3 H	7	3100, 1662, 1520, 1420, 1380, 1369, 1304,
O=CN$(Et)_2$				t 1.49	3 H	7	1269, 1212, 1150, 1135, 1117, 1099, 1073,
				q 3.60	2 H	7	877, 815, 745, 728
				q 3.88	2 H	7	
				m 7.82	4 H		
R_8		215–217 dec	51	d 1.4	6 H	6	3110, 1660, 1525, 1452, 1435, 1365, 1330,
O=CN$(i\text{-}Pr)_2$				d 1.65	6 H	6	1310, 1252, 1212, 1160, 1140, 1065, 1050,
				m 3.39–4.29	2 H		881, 748, 720
				m 7.75	4 H		
R_9		200–202 dec	65	m 3.65–4.2	8 H		1670, 1520, 1365, 1300, 1275, 1245, 1190,
morpholino carbonyl				m 7.81	4 H		1140, 1105, 1065, 1030, 845, 750
R_{10}		205–206 dec	50	s 3.77	3 H		1670, 1590, 1519, 1490, 1405, 1352, 1295,
O=CNCH_2Ph				s 7.39	5 H		1278, 1140, 1108, 1075, 1035, 875, 775, 745
				m 7.71	4 H		
R_{11}		>300 dec	40	m 7.75			3400, 1660, 1590, 1490, 1350, 1250, 1210,
O=COH							1150, 1085, 1000, 925, 875, 740

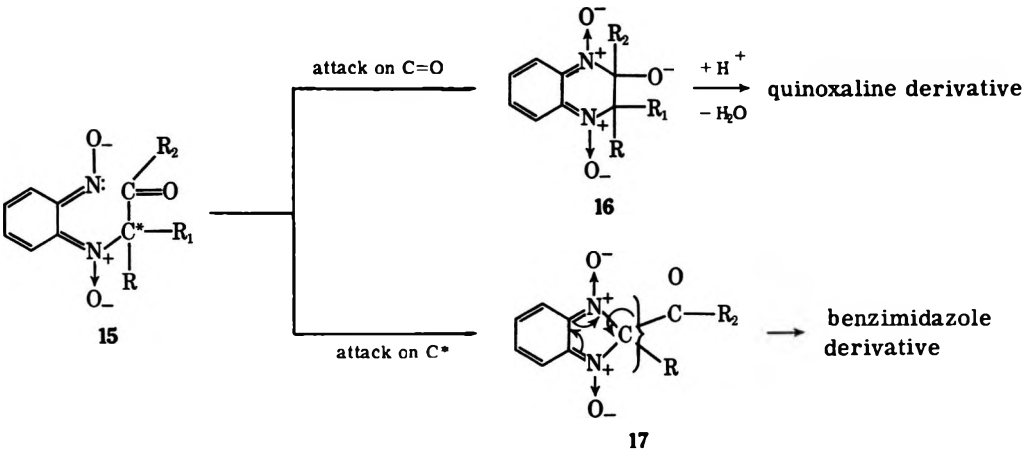
[a] Except for $4R_{11}$, which resisted recrystallization, the analyses of these compounds checked within 0.35%.

ppm (1 H, J = 8 Hz). In this case deshielding is reduced at position 8 and only the 5 proton absorbs downfield. The ir spectrum of **10** showed two bands at 1360 and 1340 cm^{-1} (N-oxide) in addition to the sulfone bands at 1318, 1165, and 1088 cm^{-1}. Further proof for the structural assignment of these compounds was based on their elemental analyses and on the fact that similar enolate anions gave the corresponding quinoxaline 1,4-dioxides.[2,3,4]

Under the reaction conditions none of the starting materials **2** or **3** were cleaved, thus eliminating the possibility of cleavage of either the sulfone or the carbonyl group in $2R_1$ as the initial step leading to product formation. Also, the synthesis of 1-hydroxy-2-phenyl-3-oxobenzimidazole failed due to the ease of cleavage of 2-phenyl-2-benzenesulfonylacetophenone to give phenyl benzyl sulfone and benzoic acid. This cleavage was also confirmed in the absence of benzofurazan oxide. Benzofurazan oxide is known to be readily reduced in alcoholic potassium hydroxide solution to give o-quinone dioxime;[11] however, o-quinone dioxime was also eliminated as a possible intermediate since it did

(11) D. L. Hammick, W. A. M. Edwardes, and E. R. Steimer, *J. Chem. Soc.*, 3308 (1931).

SCHEME IV



not react with 2-benzenesulfonylacetophenone under the reaction conditions. Benzofurazan oxide reacted when treated separately with sodium benzenesulfinate under the same reaction conditions to give *o*-nitrobenzenesulfoanilide (**5**) nearly quantitatively.

These data suggest that 1-hydroxy-3-oxobenzimidazole derivatives **4** and the substituted quinoxaline 1,4-dioxide **8** could have been formed through a mechanism involving an initial attack by the enolate anion on N_1, N_2, and/or on the dinitroso intermediate of the equilibrating benzofurazan oxide tautomers[12] to lead to intermediate **15**. It is not discernible at this time where the initial attack occurs or if different modes of attack result in different products. Once it is formed, intermediate **15** could cyclize by an internal condensation at the carbonyl carbon to lead through **16** to the quinoxaline derivative, and could also cyclize by a nucleophilic substitution at C* to lead through **17** to the benzimidazole derivative depending on the nature of R_1 (Scheme IV). A phenylsulfonyl group facilitates substitution because it is a better leaving group (pK_a of its corresponding acid is 1.84),[13] when compared with the thiophenoxide group (pK_a of its corresponding acid is 6.52).[14] Furthermore, the partial positive charge on the sulfur induces a positive charge on C*, thus making it more susceptible to nucleophilic attack. A similar case where the benzenesulfonyl group leaves very easily is the immediate reaction of 2-benzenesulfonyl-3-phenylquinoxaline 1,4-dioxide (**10**) with potassium hydroxide to give the corresponding ketone **9** and potassium sulfinate (Scheme II). A thiophenoxide or benzoyl group for R_1 makes substitution difficult in the first case and rather impossible in the latter case since neither one is a good leaving group. When a poor leaving group is present the attack is on the carbonyl carbon and the quinoxaline derivative forms. Once the five-membered ring **17** is formed, abstraction of the proton when R = H or cleavage of the ketone group when R = alkyl could lead directly to the product. Attempts to trap intermediate **17** by replacing R by a methyl and (COR_2) by a substituted amide failed and no reaction was observed between benzofurazan oxide and 2-benzenesulfonyl-*N*,*N*-diethylpropionamide.

(12) A. R. Katritzky and A. J. Boulton, "Advances in Heterocyclic Chemistry," Vol. 10, Academic Press, New York and London, 1969, p 5.

(13) R. K. Burkhard, D. E. Sellers, F. Decay, and J. L. Lambert, *J. Org. Chem.*, **24**, 768 (1959).

(14) M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, and L. T. Ditsch, *J. Amer. Chem. Soc.*, **82**, 4899 (1960).

Experimental Section

Melting points were obtained on a Mel-Temp apparatus and were uncorrected. Microanalyses were performed by M-H-W Laboratories. Infrared spectra were determined on a Perkin-Elmer Model 621 spectrometer. Nuclear magnetic resonance spectra were obtained with a Varian Model HA-60 spectrometer. Chemical shifts are reported in units using tetramethylsilane as an internal reference.

General Procedure for the Reaction of Benzofurazan Oxide with β-Carbonyl Sulfones.—In an erlenmeyer flask were placed 0.02 mol of the β-carbonyl sulfone, 5.44 g (0.04 mol) of benzofurazan oxide, and 50 ml of methanol. The crystals were dissolved by warming and 50 ml of 8% methanolic KOH solution was added. The solution was left at room temperature for 12 hr and was filtered from any *o*-nitrobenzenesulfonanilide (potassium salt) that could have formed. The solvent was evaporated to dryness and 15 ml of water was added to the resulting black residue. Stirring and cooling crystallized another portion of *o*-nitrobenzenesulfonanilide (potassium salt). The mixture was filtered and the black aqueous filtrate was neutralized with concentrated HCl until a few droplets of oil formed. The oil was extracted with ether and the aqueous layer was separated and neutralized further with concentrated HCl to give an oily precipitate. The precipitate was triturated with acetone to give fairly pure crystals of the 1-hydroxy-3-oxobenzimidazole derivative. The products were all soluble in acidic and basic media and insoluble in acetone and were recrystallized from methanol, ethanol, and/or water.

A.—When 2-alkyl-2-benzenesulfonylacetophenones (**2**) were allowed to react, the reaction mixture was warmed to 40–60° for 8 hr, then worked up.

B.—The reaction mixture with 2-benzenesulfonylacetamide (**3**, R = $CONH_2$) was warmed for 30 min and was then worked up.

C.—The reaction mixture with ethyl 2-benzenesulfonylacetate was warmed to 50° for 3 hr and the resulting 1-hydroxy-3-oxobenzimidazole-2-carboxylic acid was recrystallized by dissolving it several times in 1% KOH solution and neutralizing with HCl.

Reaction of Benzofurazan Oxide with 2-Phenylthioacetophenone (7).—In an erlenmeyer flask were placed 6 g (0.027 mol) of **7**, 3.6 g (0.027 mol) of benzofurazan oxide, and 100 ml of 1% ethanolic KOH solution. The mixture was kept at room temperature by cooling and was then stirred for 45 min. The solution was cooled in an ice bath and the heavy precipitate that formed was collected and recrystallized from ethanol to give 2.9 g (29%) of yellow crystals of 2-phenylthio-3-phenylquinoxaline 1,4-dioxide (**8**): mp 205–207°; nmr ($DCCl_3$) 7.07 (s, 5 H), 7.30 (s, 5 H), 7.69 (m, 2 H), 8.40 ppm (m, 2 H); ir 1340, 1310, 1265, 1080, 1020, 910, 783, 750, 740, 695 cm^{-1}.

Anal. Calcd for $C_{20}H_{14}N_2O_2S$: C, 69.36; H, 4.05; N, 8.10; S, 9.24. Found: C, 69.50; H, 4.05; N, 7.96; S, 9.13.

The methanolic filtrate from above was evaporated and the black oily residue was dissolved in 35 ml of water and extracted with ether to rid it of phenyl disulfide. The aqueous layer was neutralized with concentrated HCl until an oily precipitate formed. Recrystallization from ethanol afforded 1.83 g (26%) of hairy needles of 1-hydroxy-3-phenylquinoxalin-2-one 4-oxide (9): mp 195–196°; nmr (DMSO) 7.88 (m, 8 H), 8.40 ppm (d, 1 H); ir 3460, 1608, 1590, 1350, 1315, 1250, 1225, 1080, 890, 850, 760, 690 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.94; N, 11.02. Found: C, 66.36; H, 3.88; N, 11.16.

Reaction of 2-Phenylthio-3-phenylquinoxaline 1,4-Dioxide (8) with Peroxyacetic Acid.—In an erlenmeyer flask were placed 1 g (0.003 mol) of 8 and 30 ml of acetic acid. The solution was warmed to dissolve all the crystals and 6 ml of peroxyacetic acid was introduced. The solution was left for 24 hr and the precipitate that formed was collected and recrystallized from methanol to give 0.4 g (35%) of yellow needles of 10: mp 231–233°; nmr (CF_3COOH) 7.59 (m, 8 H), 8.40 (m, 4 H), 8.56 ppm (m, 2 H); ir 1360, 1340, 1318, 1270, 1165, 1088, 920, 780, 765, 730, 710, 690 cm^{-1}.

Anal. Calcd for $C_{20}H_{14}N_2O_4S$: C, 63.49; H, 3.57; N, 7.41; S, 8.47. Found: C, 63.40; H, 3.57; N, 7.28; S, 8.61.

Reaction of 1-Hydroxy-3-oxobenzimidazole ($4R_1$) with CS_2.—In an erlenmeyer flask was placed a mixture of 1.59 g (0.01 mol) of $4R_1$, 50 ml of methanol, and 8.6 g (0.1 mol) of CS_2 and the mixture was stirred vigorously until most of the crystals dissolved. The solution was filtered and the solvent was evaporated to dryness. The yellowish oily residue was freed of sulfur by triturating with CS_2. The oil that was left was recrystallized from ethanol to give 0.5 g (37%) of yellow crystals of 1-hydroxybenzimidazole (11): mp 210–212° (lit.[9] mp 210–212°); ir 3175, 1590, 1360, 1318, 1230, 1122, 1090, 990, 910, 840, 765, 750, 740, 720 cm^{-1}. Product 11 was identical (mixture melting point, superimposable ir spectra) with an authentic sample prepared by the reduction of *o*-nitroformanilide with ammonium sulfide.

Reaction of 1-Hydroxy-3-oxobenzimidazole ($4R_1$) with Raney Ni.—In a beaker were placed 1.5 g (0.01 mol) of $4R_1$ and 15 ml of 12% KOH solution. A total of 2 g of Raney Ni was introduced at several intervals of time while warming. The solution was filtered and was neutralized with concentrated HCl. The precipitate that formed was filtered and the neutral filtrate was extracted with ether. The precipitate was boiled with 75 ml of acetone and filtered. The ether extract and acetone filtrate were mixed and the solvent was evaporated. The resulting oil was recrystallized from water to give 0.15 g (13%) of benzimidazole 14: mp 171–172° (lit.[15] mp 171–172°); ir 3115, 1590, 1480, 1368, 1300, 1276, 1247, 1201, 1137, 1006, 960, 890, 770, 750 cm^{-1}. Product 14 was identical (mixture melting point, superimposable ir spectra) with an authentic sample of benzimidazole.

Reaction of 2-Phenylthio-3-phenylquinoxaline 1,4-Dioxide (8) or 2-Benzenesulfonyl-3-phenylquinoxaline 1,4-Dioxide (10) with Potassium Hydroxide.—In an erlenmeyer flask were placed 0.1 g of either 8 or 10 and 5 ml of 4% methanolic KOH solution. The solution was warmed for 2 hr, neutralized with HCl, and cooled in an ice bath. The crystals that formed were recrystallized from ethanol to give a product that was identical (mixture melting point, superimposable ir spectra) with 1-hydroxy-3-phenylquinoxalin-2-one 4-oxide (9).

Reaction of 1-Hydroxy-3-oxobenzimidazole-2-carboxamide ($4R_5$) with HCl.—In a round-bottomed flask equipped with a reflux condenser were placed 0.30 g of $4R_5$, 10 ml of H_2O, and 10 ml of concentrated HCl. The solution was refluxed for 12 hr, cooled, filtered, and neutralized with 40% KOH solution. The crystals that formed were collected, washed with water, and identified as a mixture of 1-hydroxy-3-oxobenzimidazole-2-carboxylic acid and its potassium salt $4R_{11}$.

Registry No.—$4R_1$, 15966-49-1; $4R_2$, 15966-52-6; $4R_3$, 31980-09-3; $4R_4$, 34759-66-5; $4R_5$, 34759-67-6; $4R_6$, 34759-68-7; $4R_7$, 34759-69-8; $4R_8$, 34759-70-1; $4R_9$, 34759-71-2; $4R_{10}$, 34759-72-3; $4R_{11}$, 34759-73-4; 8, 34759-74-5; 9, 33074-74-7; 10, 34759-76-7.

Acknowledgment.—This work was supported, in part, by a Faculty Research Grant from Memphis State University.

(15) Grassi, Gristaldi, and Lambardi, *Gazz. Chim. Ital.*, **25I**, 225 (1885).

Sulfonium Salts. V. The Pummerer Reaction of Dibenzyl Sulfoxide

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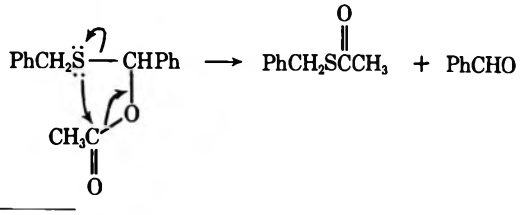
Received February 18, 1972

Dibenzyl sulfoxide reacts with acetic anhydride in chloroform and in carbon tetrachloride to provide α-acetoxybenzyl benzyl sulfide as the kinetically controlled product. Longer reaction times led to the products of thermodynamic control, α,α-bisbenzylthiotoluene and benzaldehyde. Benzyl sulfide and benzyl disulfide arise from attack of benzyl mercaptan on the intermediate acetoxysulfonium salt. A competitive kinetic isotope effect of *ca.* 9 characterizes the early stages of the Pummerer reaction.

Benzaldehyde, benzyl mercaptan, benzyl thiolacetate, and α,α-bisbenzylthiotoluene were reported in 1909 by Smythe[2] as the products[3] of the reaction of benzyl sulfoxide with acetic anhydride at 150°. Horner and Kaiser[4] reported that benzyl sulfoxide reacts slowly



with acetic anhydride in chloroform to provide benzaldehyde and benzyl thiolacetate, probably derived from α-acetoxybenzyl benzyl sulfide by an internal rearrangement, but no data supporting the structural assignments were given. The reaction with acetic anhydride has also been compared with the acid-catalyzed transformations of sulfoxides.[5]

Transformations of sulfoxides to α-acetoxy sulfides using acetic anhydride were observed by Pummerer[6] as early as 1909, and this classical reaction[6] bears his name. Since that time the scope of the reaction has been enlarged to encompass a group of similar reactions involving at some point reduction of a sulfonium sulfur atom in an organic molecule with subsequent oxidation of the α-carbon atom. Examples are varied, includ-

(1) Abstracted from a Ph.D. thesis to be submitted by C. J. Strong to the Graduate School of the Polytechnic Institute of Brooklyn in June 1973.

(2) J. A. Smythe, *J. Chem. Soc.*, **95**, 349 (1909).

(3) A recent review erroneously depicts the product as α-acetoxybenzyl benzyl sulfide: G. A. Russell and G. J. Mikol in "Mechanisms of Molecular Migrations," Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1968, p 157.

(4) L. Horner and P. Kaiser, *Justus Liebigs Ann. Chem.*, **626**, 19 (1959).

(5) D. A. Davenport, D. B. Moss, J. E. Rhodes, and J. A. Walsh, *J. Org. Chem.*, **34**, 3353 (1969).

(6) (a) R. Pummerer, *Ber.*, **42**, 2282 (1909); (b) C. R. Johnson and W. G. Phillips, *J. Amer. Chem. Soc.*, **91**, 682 (1969).

ing rearrangements of halosulfonium salts to form α-halo sulfides,[7] reactions of sulfoxides with acids to form α-hydroxy sulfides,[7,8] and reactions of methoxysulfonium tetrafluoroborate salts with base to form α-methoxy sulfides.[9]

We initiated our studies on the benzyl sulfoxide–acetic anhydride reaction to provide a direct comparison with the benzyl sulfide–chlorine reaction and to better understand the mechanism of the Pummerer reaction.

Results

Reactions of benzyl sulfoxide with acetic anhydride were conducted at 76° as solutions in deuteriochloroform solution and as suspensions in carbon tetrachloride. Product appearance was followed by quantitative nmr techniques.

The products initially formed were α-acetoxybenzyl benzyl sulfide (I) and acetic acid (II); however, benzyl disulfide (III), benzyl sulfide (IV), benzaldehyde (V), and α,α-bisbenzylthiotoluene (VI) appeared subsequently. After extended reaction periods an additional product, benzyl thiolacetate, was found in small quantities.

The identity of the products II–VI in the mixture

$$PhCH_2\overset{\overset{O}{\|}}{S}CH_2Ph \xrightarrow{Ac_2O} \underset{I}{PhCH(OAc)SCH_2Ph} + \underset{II}{HOAc} + \underset{III}{(PhCH_2S)_2} + \underset{IV}{(PhCH_2)_2S} + \underset{V}{PhCHO} + \underset{VI}{(PhCH_2S)_2CHPh}$$

was established by enhancement of appropriate peaks in the nmr spectra caused by addition of authentic materials. Chemical shift assignments are presented in Table I. No benzyl mercaptan was observed in any reaction.

TABLE I

CHEMICAL SHIFTS OF COMPONENTS OF THE REACTIONS OF BENZYL SULFOXIDE WITH ACETIC ANHYDRIDE[a]

Compd	Proton	δ_{DCCl_3}
Benzyl sulfoxide	CH_2	3.75, 4.00[b]
α-Acetoxybenzyl benzyl sulfide	CH_2	3.60, 3.97[b]
	CH	6.92
Dibenzyl sulfide	CH_2	3.55
Dibenzyl disulfide	CH_2	3.58
Benzyl thiolacetate	CH_2	4.10
	CH_3	2.30
Benzaldehyde	CH	10.00

[a] In parts per million downfield from TMS. [b] J = 13 Hz.

α-Acetoxybenzyl benzyl sulfide (I), a compound which has previously eluded detection in the reaction of benzyl sulfoxide with acetic anhydride,[3b,4,8] was isolated in nearly pure form from the reaction mixture.

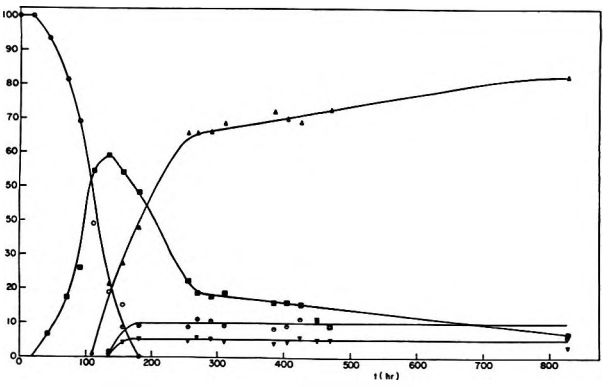


Figure 1.—Reactants and products for the Pummerer reaction of dibenzyl sulfoxide in $DCCl_3$: ■, α-acetoxybenzyl benzyl sulfide; ○, dibenzyl sulfoxide; △, α,α-bisbenzylthiotoluene; ◓, dibenzyl sulfide; ▼, dibenzyl disulfide.

This was accomplished by neutralizing the acetic acid in a carbon tetrachloride reaction. Solid potassium hydroxide was found to quench the acid-catalyzed conversion of I to V and VI to prevent the hydrolysis of the product. The nmr parameters of I are given in Table I. The mass spectrum of this material did not show a molecular ion, the highest mass peak corresponding to the ion derived by loss of ketene from the molecular ion. In spite of several attempts, the compound could not be obtained analytically pure by chromatographic methods or by distillation.

We have found the reaction of benzyl sulfoxide with acetic anhydride to be highly sensitive to the presence of traces of impurities. Reactions employing carefully recrystallized sulfoxide[10] and carefully cleaned glassware from which traces of acids had been removed by an ammonia rinse followed by a water rinse and oven drying at 120° had half-lives for the disappearance of sulfoxide on the order of a few days (Figure 1). At this time the product was mainly I. Reactions employing slightly impure material in both carbon tetrachloride and deuteriochloroform go to completion in less than 1 day and provide mainly V and VI. We have been unable to obtain sulfoxide dependably free from all trace impurities so that reliable rate data could be obtained. It was observed that addition of either acetic acid or *p*-toluenesulfonic acid resulted in rapid disappearance of starting material and the formation of V and VI. On the other hand, runs in both carbon tetrachloride and deuteriochloroform on several carefully degassed samples showed the reaction velocity and product distribution to be insensitive to dissolved oxygen.

Benzyl sulfoxide-α,α-d_2 for competitive kinetic isotope studies was obtained by oxidation of the sulfide with sodium metaperiodate.[11] In accord with previous observations,[12] no molecular ion for the sulfoxide could be obtained even at low ionizing voltages in the mass spectrometer, the peak at highest mass being that arising through loss of an oxygen atom.

Competitive kinetic isotope effects were obtained at regular intervals for several runs. The data for a

(7) For lead references, see G. E. Wilson, Jr., and M. G. Huang, *J. Org. Chem.*, **35**, 3002 (1970).

(8) H. D. Becker, *ibid.*, **29**, 1358 (1964); J. A. Walsh, *ibid.*, **34**, 3353 (1969).

(9) (a) C. R. Johnson, J. C. Sharp, and W. G. Phillips, *Tetrahedron Lett.*, 5299 (1967); (b) C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, **32**, 1926 (1967).

(10) Some samples of the sulfoxide still contained trace amounts of the sulfone which could not be removed by further recrystallization from water–ethanol mixtures. We could not detect any effect of sulfone on the rate of disappearance of sulfoxide.

(11) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

(12) J. H. Bowie, D. H. Willlams, S.-O. Lawesson, J. Ø. Madsen, C. Nolde, and G. Schroll, *Tetrahedron*, **22**, 3515 (1966).

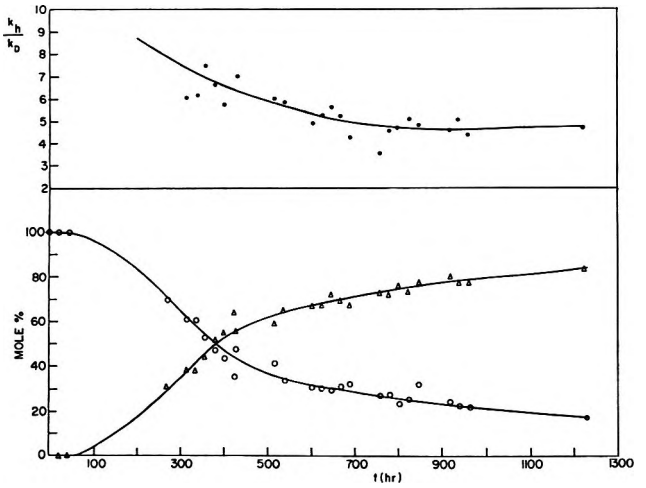


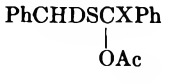
Figure 2.—Competitive kinetic isotope effect (top curve) and reaction progress (bottom curves) as functions of time: △, α-acetoxybenzyl benzyl sulfide; ○, dibenzyl sulfoxide.

typical run are presented in Figure 2. The competitive kinetic isotope effect was calculated from the integrals of the methine and methylene protons of VII and VIII,

VII VIII

respectively. The integrals of only half of the AB quartet of VIII were used because of interference from the proton signals of III and IV. Values of k_H/k_D were high at the onset of the reaction (see Figure 2) (~9) but the low concentration of product makes the accuracy at this point poor. Toward the end of the reaction the isotope effect decreased to a limiting value of *ca.* 4.5.

Scrambling of the label in α-acetoxy sulfide due to a preequilibrium would give rise to IX in addition to VII



IX, X = H, D

and VIII and this would give rise to peaks for an unsplit proton symmetrically placed within the halves of the AB quartet of the methylene group of VIII. A careful scrutiny of this region using a 220-MHz spectrometer failed to reveal the presence of any such peaks. Under the conditions of the experiment we would expect to be able to observe a 5% contribution from IX.

In all runs the formation of benzyl disulfide takes place only so long as unreacted dibenzyl sulfoxide is present. The concentrations of disulfide and sulfide become constant before the complete disappearance of sulfoxide. The formation of disulfide was also shown to be independent of dissolved oxygen.

Experimental Section

Benzyl Sulfide-α,α-d_2.—This compound was prepared according to the procedure of Wilson and Huang.[7]

Dibenzyl Sulfoxide-α,α-d_2.—To a cold solution of 8.8 g of sodium metaperiodate in 40 ml of water and 40 ml of dioxane was added 8.8 g of benzyl sulfide-α,α-d_2. The resulting slurry was stirred for 72 hr with ice cooling, after which time 100 ml of methylene chloride was added. The methylene chloride layer was separated and dried over anhydrous sodium sulfate. The solvent was removed under vacuum, and the resulting solid dibenzyl sulfoxide-α,α-d_2, 6.25 g (65% of theory), was recrystallized from ethanol–water to yield colorless plates, mp 131–134°. The absence of sulfide contamination was established by nmr. The compound shows ir absorption at $\nu_{max}^{CHCl_3}$ 1073, 769, and 700 cm^{-1}, and nmr resonances at δ_{CDCl_3} 7.3 (m, 5) and 3.9 ppm (s, 2).

General Procedure for Pummerer Reactions.—Solutions in deuteriochloroform containing 10–15% by weight of benzyl sulfoxide and 1.0–1.5 equiv of freshly distilled, acetic acid free acetic anhydride in sealed nmr tubes were maintained at 76° by total immersion in a constant-temperature bath. The insolubility of benzyl sulfoxide in carbon tetrachloride necessitated that these reactions be initiated as slurries. Solution was achieved as the reaction progressed. In several runs the samples were degassed and sealed under vacuum using three freeze–thaw cycles. In some runs methylene chloride was added as an internal standard for integration. In others, *p*-toluenesulfonic acid, pyridine, or acetic acid was added. The samples were removed at approximately 20-hr intervals and subjected to 60-MHz nmr analysis at ambient temperature.

Oxidation of Benzyl Mercaptan by Benzyl Sulfoxide and Acetic Anhydride.—Sulfone-free benzyl sulfoxide, 10% benzyl mercaptan (1.1 equiv), acetic anhydride (1.2 equiv), and methylene chloride as internal standard in deuteriochloroform solution were sealed in an nmr tube and kept in a constant-temperature bath at 76°. Quantitative conversion of benzyl sulfoxide to benzyl sulfide and conversion of most of the benzyl mercaptan to benzyl disulfide were observed by nmr after 15 hr.

Oxidation of Benzyl Mercaptan with Benzyl Sulfoxide.—A solution of benzyl mercaptan and excess sulfone-free benzyl sulfoxide in deuteriochloroform was sealed in an nmr tube and kept in an oil bath at 76°. After 8 days, no reaction had occurred, but after 2 months 50% of the starting benzyl mercaptan had been converted to benzyl disulfide.

α,α-Bisbenzylthiotoluene.—Benzyl mercaptan and excess benzaldehyde in carbon tetrachloride solution were heated under reflux for 15 hr. The resulting solution was analyzed by nmr and found to contain an aldehyde proton singlet and phenyl multiplet that corresponded to benzaldehyde. An AB quartet (δ 3.58), methinyl singlet (δ 4.50), and phenyl singlet (δ 7.3) were assigned to α,α-bisbenzylthiotoluene.

Oxidation of *p*-Methylbenzyl Mercaptan by Benzyl Sulfoxide and Acetic Anhydride.—To a 12% solution of benzyl sulfoxide in carbon tetrachloride in an nmr tube was added 1 equiv of *p*-methylbenzyl mercaptan and 1.2 equiv of acetic anhydride, and the reaction mixture was maintained at 76° for 18 hr. At this time the sulfoxide had disappeared completely and new peaks were present 213 and 215 Hz downfield from TMS for sulfide and disulfide methylene groups. Separation of the mixture by preparative tlc and analysis of the two fractions by mass spectroscopy showed a molecular ion at *m/e* 214 for the fastest moving spot (dibenzyl sulfide). The slower moving spot, di-*p*-methylbenzyl disulfide, gave no molecular ion, but a peak at *m/e* 137 assignable to $p\text{-}CH_3C_6H_4CH_2S^+$.

Discussion

Sulfonium salts bearing one heteroatom attached directly to the sulfur atom are subject to destruction by anions through a variety of routes having roughly comparable free energies of activation. Thus attack of the anion on sulfonium salt IX may in principle take place

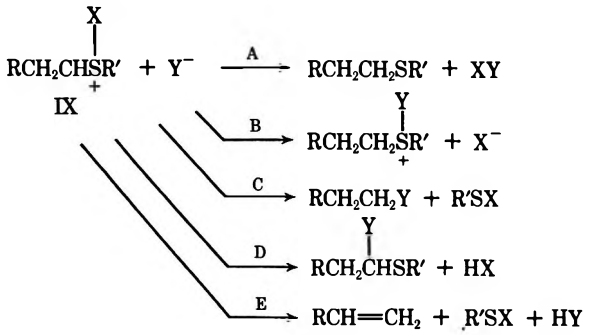


TABLE II

PRODUCT DISTRIBUTION FROM THE REACTIONS OF BENZYL SULFOXIDE WITH ACETIC ANHYDRIDE[a]

Reactants			Time, hr	Sulfoxide	α-Acetoxy sulfide	Sulfide	Disulfide	Thio-acetal	Benzyl-thiol acetate
$(PhCH_2)_2SO$	Ac_2O		20	100					
8% in $CDCl_3$	1.5 equiv		500	18	(max) 52	10	20		
			1000		38	15	30	17	
$(PhCH_2)_2SO$	Ac_2O		20	98	2				
9% in $CDCl_3$	1.2 equiv		130	27	(max) 58	1	2	12	
			1000		5	5	10	70	
$(PhCH_2)_2SO$	Ac_2O	AcOH	20	16	39	13	26	6	
20% in $CDCl_3$	0.6 equiv	0.4 equiv	40			33	66		
$(PhCH_2)_2SO$	Ac_2O	p-CH_3PhSO_3H	20			33	66		
20% in CCl_4	1.8 equiv	Trace							
			20	34	66				
$(PhCH_2)_2SO$	Ac_2O	Pyridine	200	5	66			2	
16% in $CDCl_3$	1.2 equiv	1.5 equiv	1000						
$(PhCH_2)_2SO$	Ac_2O	$PhCH_2SH$	20			100	*b*		
20% in $CDCl_3$	1.2 equiv	1.1 equiv							
$(PhCH_2)_2SO$		$PhCH_2SH$	20	100					
20% in $CDCl_3$		0.7 equiv	2000	66		33	*b*		
$(PhCH_2)_2SOCD_2Ph$	Ac_2O		20	20					
19% in $CDCl_3$	1.9 equiv		300	3	94	1	2		
$(PhCH_2)_2SO$	Ac_2O		20	98	2				
8% in CCl_4	1.5 equiv		1000	14	80	2	4		

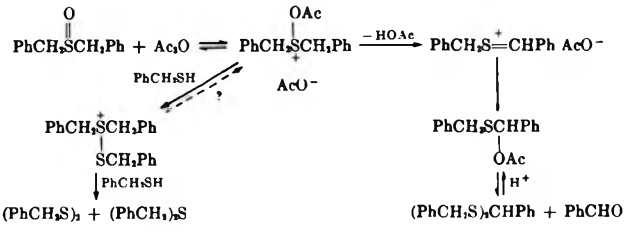
[a] Yields represent the distribution of the sulfur atoms from dibenzyl sulfoxide. Reaction temperatures were 76°. [b] For each mole of benzyl sulfide, one mole of benzyl disulfide is produced; however, this is formed entirely from the added mercaptan.

at the heteroatom (pathway A) to yield a sulfide, at the sulfur atom (pathway B) to yield a new sulfonium salt, at the α-carbon atom (pathway C) to produce products of carbon–sulfur bond cleavage, at the α proton (pathway D) to generate ultimately an α-substituted sulfide or its equivalent, or at the β-hydrogen atom (pathway E) to lead to an olefin and a sulfenyl derivative.

Minor changes in reagents or conditions can divert the entire reaction from one pathway to another. In the reduction of sulfoxides by aqueous hydrogen iodide it is clear that the final step must involve iodide ion attack at the iodine atom of an iodosulfonium salt.[13] By contrast, for the racemization of sulfoxides by hydrogen chloride in aqueous dioxane[14] the chlorosulfonium salt intermediate undergoes displacement by water at the sulfur atom. Chlorination of sulfides in nonnucleophilic solvents, on the other hand, leads to a chlorosulfonium chloride which usually decomposes to produduce α-halo sulfides.[7] Structural changes in the sulfide that stabilize positive charge on the α-carbon atom can lead to partial or total C–S bond cleavage.[7,15]

The reaction of benzyl sulfoxide with acetic anhydride represents a case where several pathways are followed concurrently. At the outset of the reaction (Figure 1) the kinetically favored process for decomposition of the postulated[16] acetoxysulfonium salt intermediate leads to α-acetoxy sulfide, probably by way of a sulfocarbonium ion as shown in Scheme I. In marked contrast to the chlorination of dibenzyl sulfide, in which nucleophilic displacement at the α carbon atom of the chlorosulfonium salt to produce benzyl chloride is an important side reaction throughout, the acetoxysulfonium salt does not suffer carbon–sulfur bond cleavage to provide benzyl acetate.

SCHEME I



The disproportionation of α-acetoxy sulfide takes place in what is probably a series of readily reversible, acid-catalyzed steps to produce the thermodynamically more stable couple, dithioacetal and benzaldehyde. This process must involve the production of benzyl mercaptan as an intermediate at some stage. As expected, the disproportionation becomes more severe as the progress of the Pummerer reaction effects an increase of the acetic acid concentration. Likewise it may be catalyzed by initially added acetic acid or p-toluenesulfonic acid (Table II). Significantly, the disproportionation is greatly retarded by the addition of pyridine (Table II), and this suggests that similar treatment might prove useful to ensure high yields of α-acetoxy sulfides in preparative reactions where disproportionation is troublesome.

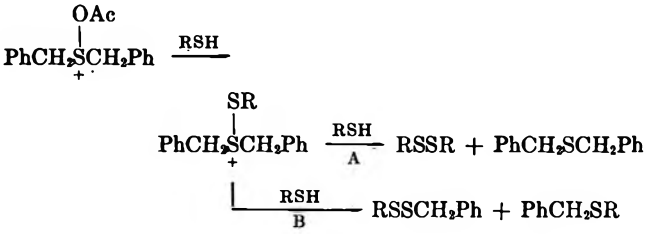
Benzyl mercaptan, when made available in low concentration through the disproportionation reaction, successfully competes with acetate anion to destroy the acetoxysulfonium salt intermediate of the Pummerer reaction, thus forming dibenzyl sulfide and dibenzyl disulfide. This can be seen in Figure 1, where sulfide and disulfide appear concurrently with dithioacetal. In fact, we have shown independently that the addition of benzyl mercaptan to a mixture of sulfoxide and acetic anhydride completely diverts the

(13) R. A. Strecker and K. K. Andersen, *J. Org. Chem.*, **33**, 2234 (1968).
(14) K. Mislow, T. Simmons, J. T. Melillo, and A. L. Ternay, Jr., *J. Amer. Chem. Soc.*, **86**, 1452 (1964).
(15) G. E. Wilson, Jr., *ibid.*, **87**, 3785 (1965); (b) K. C. Schreiber and V. P. Fernandez, *J. Org. Chem.*, **26**, 2910 (1961); (c) H. Kwart and J. Miller, *J. Amer. Chem. Soc.*, **80**, 884 (1958).
(16) See, for example, S. Oae and M. Kise, *Tetrahedron Lett.*, 1409 (1967).

reaction toward oxidation of mercaptan to disulfide. By contrast, in the absence of acetic anhydride only a very slow reaction occurs (Table II). Finally, it is interesting to note that the acetoxysulfonium salt does not act as an active ester toward mercaptan; only minor quantities of benzyl thiolacetate are isolated and only after extended reaction periods.

There are two possible loci for attack of a mercaptan on the thiosulfonium salt which must be formed as an intermediate (Scheme II): the α-carbon atom and

SCHEME II

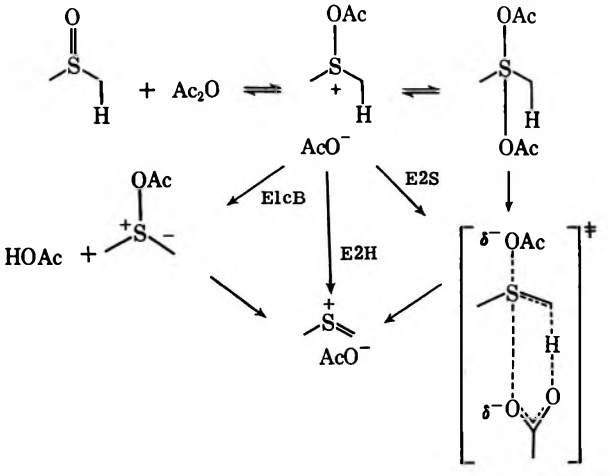


the monoalkylated sulfur atom. In the bromination of dibenzyl sulfide, in which a similar thiosulfonium salt intermediate could be imagined, bromide ion displacement at the α-carbon atom could be excluded as a source of disulfide because of the absence of benzyl bromide as a product in the reaction of benzylsulfenyl bromide with benzyl sulfide.[7] In the present case, the isolation of dibenzyl sulfide and di-*p*-methylbenzyl disulfide from the reaction of *p*-methyl benzyl mercaptan with benzyl sulfoxide and acetic anhydride establishes that mercaptan attack *via* pathway A (Scheme II) has occurred.

Such attack on sulfur is not an unreasonable hypothesis,[17] and it is well known that mercaptides are more thiophilic than nucleophilic. Although attack at the thiol sulfur might not have been expected to be as favorable as attack at the sulfonium sulfur atom, it is clear by inspection that the latter process is a nonproductive one. It may, in fact, be occurring much more rapidly than disulfide formation.

We envision a number of possible means of proton removal from the α-carbon atom (Scheme III) of a

SCHEME III



sulfoxide to produce the sulfocarbonium ion intermediate, all of which would lead to second-order kinetics as observed by Oae and Kise for the Pummerer reaction of aryl methyl sulfoxides.[16] According to current theory,[18,19] the irreversible E1cb route, which should be observed in the aprotic solvents generally used for these reactions, should provide an isotope effect near unity. The remaining three pathways should show $k_H/k_D > 1$, with a magnitude which varies as a function of the transition state symmetry.[20] Those features which make an elimination E1cb-like, an increase in leaving group ability or an increase in base strength, should lead to decreases in the magnitude of k_H/k_D. Since the acetate ion is roughly comparable to chloride ion in leaving ability and of similar basicity in aprotic solvents, we anticipated that the isotope effects on the proton removal steps should both be fairly large. This is indeed the case.

A noncompetitive isotope effect of 2.9 has been previously observed for the Pummerer reaction of aryl methyl sulfoxides by Oae and Kise[16] in a study where they also established that the reaction was overall second order. Noncompetitive isotope effects greater than unity are useful to provide assurance that a proton is being transferred in the slow step of a reaction. Although the k_H/k_D obtained by Oae and Kise[16] is lower than we would have expected, the magnitude depends upon the history of the species undergoing proton transfer. Thus it should reflect the isotope effects on all equilibria preceding proton removal as well as on the slow step. Therefore, we consider our data complementary to that of Oae and Kise,[16] and we consider that taken together they are most compatible with a direct elimination by an E2 or diacetoxysulfurane route not involving an ylide.

The decrease of k_H/k_D as the reaction proceeds is probably attributable to protonation of the acetate oxygen of the acetoxysulfonium salt or diacetoxysulfurane intermediates, thus increasing their leaving group ability.

We do not believe that these results rule out the possibility of an ylide intermediate in other Pummerer reactions, but we expect to observe this alternative pathway only when a strong base is available to remove the α proton. Investigations are in progress to evaluate this possibility.

Registry No.—Dibenzyl sulfoxide, 621-08-9; acetic anhydride, 108-24-7; α-acetoxybenzyl benzyl sulfide, 34804-03-0; dibenzyl sulfoxide-α,α-d_2, 34804-04-1.

Acknowledgment.—We thank the donors of the Petroleum Research Fund of the American Chemical Society for partial support of this project (PRF No. 2679 A1,4). The research was also supported in part from a grant by the National Science Foundation (Grant GV 12278) and grants from the Research Corporation and Sloane Foundation to a consortium at the Rockefeller University for a 220-MHz nuclear magnetic resonance facility. Finally, we express our appreciation for an NDEA traineeship to C. J. S.

(17) See, for example, J. L. Kice and G. B. Large, *J. Amer. Chem. Soc.*, **90**, 4069 (1968).

(18) Z. Rappoport, *Tetrahedron Lett.*, 3601 (1968).

(19) The validity of k_H/k_D as a measure of the extent of proton transfer in the transition state has recently been questioned: F. G. Bordwell and W. J. Boyle, Jr., *J. Amer. Chem. Soc.*, **93**, 512 (1971).

(20) These arguments are based on an assumed analogy between base-promoted elimination reactions and sulfocarbonium ion formation, both of which involve the loss of HX from vicinal atoms and the development of p_π–p_π overlap.

The Reaction of the Bromo- and Fluoronaphthalenes with Butyl Mercaptide in Dimethyl Sulfoxide[1]

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Received January 18, 1972

1-Fluoro- and 1-bromonaphthalenes reacted with *n*-butyl mercaptide in DMSO to give *n*-butyl 1-naphthyl sulfide in good yields. 2-Fluoro- and 2-bromonaphthalenes reacted in a similar manner to yield *n*-butyl 2-naphthyl sulfide. *tert*-Butyl mercaptide reacted with the fluoro- and bromonaphthalenes to give the corresponding *tert*-butyl naphthyl sulfides. These reactions proved to be direct aromatic nucleophilic substitution reactions.

In a continuation of our interest in the base-catalyzed reactions of the halonaphthalenes,[3,4] we have treated the bromo- and fluoronaphthalenes with *n*-butyl and *tert*-butyl mercaptides in dimethyl sulfoxide (DMSO). The products of these reactions were the corresponding alkyl naphthyl sulfides.

Although there is much knowledge concerning the reactions of thiophenoxide and thiocyanate with aromatic halogen compounds[5-7] very little work has been done with the alkyl mercaptides. Miller has reported that methyl mercaptide is a much stronger nucleophile in aromatic nucleophilic substitution than thiophenoxide.[8,9] Caubere and coworkers have studied the reactions of ethyl mercaptide with bromo- and fluorobenzene in hexamethylphosphotriamide (HMPT).[10,11]

Results and Discussion

A mixture of the halonaphthalene, butanethiol, sodium methoxide, and DMSO was heated at reflux for 1 hr. Sodium methoxide was used as the base since the thiol is a much stronger acid than methanol.[12] Thus the solution would contain methanol and sodium butyl mercaptide. The completed mixture was added to water. The neutral fraction was separated and the products were analyzed by vapor phase chromatography (vpc).

The products proved to be the appropriate alkyl naphthyl sulfide and the dibutyl disulfide. For example, *n*-butyl 2-naphthyl sulfide was obtained in the reaction using *n*-butyl mercaptide and 2-bromo- or 2-fluoronaphthalene. No methyl naphthyl ether was observed in any of these reactions. Also no evidence of the 1,2-dehydronaphthalene intermediate, previously observed,[3,4] was detected. This was shown by the fact that no 2-napththyl sulfide was isolated from 1-bromo- or 1-fluoronaphthalene.

These results are very different from those previously observed for the reaction of bromonaphthalene with potassium *tert*-butoxide.[3,4] Both 1- and 2-bromonaphthalene (as well as the chloro- and iodonaphthalenes) gave a mixture of *tert*-butyl 1-naphthyl ether and *tert*-butyl 2-naphthyl ether with a product ratio of 0.36.[3,4] Fluoronaphthalene, on the other hand, gave only direct nucleophilic substitution products.[3] Direct nucleophilic substitution was observed in this latter case presumably because the electron-withdrawing fluorine atom facilitates attack by the nucleophile. This in effect makes fluoride ion a superior leaving group in aromatic nucleophilic substitutions. Indeed, the rate for nucleophilic substitution of various para-substituted halobenzenes is hundreds of times faster with fluorobenzene than bromobenzene.[13] This two orders of magnitude enhancement of the rate for nucleophilic substitution is enough to change the dehydronaphthalene mechanism to direct nucleophilic substitution in the case of the oxide bases.[3]

In the present work, only direct nucleophilic substitution was observed even in the case of bromonaphthalene. The alkyl mercaptides are very powerful nucleophiles. Miller has shown that thiomethoxide is 87 times more reactive to 1-fluoro-2,4-dinitrobenzene than methoxide in methanol solvent.[8] This type of enhancement in nucleophilicity may even be greater in DMSO. Bartoli and Todesco show a rate enhancement of over 100 for the reaction of *p*-nitrobromobenzene with phenoxide and thiophenoxide in DMSO.[7] Thus we would expect *tert*-butyl mercaptide to be about two orders of magnitude more reactive than *tert*-butoxide toward aromatic nucleophilic substitution. This enhancement toward nucleophilic substitution again would tip the scales from the dehydronaphthalene mechanism to direct nucleophilic substitution in the case of bromonaphthalene.

One other factor probably greatly affects this reaction. The alkoxides are very powerful bases in DMSO. *tert*-Butyl alcohol has a pK in DMSO of 29.2.[14] A comparable number for an alkyl mercaptan is not known. However, the pK probably would be below the alcohols. The use of a base which is weaker than *tert*-butoxide can change this reaction from the dehydronaphthalene mechanism to direct nucleophilic substitution. This is shown by the fact that the reaction of bromanaphthalene with *tert*-butoxide (pK 29.2)[14] gave the dehydronaphthalene mechanism;[4] with *n*-butoxide (pK probably the same as *n*-propyl alcohol = 28.0),[14] both dehydronaphthalene and direct nucleo-

(1) (a) Presented in part at the 26th Northwest Regional Meeting of the American Chemical Society, Bozeman, Mont., June 16–18, 1971. (b) This work was supported by the Research Division, Brigham Young University.

(2) National Defense Education Act Fellow, 1967–1970.

(3) R. H. Hales, J. S. Bradshaw, and D. R. Pratt, *J. Org. Chem.*, **36**, 314 (1971).

(4) J. S. Bradshaw and R. H. Hales, *ibid.*, **36**, 318 (1971).

(5) A. J. Parker, "Organic Sulfur Compounds," Vol. 1, N. Kharasch, Ed., Pergamon Press, New York, N. Y., 1961, p 103.

(6) A. J. Parker, "Advances in Physical Organic Chemistry," Vol. 5, V. Gold, Ed., Academic Press, London, 1965, p 173.

(7) G. Bartoli and P. E. Todesco, *Tetrahdron Lett.*, 4867 (1968).

(8) J. Miller and K. W. Kong, *Aust. J. Chem.*, **18**, 117 (1965).

(9) See also J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N. Y., 1968, pp 180–233.

(10) P. Caubere and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 3008 (1968).

(11) P. Caubere and M.-F. Hochu, *ibid.*, 2854 (1969).

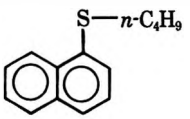
(12) See, for example, J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure," McGraw-Hill, New York, N. Y., 1968, p 220.

(13) See J. Miller, ref 9, pp 137–176, for specific examples.

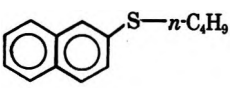
(14) See J. F. Coetzee and C. D. Ritchie, "Solute–Solvent Interactions," Marcel Dekker, New York, N. Y., 1969, Chapter 4.

TABLE I

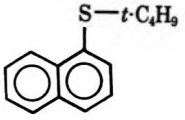
REACTION OF FLUORO- AND BROMONAPHTHALENE WITH SODIUM *n*-BUTYL AND *tert*-BUTYL MERCAPTIDES IN DIMETHYL SULFOXIDE[a]



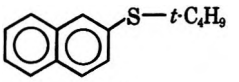
I



II



III



IV

Run	Registry no.	ArX	Registry no.	RS⁻	Time, hr	Conversion, %	Product yield, %[b] I	II	III	IV	Remarks
1	321-38-0	1-F	20733-16-8	*n*-Bu	1	96	83				Initial run gave 47%
2	323-09-1	2-F		*n*-Bu	1	80		51			
3	90-11-9	1-Br		*n*-Bu	1	80	96				Initial run gave 66%
4	580-13-2	2-Br		*n*-Bu	1	86		67			
5		1-F	20733-19-1	*t*-Bu	24	61			73		
6		2-F		*t*-Bu	24	55				48	
7		1-Br		*t*-Bu	24	41			54		Initial run gave 44%
8		2-Br		*t*-Bu	24	56				57	Initial run gave 47%

[a] A ratio of 1 mol of substrate, 2 mol of mercaptide, 3 mol of mercaptan, 15 mol of DMSO and 2 mol of methanol was used in all reactions. [b] Registry numbers: I, 5826-44-2; II, 5826-43-1; III, 25752-97-0; IV, 32689-97-7.

philic substitution were observed;[4] and with methoxide (pK 27.0),[14] only direct nucleophilic substitution was found.[15] It appears that relatively small changes in the pK can greatly affect this reaction. The fact that even *tert*-butyl mercaptide gave direct nucleophilic substitution (as contrasted to the oxide reactions[4]) probably means that the pK of *tert*-butyl mercaptan is less than 27.

Experimental Section

Materials and Apparatus.—The halonaphthalenes in this study were used as received: 1- and 2-bromonaphthalenes from J. T. Baker, 1-fluoronaphthalene from Aldrich Chemical, and 2-fluoronaphthalene from PCR Inc. The thiols were used as obtained from Aldrich Chemical. Sodium methoxide (Matheson, Coleman and Bell) was stored in a sealed container and used as received. J. T. Baker Reagent Grade dimethyl sulfoxide (DMSO) was passed through silica gel and stored over Linde 4A molecular sieves (Alfa Inorganic Chemical Co.).

All reaction runs were analyzed and the products were isolated using a Varian Aerograph 202-B temperature-programming vapor-phase chromatograph (vpc). All infrared (ir) spectra were obtained on a Perkin-Elmer 457 spectrophotometer. A Varian A-60A spectrometer[16] was used to obtain the nuclear magnetic resonance (nmr) spectra.

1-Fluoronaphthalene–*n*-Butyl Mercaptide Reaction (Run 1).—A stirred mixture of 11.25 g (0.125 mol) of *n*-butyl mercaptan, 2.7 g (0.05 mol) of sodium methoxide, and 78.0 g (0.375 mol) of DMSO was heated to 80° in a 100-ml, three-necked, round-bottom flask equipped with a reflux condenser, thermometer, addition funnel, heating mantle, and magnetic stirrer. 1-Fluoronaphthalene (3.65 g, 0.025 mol) was added and the stirred mixture was heated and refluxed (110°) for 1 hr. The reaction mixture was then added to 100 ml of ice water and extracted four times with 100-ml portions of ethyl ether. The combined ether extracts were washed with aqueous sodium hydroxide and dried over anhydrous magnesium sulfate. The oily residue (4.36 g) left after the ether was evaporated was the neutral fraction.

The aqueous layer from the reaction mixture was acidified and extracted with ethyl ether After drying and evaporation, the ether extract yielded less than 20 mg of an oily liquid. This same amount of material was found in the acidic layer of every run. The yield was so small that this material was not analyzed.

The neutral fraction was separated on the vpc using a 6 ft × 0.25 in. column packed with a mixture of 6% Carbowax 20M and 6% SE-30 on 60–80 mesh Chromosorb G, acid washed, at 200°. Analysis was done using 1-bromo-4-methylnaphthalene as an internal standard[17] for the *n*-butyl sulfide products and 1,4-dimethylnaphthalene as an internal standard for the *tert*-butyl sulfide products. The vpc was temperature programmed from 80 to 200° at a rate of 12° per minute.

Three compounds were isolated from the reaction mixture. These proved to be di-*n*-butyl disulfide[18] [*Anal.* Calcd for $C_8H_{18}S_2$: C, 53.87; H, 10.17; S, 35.95. Found: C, 53.85; H, 10.03; S, 35.78],[20] n^{29}D 1.4918 (lit.[21] n^{20}D 1.4926), 1-fluoronaphthalene (30%), and *n*-butyl 1-naphthyl sulfide (I, 47%, n^{29}D 1.6044). The *n*-butyl 1-naphthyl sulfide exhibited ir bands at 3055, 2955, 2930, 2875, 1590, 1560, 1500, 1460, 1380, 1260, 1215, 1200, 1025, 975, 790, 770, and 665 cm^{-1} and the following nmr peaks: δ 8.4 (m, 1), 7.3–7.8 (m, 6), 2.95 (t, 2), 1.40–1.80 (m, 4), 0.95 (t, 3). *Anal.* Calcd for $C_{14}H_{16}S$: C, 77.73; H, 7.46; S, 14.82. Found: C, 77.65; H, 7.57; S, 14.82.

2-Fluoronaphthalene–*n*-Butyl Mecaptide Reaction (Run 2).—This reaction was carried out in the same manner as the 1-fluoronaphthalene reaction except that a small portion of the DMSO was used to dissolve the 2-fluoronaphthalene in order to facilitate the addition. The reaction yielded 20% recovered 2-fluoronaphthalene and *n*-butyl 2-naphthyl sulfide (II, 51%, n^{29}D 1.6196). Compound II exhibited ir bands at 3080, 2960, 2930, 2870, 1625, 1590, 1570, 1500, 1460, 1430, 1380, 1335, 1270, 1220, 1190, 1130, 1070, 1015, 960, 940, 880, 850, 810, 740, and 600 cm^{-1} and the following nmr peaks: δ 7.10–7.80 (m, 7), 2.90 t, 2), 1.20–1.90 (m, 4), 0.90 (t, 3). *Anal.* Calcd for $C_{14}H_{16}S$: C, 77.73; H, 7.46; S, 14.82. Found: C, 78.00; H, 7.50; S, 14.96.

1-Bromo- and 2-Bromonaphthalene–*n*-Butyl Mercaptide Reactions (Runs 3 and 4).—These reactions were carried out the same as runs 1 and 2. The conversions and yields are given in Table I.

1-Fluoronaphthalene–*tert*-Butyl Mercaptide Reaction (Run 5).—This reaction was carried out the same as run 1 except that *tert*-butyl mercaptan was used and the reaction was refluxed at 95° for 24 hr. The products of this reaction proved to be di-*tert*-butyl disulfide (the ir spectrum of this material was similar to that of the di-*n*-butyl disulfide product) and *tert*-butyl 1-naphthyl sulfide (III, 73%, mp 53.5–55°). The ir spectrum for III exhibited bands at 3070, 3050, 2960, 2940, 2920, 2900, 2860, 1590, 1560, 1500, 1470, 1455, 1390, 1380, 1365, 1325, 1250, 1215, 1200, 1165, 1155, 1135, 1060, 1020, 975, 955, 865, 800, 775, 735, 670, 630, and 580 cm^{-1}. The nmr spectrum for III contained peaks at δ 8.60–8.80 (m, 1), 7.10–7.80 (m, 6), and 1.20 (s, 9). *Anal.* Calcd for $C_{14}H_{16}S$: C, 77.73; H, 7.46; S, 14.82. Found: C, 77.96; H, 7.46; S, 14.92.

(15) J. S. Bradshaw and E. Y. Chen, unpublished observations.

(16) The Varian A-60A spectrometer was purchased under the National Science Foundation Grant GP-6837.

(17) A. B. Littlewood, "Gas Chromatography, Principles, Techniques and Applications," Academic Press, New York, N. Y., 1962, p 246.

(18) This product was isolated when the reaction mixture without 1-fluoronaphthalene was subjected to the same conditions and work-up. Indeed, mercaptans are easily oxidized to disulfides.[19]

(19) T. J. Wallace, A. Schriesheim, and W. Bartok, *J. Org. Chem.*, **28**, 1311 (1963).

(20) C–H–S analysis was performed by M-H-W Laboratories, Garden City, Mich.

(21) R. C. West, Ed., "Handbook of Chemistry and Physics," 50th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1969–1970, p C-273.

2-Fluoronaphthalene–*tert*-Butyl Mercaptide Reaction (Run 6). This reaction was carried out in the same manner as run 5. *tert*-Butyl 2-naphthyl sulfide (IV, 48%, mp 58.5–59.5°) was the only aromatic product. Compound IV exhibited ir bands at 3060, 3040, 2980, 2960, 2940, 2920, 2900, 2860, 1585, 1470, 1455, 1360, 1350, 1340, 1270, 1240, 1220, 1170, 1150, 1130, 1075, 1020, 965, 950, 900, 865, 825, 745, 650, and 635 cm^{-1} and the following nmr peaks: δ 7.98 (m, 1), 7.25–7.80 (m, 6), and 1.30 (s, 9). *Anal.* Calcd for $C_{14}H_{16}S$: C, 77.73; H, 7.46; S, 14.82. Found: C, 77.68; H, 7.24; S, 14.58.

1-Bromo- and 2-Bromonaphthalene–*tert*-Butyl Mercaptide Reactions (Runs 7 and 8).—These reactions were carried out the same as runs 5 and 6. The conversions and yields are listed in Table I.

Registry No.—DMSO, 67-68-5.

Acknowledgment.—The authors wish to thank Professor R. T. Hawkins for his many helpful discussions.

The Specific Deuteration of the Camphor Skeleton. Reduction of Chlorosulfoxides[1]

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Received January 4, 1972

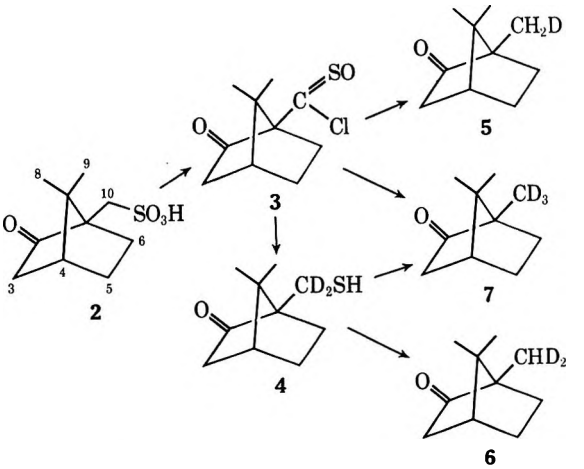
A convenient and inexpensive method has been developed for preparation of 9- and 10-deuterated camphors by the stepwise reduction of the corresponding chlorosulfoxide (oxythio acyl chloride) with deuterated amalgamated aluminum and/or Raney nickel. Simple procedures for stereoselective deuteration of camphor at C-3, C-4, C-5, and C-6 are also described.

For a proposed study of the stereochemistry of halogenation of camphor (**1**) and its enol derivatives, the analysis of product mixtures was to be done by nmr spectroscopy, a technique which had proved invaluable in a similar study with 3-keto steroid derivatives.[3] In particular, the chemical shifts of the C-8 methyl group and the C-3 and C-4 protons were to be used to assign halogen stereochemistry in the products. Therefore, it was essential to be certain which of the three methyl peaks belonged to C-8 in each of the compounds involved, and for this purpose deuterium labeling of methyl groups was the logical tool. Rather than deuterate the C-8 methyl group,[4] it appeared from the known chemistry of camphor to be easier and more generally useful to label the C-9 and C-10 methyl groups. Of the three reported procedures[6] for so doing, (a) reduction of the appropriate carboxylic acid to the primary alcohol and thence by way of hydride reduction of the tosylate to a methyl group,[6a,b] (b) zinc reduction of the C-9 primary bromide,[6c] and (c) hydride reduction of the appropriate primary sulfonyl chloride to a methyl group,[6d] two (a and c) require the use of the expensive lithium aluminum deuteride, while the third (b) gives a fragmentation side product.

Therefore, a convenient, inexpensive three- or four-step method has been developed for the incorporation of one, two, or three deuterium atoms into the C-9 and C-10 methyl groups of camphor.[1] The method involves the previously unreported stepwise reduction of the chlorosulfoxide group (oxythio acyl chloride or thioacyl chloride *S*-oxide) in the readily available camphor-10-chlorosulfoxide (**3**) and 3-*endo*-bromocamphor-9-chlorosulfoxide (**9**) with the cheapest source of deuterium, deuterium oxide. Since our halogenation study also required deuterium at C-4, it seemed worthwhile to develop practical procedures for stereoselective deuteration of C-6, C-5, and C-3 as well.

Very recently, Rodig and Sysko[7] have reported a nine-step synthesis of racemic camphor from norbornanone. Their synthesis has the advantage of allowing C labeling as well as H labeling of the methyl groups, but for H labeling it has the disadvantages, compared to the presently described synthesis, of being longer, of giving racemic camphor, and of not readily permitting the preparation of 9- or 10-mono- or dideuteriocamphor. Thus the two syntheses are complementary.

Our 10-methyl deuteration begins with conversion of the commercially available sulfonic acid **2** *via* the



sulfonyl chloride into the chlorosulfoxide **3** by the pyridine–toluenesulfonyl chloride procedure.[8] The chlorosulfoxide could now be reduced in stages by a suitable combination of two neutral reagents: (a) Raney nickel (Ra Ni) and (b) amalgamated aluminum (Al/Hg) with or without deuterium oxide. Raney nickel was found to reduce the chlorosulfoxide all the

(1) Presented in part at the 51st Canadian Chemical Conference, Vancouver, 1968, and taken from the Ph.D. Thesis of G. C. J., 1968.

(2) Commonwealth Scholar, 1964–1968; Defence Research Laboratory (Materials), Kanpur, India.

(3) E. W. Warnhoff, *J. Org. Chem.*, **28**, 887 (1963).

(4) In principle, the C-10 methyl group of *d*-camphor could be labeled and then transformed into the C-8 methyl group of *l*-camphor by racemization and resolution,[5] but this procedure promised to be more tedious than the one adopted and would have given at most 50% yield per cycle.

(5) A. M. T. Finch and W. R. Vaughan, *J. Amer. Chem. Soc.*, **87**, 5520 (1965); *ibid.*, **91**, 1416 (1969).

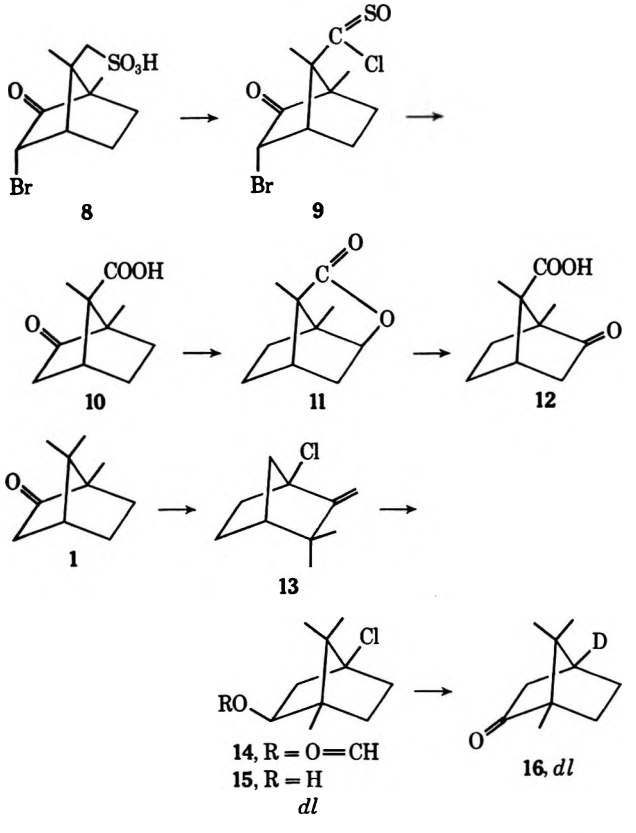
(6) (a) J. D. Connelly and R. McCrindle, *Chem. Ind. (London)*, 379 (1965); (b) W. L. Meyer and A. P. Lobo, *J. Amer. Chem. Soc.*, **88**, 3181 (1966); W. L. Meyer, A. P. Lobo, and R. N. McCarty, *J. Org. Chem.*, **32**, 1754 (1967); (c) K. M. Baker and B. R. Davis, *Tetrahedron*, **24**, 1655 (1968); (d) D. R. Dimmel and J. Wolinsky, *J. Org. Chem.*, **32**, 410 (1967).

(7) O. R. Rodig and R. J. Sysko, *J. Org. Chem.*, **36**, 2324 (1971).

(8) J. Strating, *Recl. Trav. Chim. Pays-Bas*, **83**, 94 (1964).

way to a methyl group, and camphor-*10,10,10-d*$_3$ (**7**) was prepared from **3** after the hydrogen on the Ra Ni had been exchanged for deuterium by equilibration with deuterium oxide. However, the amalgamated aluminum reagent[9] only reduces the chlorosulfoxide group to the thiol level.[10] Thus the action of Al/Hg and deuterium oxide on **3** gave camphor-10-thiol-*10,10-d*$_2$ (**4**) which was hydrogenolyzed by Ra Ni to camphor-*10,10-d*$_2$ (**6**).[11] The deuterated Ra Ni reduction of **4** (as done in the 9-chlorosulfoxide reductions) would be an alternative route to camphor-*10,10,10-d*$_3$ (**7**). On the other hand, camphor-*10-d*$_1$ (**5**) would result from the Al/Hg–water and Ra Ni–D_2O sequence.

The synthesis of the mono-, di- and tri-9-deuteriocamphors employs the same procedures except that the 3-*endo*-bromo-9-sulfonic acid **8** is the starting material because its preparation by sulfonation of 3-bromocamphor gives better and more reproducible yields than sulfonation of camphor. Moreover, optically active 3-bromocamphor affords optically active **8**, but sulfonation of camphor itself gives racemized camphor-9-sulfonic acid. The 3-bromo substituent is removed during the Al/Hg reduction of the 3-bromo-9-chlorosulfoxide **9**. In the use of this general deuteration

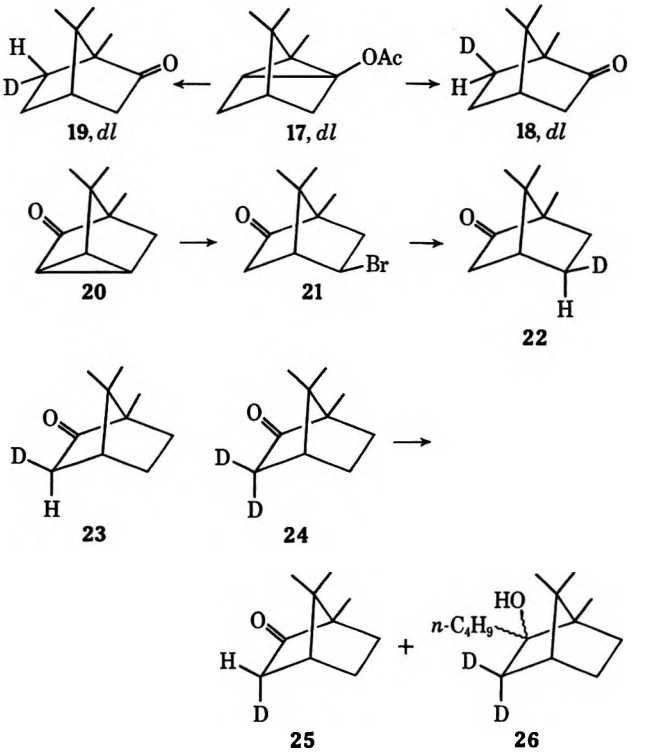


method there are two points requiring attention: the possible partial reduction of the carbonyl group if the Ra Ni is not sufficiently inactive and the introduction of deuterium at C-3 by enolization. Any difficulties from these side reactions can be overcome by oxidation and/or exchange.

The 3-*endo*-bromo-9-sulfonic acid **8** can also be used for deuteration of the 8-methyl group of camphor because the 3-*endo*-bromo-9-sulfonyl chloride or 9-chlorosulfoxide **9** can be oxidatively hydrolyzed and debrominated in high yield to isoketopinic acid (**10**) (see Experimental Section). The known transformation[13] of isoketopinic acid *via* the lactone **11** to keto acid **12** in effect converts the C-9 carboxyl into a C-8 carboxyl which would be reducible to an 8-deuteriomethyl camphor by appropriate modification of the earlier published method.[6a,b]

The 4 position of camphor was deuterated by sodium–ethanol-*O-d* reduction of 4-chloroisoborneol (**15**) followed by oxidation to camphor-*4-d*$_1$ (**16**), a procedure used by Nickon, *et al.*, to make norbornanone-*4-d*$_1$.[14] 4-Chloroisoborneol was available by known reactions from camphor (**1**) → 1-chlorocamphene (**13**) → 4-chloroisobornyl formate (**14**) → **15**.[15] A possible disadvantage of this sequence is that racemization by 6,2-hydride shift occurred during formic acid solvolysis of **13**, and the 4-chloroisoborneol is racemic. Racemization could presumably be avoided by the use of other solvolytic media.[15]

Monodeuteration at C-6 with a high degree of stereoselectivity was achieved by application of the findings of Nickon, *et al.*,[16] with 1-acetoxynortricyclene to the now readily available camphor 2,6-homoenol acetate (**17**).[17] Basic hydrolysis of **17** with potassium deuteroxide in methanol-*O-d* gave camphor-*6-exo-d*$_1$ (**18**),



(9) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

(10) Other reagents, such as tin (or zinc) and hydrochloric acid, and lithium aluminum hydride, which will also reduce sulfonyl chlorides to mercaptans, could probably be used on chlorosulfoxides, but the conditions would not be as mild or selective toward other functional groups.

(11) The nickel boride reagent[12] was also used for hydrogenolysis of this mercaptan but it offered no advantages over Raney nickel. In fact, there was more carbonyl reduction with nickel boride.

(12) W. E. Truce and F. M. Perry, *J. Org. Chem.*, **30**, 1316 (1965).

(13) E. J. Corey, M. Ohno, S. W. Chow, and R. A. Scherrer, *J. Amer. Chem. Soc.*, **81**, 6305 (1959).

(14) A. Nickon, J. L. Lambert, and J. E. Oliver, *ibid.*, **88**, 2787 (1966).

(15) J. Houben and F. Pfankuch, *Justus Liebigs Ann. Chem.*, **489**, 193 (1931).

(16) A. Nickon, J. L. Lambert, R. O. Williams, and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **88**, 3354 (1966).

(17) G. C. Joshi, W. D. Chambers, and E. W. Warnhoff, *Tetrahedron Lett.*, 3613 (1967).

whereas acidic hydrolysis of **17** in trifluoroacetic acid–deuterium oxide produced camphor-*6-endo*-d_1 (**19**).

For deuteration at C-5, the starting material was 3,5-cyclocamphanone (**20**), whose cyclopropyl ketone system is opened by hydrobromic acid to 5-*exo*-bromocamphor (**21**).[18] The bromine atom of **21** was replaced by deuterium without reduction of the ketone by use of the Al/Hg–deuterium oxide reagent. The 5-deuterium atom was largely *exo* because the long-range coupling of the 5-exo hydrogen was missing from the 3-exo hydrogen pattern in the nmr spectrum of **22**.

For stereoselective 3-monodeuteration of camphor, advantage was taken of the well-studied preference for 3-exo protonation of the enolate anion.[19] The enolate was prepared conveniently and quantitatively by the action of commercial *n*-butyllithium on a solution of camphor in tetrahydrofuran,[17] and it was then protonated by addition to an excess of acetic acid-d_4–deuterium oxide under conditions hopefully approaching irreversibility. As far as could be judged by nmr spectra (see Experimental Section), the deuterium atom in the product **23** was entirely exo. For the preparation of the 3-*endo*-deuterium epimer **25** the same procedure was applied to camphor-*3,3*-d_2 (**24**), which was made by zinc–acetic acid-d_4 reduction of 3,3-dibromocamphor. The lithium enolate was protonated by addition to acetic acid–water. The deuterium atom in the camphor-*3*-d_1 was almost entirely endo according to the nmr coupling pattern of the CHOH proton in the derived isoborneol. The camphor-*3-endo*-d_1 was accompanied by about 25% of the tertiary alcohol **26** resulting from addition of *n*-butyllithium to the carbonyl group of camphor-*3,3*-d_2, whereas this product was absent from the reaction of *n*-butyllithium with camphor. The relative rates of 3-proton abstraction and carbonyl addition are so close that the decreased proton abstraction rate caused by deuterium substitution now allows carbonyl addition to become a product-forming process: the product composition is thus determined by the deuterium isotope effect.

Experimental Section

For general details see ref 20. Deuterium oxide was >98% isotopically pure. Acetic acid-d_4 (Merck) contained 99.5 atom % excess D. The conditions for deuteration were not optimized and further improvement is to be expected. Unless otherwise specified, petroleum ether refers to the fraction of bp 30–60°.

***d*-Camphor-10-chlorosulfoxide (3).**—*d*-Camphor-10-sulfonic acid (**2**) (50 g, 0.21 mol, Aldrich Chemical Co.) was added with swirling to a mixture of 50 g of $CaCO_3$ and 100 ml of freshly distilled $SOCl_2$. The reaction mixture was refluxed for 4 hr. Excess $SOCl_2$ was removed by distillation with a petroleum ether (bp 60–80°) chaser. The product was separated from inorganic salts by solution in ether and filtration. The residue from evaporation of the filtrate was recrystallized from petroleum ether to give 45 g (83%) of white flakes of the sulfonyl chloride: mp 66–66.5° (lit.[21] mp 67–68°); nmr δ 0.93 (s, CH_3), 1.13 (s, CH_3), 3.73 and 4.29 ppm (AB of CH_2SO_2Cl, J = 15 Hz).

d-Camphor-10-sulfonyl chloride (50 g, 0.20 mol) dissolved in 30 ml of hot dioxane was added dropwise during 45 min to a hot (90°) stirred mixture of 38 g (0.20 mol) of *p*-toluenesulfonyl chloride (TsCl) and 40 ml of pyridine.[8] Heating and stirring were continued for 1 hr. The cooled reaction mixture was vigorously stirred with 600 ml of refluxing ether. Filtration to remove pyridine hydrochloride and evaporation of the ethereal solution left a residue which was recrystallized from petroleum ether (bp 80–100°). Two crops of light pinkish yellow crystals totaling 39 g (85%) of the chlorosulfoxide **3**, mp 84.5–85° (lit.[22] mp 85°), were obtained, nmr δ 1.13 (s, 2 CH_3).

Hydrogenolysis of *d*-Camphor-10-chlorosulfoxide (3).—A solution of 200 mg (0.92 mmol) of **3** in 10 ml of absolute ethanol was refluxed with 1 g of W-4 Raney nickel[23] for 3 hr. Filtration, evaporation, dilution with water, and extraction with ether gave 85 mg (64%) of *d*-camphor (**1**): $[\alpha]_D$ +39.6° (*c* 2.36, EtOH) (lit.[24] $[\alpha]_D$ +41–43°); nmr δ 0.84 (s, CH_3), 0.92 (s, CH_3), and 0.96 (s, CH_3).

***d*-Camphor-*10,10,10*-d_3 (7).**—The hydrogen on W-6 Raney Ni[25] was replaced by D by heating the Ni with D_2O and a trace of DCl for several hours after decantation of EtOH and rinsing with D_2O. A solution of 382 mg (1.63 mmol) of the 10-chlorosulfoxide **3** in 5 ml of EtOD containing 2 ml of D_2O was refluxed for 4 hr with 2 g of the deuterated Raney Ni. Filtration and evaporation left 225 mg (90%) of crude deuterated camphor which contained small amounts of two more polar (tlc) impurities. In the nmr spectrum the methyl peak at δ 0.91 was very weak in relation to the two methyl peaks at δ 0.84 and 0.96, indicating that the product was mainly camphor-*10,10,10*-d_3.

***d*-Camphor-10-thiol-*10,10*-d_2 (4).**—Aluminum metal (15 g, granular, <20 mesh, Fisher Co.) was amalgamated with a solution of 1 g of $HgCl_2$ dissolved in 100 ml of dry THF. The amalgamated metal was washed repeatedly by decantation with small portions of THF (200 ml total). Then 200 ml of dried THF (distilled from $LiAlH_4$)[26] and 10 g (43 mmol) of the 10-chlorosulfoxide **3** were added with stirring to the Al metal while the reaction mixture was protected from moisture by a $CaCl_2$ tube. A solution of 10 ml of D_2O in 50 ml of the dried THF was added dropwise with stirring during 30 min. The reaction mixture was heated to reflux and stirred for 10 hr with the addition of 100 mg of $HgCl_2$ and 5 ml of D_2O after the first 4 hr. The hot solution was filtered and the filtrate was concentrated to leave 7.7 g (96%) of crude *d*-camphor-10-thiol-*10,10*-d_2 (**4**). Recrystallization from petroleum ether gave colorless crystals: mp 65.5–66°; $[\alpha]_D$ +4.0° (c 1.37, EtOH) [lit.[27] mp 66°; $[\alpha]_D$ +6° (c 10, acetone) for non-*d* compound]; nmr δ 0.92 (s, CH_3) and 1.03 ppm (s, CH_3). As Lowry says,[27] the compound has "a characteristic and not unpleasant odour, faintly recalling with camphor the odour of burnt india-rubber."

***d*-Camphor-*10,10*-d_2 (6).**—A solution of 3.71 g (20 mmol) of *d*-camphor-10-thiol-*10,10*-d_2 (**4**) in 100 ml of absolute ethanol was refluxed and stirred with 40 g of W-4 Raney Ni[23] for 10 hr. The catalyst was removed by filtration and washed with fresh ethanol. The filtrate was concentrated to ~10 ml, diluted with water, and extracted with petroleum ether. The dried extracts were evaporated to leave 2.25 g (73%) of colorless camphor-*10,10*-d_2 (**6**). The crude product was sublimed at atmospheric pressure to give crystals: mp 177–177.5° (sealed capillary); nmr δ 0.84 (s, CH_3), 0.91 (s, CHD_2), and 0.95 ppm (s, CH_3). Analysis by mass spectroscopy gave 4% d_3, 81% d_2, 12.5% d_1, and 2.5% d_0.

***3-endo*-Bromo-*d*-camphor-9-chlorosulfoxide (9).**—The sodium salt of 3-bromo-*d*-camphor-9-sulfonic acid (**8**) was prepared by sulfonation of 3-*endo*-bromo-*d*-camphor with 10% fuming sulfuric acid according to the procedure of Kipping and Pope.[28] The crude sodium salt (29.3 g, contaminated with Na_2CO_3) was triturated with 25 g of PCl_5 in a mortar. The slurry was leached with 200 ml of chloroform. The chloroform solution was washed (H_2O), dried, and evaporated to leave a residue which was recrystallized from petroleum ether. There was obtained 11.5 g (~55%) of ill-defined crystals. Recrystallization from CH_2Cl_2 gave better crystals of the endo bromo sulfonyl chloride: mp 138–139° (lit.[28] mp 137°); nmr δ 1.04 (s, CH_3), 1.33 (s,

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(25) H. R. Billica and H. Adkins, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 176.

(26) If the THF was not distilled from $LiAlH_4$, no reduction took place, and starting material was recovered.

(27) T. M. Lowry and G. C. Donington, *J. Chem. Soc.*, **83**, 479 (1903).

(28) F. S. Kipping and W. J. Pope, *ibid.*, **63**, 548 (1893).

CH_3), 3.05 (1 H, m, C_4 H), 3.83 and 4.12 (AB of CH_2SO_2Cl), and 2.78 ppm (b d, $J \cong 5$ Hz, CHBr).

Crude 3-bromo-*d*-camphor-9-sulfonyl chloride (66 g, 0.20 mol, a mixture of endo and exo bromo isomers) was treated with 38 g (0.20 mol) of TsCl and 40 ml of pyridine according to the procedure described for the preparation of *d*-camphor-10-chlorosulfoxide. Crystallization from petroleum ether gave 44 g (71%) of a gray, powdery mass which was a mixture of 3-*exo*-bromo and 3-*endo*-bromo stereoisomers, nmr δ 4.23 (s, 3-endo H of CHBr) and 4.85 ppm (d, $J \cong 5$ Hz, 3-exo H of CHBr). Recrystallization from acetone gave buff-colored powdery **9**: mp 156.5–157°; $[\alpha]_D$ +23.7° (*c* 3.18, benzene) [lit.[29] mp 159°; $[\alpha]_D$ +31° (*c* 5.5, benzene)]; nmr δ 1.33 (s, CH_3), 1.37 (s, CH_3), 3.08 (m, C_4 H), and 4.70 ppm (d, $J \cong 5$ Hz, 3 exo H of CHBr).

Isoketopinic Acid (10) by Oxidative Hydrolysis of 9.—To a stirred (magnetic bar) solution of 20 g of crude 3-bromocamphor-9-chlorosulfoxide in 100 ml of acetone and 100 ml of water was added 40 g of $Na_2CO_3 \cdot 10H_2O$ followed by 40 g of $KMnO_4$ over a period of 1.5 hr. After another hour the mixture was filtered, acidified with concentrated HCl, and extracted with ether. The crude 3-bromoisoketopinic acid (12.6 g) obtained was a mixture of 3-*exo*- and 3-*endo*-bromo stereoisomers, nmr δ 1.25 (s, 2 CH_3), 4.16 (s, 3 endo H of CHBr, minor), 4.80 (d, $J \cong 5$ Hz, 3-exo H of CHBr, major), and 9.38 ppm (s, COOH). The bromine was removed by Zn dust (7 g) reduction of 12.2 g of the bromo acid in a refluxing mixture of 30 ml of dioxane and 10 ml of HOAc. Filtration, dilution with water, and extraction with ether gave 7.6 g (91%) of crude isoketopinic acid (**10**). Recrystallization from petroleum ether gave 4.6 g of white crystals: mp 248–249.5°; $[\alpha]_D$ +54° (*c* 4.95, EtOH) (lit.[22] mp 250°; $[\alpha]_D$ +28° in benzene); nmr δ 1.15 (s, 2 CH_3) and 10.36 ppm (s, COOH).

***d*-Camphor-*9,9-d*$_2$.**—A solution of 13.4 g (42 mmol) of 3-bromo-*d*-camphor-9-chlorosulfoxide (**9**) in 200 ml of THF[26] was reduced with 15 g of Al/Hg and a total of 15 ml of D_2O in the same way as described for the preparation of *d*-camphor-10-thiol-*10,10-d*$_2$. There was obtained 8.0 g (99%) of oily liquid camphor-9-thiol-*3,9,9-d*$_3$ (**27**): $[\alpha]_D$ +103° (c 5.12, EtOH) (lit.[30] mp 94°; $[\alpha]_D$ +108°, for non-D compound); nmr δ 0.94 ppm (s, 2 CH_3).

Desulfurization of 5.0 g (26 mmol) of the thiol **27** with 50 g of W-4 Raney Ni[23] in refluxing ethanol for 12 hr according to the procedure used on camphor-10-thiol-*10,10-d*$_2$ gave 3.2 g of oil which still contained considerable starting material. A second treatment with 40 g of Raney Ni for 8 hr yielded 2.5 g of solid. Percolation through Woelm neutral alumina (grade III) in petroleum ether and sublimation gave 1.19 g (28%) of camphor-*9,9-d*$_2$: $[\alpha]_D$ +43.8° (*c* 3.35, EtOH) (lit.[24] $[\alpha]_D$ +41–43° for non-D compound); nmr δ 0.85 (s, CH_3), 0.91 (s, CH_3), and 0.96 (s, CHD_2). Deuterium analysis by mass spectroscopy gave 9% d_3, 63% d_2, 15% d_1 and 13% d_0. Most of the D atom at C-3 was exchanged during the Raney Ni treatment.

***d*-Camphor-*3,9,9,9-d*$_4$.**—A solution of 425 mg (2.30 mmol) of camphor-9-thiol-*3,9,9-d*$_3$ in 10 ml of THF was added to ~2 g of deuterated (see preparation of **7**) W-5 Ra Ni[25] in 10 ml of D_2O. The suspension was stirred overnight at room temperature and then refluxed for 3 hr. Filtration, drying, and concentration gave 152 mg (43%) of crude deuterated camphor. Sublimation and thick layer chromatography (petroleum ether–ethyl acetate, 80:20) gave pure camphor-*3,9,9,9-d*$_4$. Analysis by mass spectroscopy gave 72% d_4, 24% d_3, 3% d_2, and 1% d_1.

***d*-Camphor-*9-d*$_1$.**—A stirred solution of 903 mg (2.90 mmol) of **9** in 13.5 ml of THF[26] was reduced with 1.35 g of Al/Hg (see preparation of **4**) and 0.9 ml of H_2O at reflux for 5.5 hr. The reaction mixture was filtered, dried, and evaporated to leave 480 mg (90%) of crude camphor-9-thiol. Thick layer chromatography on silica gel (petroleum ether–ethyl acetate, 80:20) gave 262 mg of pure thiol as a clear viscous oil. A solution of 120 mg of the pure camphor-9-thiol in 4 ml of THF was stirred with a suspension of ~0.6 g of deuterated (see preparation of **7**) W-5 Ra/Ni in 3 ml of D_2O for 20 hr under protection (drying tube) from atmospheric moisture. Filtration, drying, and evaporation of solvent gave camphor-*9-d*$_1$. Analysis by mass spectroscopy gave 1% d_2, 86% d_1, and 13% d_0.

4-Chloroisoborneol (15).—To a stirred solution of 15.2 g (0.10 mol) of *d*-camphor in 25 ml of CH_2Cl_2 chilled in an ice bath was added in small portions 12.8 g of PCl_3 and 22.2 g of PCl_5. After 2 hr the reaction mixture was allowed to come to room temperature for 10 hr. The reaction mixture was poured onto ice and extracted with petroleum ether. The extract was washed with water and evaporated to leave 20.8 g of clear, colorless liquid which was refluxed for 12 hr with 20 g of KOAc in 100 ml of EtOH–H_2O (75:25). The solution was then poured into water and extracted with petroleum ether. Evaporation of the washed and dried solution left 16.5 g (97%) of pale yellow 1-chlorocamphene (**13**), which was essentially pure according to its nmr spectrum, δ 1.10 (s, 6 H, *gem*-diMe), 3.91 (s, =CH), and 5.10 (s, =CH). A solution of the crude **13** (16.2 g, 0.095 mol) in 50 ml of formic acid was refluxed for 14 hr, poured onto ice, and extracted with petroleum ether. Evaporation of the washed and dried organic extract left 16.7 g (81%) of 4-chloroisobornyl formate (**14**), nmr δ 0.88 (s, CH_3), 0.93 (s, CH_3), 1.01 (s, CH_3), 4.80 (dd, X part of ABX, $J_{AX} + J_{BX} = 11$ Hz, CHOC=O), and 8.00 ppm (1 H, s, HCOO), which was saponified at room temperature for 10 hr with 5.6 g of KOH, 70 ml of MeOH, and 30 ml of H_2O. The hydrolysate was poured onto ice and extracted with five 60-ml portions of ether. Evaporation of the washed and dried extracts left a brownish solid which was recrystallized from petroleum ether (bp 80–100°). There was obtained 10.2 g (54% overall from camphor) of light yellow crystals of racemic 4-chloroisoborneol: mp 202–203° with sublimation;[31] $[\alpha]_D$ +0.18° ± 0.5 (*c* 4.90, EtOH); nmr 0.84 (s, CH_3), 0.97 (s, CH_3), 1.04 (s, CH_3), 1.80 (s, OH), and 3.67 ppm (dd, X part of ABX, $J_{AX} + J_{BX} = 12$ Hz, CHOH). Racemization most likely occurred during the reaction of 1-chlorocamphene with formic acid.

(±)-Camphor-*4-d*$_1$ (16).—The procedure of Nickon, *et al.*,[14] for the preparation of norbornanone-4-d_1 was adapted. To a refluxing solution of 8.0 g (0.042 mol) of 4-chloroisoborneol **15** in 45 g of EtOD (>99% OD) was added 12 g (0.52 g-atom) of sodium in small pieces during 1 hr. Reflux was continued for 3 hr with the addition of 2 ml of D_2O at the end of the period. Dilution of the cooled reaction mixture with 50 ml of water and extraction with five 20-ml portions of ether yielded 6.17 g (84%) of crude isoborneol-*4-d*$_1$, which was oxidized without purification.

The crude isoborneol-4-d_1 in 27 ml of acetone was stirred in an ice bath and oxidized with a solution of 3.2 g of CrO_3 dissolved in 15 ml of H_2O and 2.8 ml of concentrated H_2SO_4. After 4 hr, SO_2 was introduced until the solution became green. The layers were separated, and the lower green aqueous layer was extracted with three 25-ml portions of petroleum ether. The combined upper layer and extracts were washed, dried, and evaporated to leave 6.01 g (98%) of *dl*-camphor-*4-d*$_1$ (**16**) which was further purified by sublimation, mp 177–179° (lit.[24] mp 178.5°), $[\alpha]_D$ 0° (*c* 3.70, EtOH).

The nmr spectrum of 3-*endo*-bromocamphor prepared from **16** had a 1 H singlet at δ 4.65 instead of the doublet ($J \cong 5$ Hz) of the non-D compound because the C_4-H-exo C_3-H coupling was missing. The nmr spectrum of a sample of camphorquinone-*4-d*$_1$ prepared by SeO_2 oxidation of **16** lacked the doublet ($J \cong 4$ Hz) appearing at δ 2.63 in the protio analog.

***d*-Camphor-*5-exo-d*$_1$ (22).**—A refluxing solution of 895 mg (3.87 mmol) of 5-*exo*-bromo-*d*-camphor (**21**) (prepared by the action of HBr on 3,5-cyclocamphanone[18]) in 20 ml of dried THF was treated for 1 hr with 1 g of Al/Hg (made as described for the preparation of **4**) and 1 ml of D_2O. Filtration, evaporation, and sublimation yielded 436 mg (73%) of *d*-camphor-*5-exo-d*$_1$, nmr δ 0.85 (s, CH_3), 0.91 (s, CH_3), and 0.95 ppm (s, CH_3). A signal present as a sharp peak at δ 1.41 in the spectrum of camphor had collapsed to a broad band in the spectrum of camphor-*5-d*$_1$. Analysis by mass spectroscopy gave 4% d_2, 85% d_1, and 11% d_0.

That most of the D was in the 5-exo position was evident from the nmr spectrum of the compound. The well-separated four-line pattern of half of the 3-exo H absorption in camphor at δ 2.53 was now a two-line pattern (superimposed on residual absorption from the original four-line pattern) because the exo-C_5-H–exo-C_3-H coupling was missing.

(±)-Camphor-*6-endo-d*$_1$ (19).—A solution of 6 ml of $(CF_3CO)_2O$, 2 ml of D_2O, and 1.92 g (~60% camphor homoenol acetate **17**) of the crude product of oxidation of tricyclene with $Pb(OAc)_4$[17] was sealed in a glass tube and heated at 120° for 6 hr. The contents of the tube were poured into water and extracted with petroleum ether. The extracts were washed with aqueous

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(30) T. Tukamoto, *J. Pharm. Soc. Jap.*, **59**, 37 (1939).

(31) The racemate was synthesized by J. Houben and E. Pfankuch, *Justus Liebigs Ann. Chem.*, **501**, 219 (1933), by mixing equal quantities of *d* and *l*, but its physical properties were not reported.

$NaHCO_3$, dried, and chromatographed on 30 g of Woelm neutral alumina (grade III). Ether–petroleum ether (5:95) eluted 462 mg (~50%) of deuterated camphor. Deuterium was removed from C-3 by heating the product with acetic and hydrochloric acid in a sealed tube at 150°, and the camphor-*6-endo-d*$_1$ was finally sublimed, nmr δ 0.85 (s, CH_3), 0.91 (s, CH_3), and 0.95 ppm (s, CH_3). Analysis by mass spectroscopy gave 1% d_2, 74% d_1, and 24% d_0.

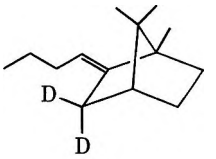
(±)-**Camphor-*6-exo-d*$_1$** (**18**).—To the solution obtained by dissolving 0.8 g of K metal in 10 ml of MeOD was added 1.94 g (~60% camphor homoenol acetate **17**) of the crude product of oxidation of tricyclene with $Pb(OAc)_4$[17] dissolved in 5 ml of MeOD and 2 ml of D_2O. After ~12 hr at room temperature the mixture was poured into water and extracted with petroleum ether. Chromatography of the crude product (1.4 g) on 40 g of Woelm neutral alumina (grade III) gave 901 mg (~97%) of deuterated camphor. Deuterium was removed from C-3 by reflux with methanolic KOH, and the camphor-*6-exo-d*$_1$ was finally sublimed at atmospheric pressure, nmr δ 0.85 (s, CH_3), 0.91 (s, CH_3), and 0.95 ppm (s, CH_3).

The stereochemistry of the D atom in each camphor-*6-d*$_1$ was proved by bromination to 3-*endo*-bromocamphor and $LiAlH_4$ reduction of the product to 3-*endo*-bromoborneol-*6-d*$_1$. In the nmr spectrum of the product from *6-exo-d*$_1$ camphor (from the basic reaction) the C-2 exo-H lacked the long range coupling to the 6-exo hydrogen which coupling was present in the product from *6-endo-d*$_1$ camphor from the acidic reaction.

d-**Camphor-*3-exo-d*$_1$** (**23**).—A solution of 7.6 g (50 mmol) of *d*-camphor in 200 ml of THF (distilled from $LiAlH_4$) under a N_2 atmosphere was treated with 40 ml (64 mmol) of 1.6 *M* *n*-butyllithium solution (Foote Mineral Co.) at room temperature for 30 min. The solution of camphor enolate was then added dropwise (stopcock in bottom of reaction flask) with stirring to a solution of 4 ml (65 mmol) of CD_3COOD and 2 ml of D_2O. After 1 hr the colorless THF solution was decanted from a white paste on the walls of the flask. The THF solution was diluted with petroleum ether, dried, filtered, and evaporated to leave 6.95 g (91%) of crude product. A 4.00-g portion was sublimed at atmospheric pressure to give 3.56 g of pure colorless crystals of *d*-camphor-3-*exo-d*$_1$. Analysis by mass spectroscopy gave 96.6% d_1 and 3.4% d_0. From the coupling pattern of the CHOH proton in the nmr spectrum of the derived ($LiAlH_4$) isoborneol the D is almost entirely exo.

d-**Camphor-*3,3-d*$_2$** (**24**).—A solution of 25.0 g (81 mmol) of 3,3-dibromo-*d*-camphor in 50 ml of dioxane (distilled from $LiAlH_4$) and 15 ml of CD_3COOD was stirred and heated (steam bath) with 15 g of Zn powder (B. D. H. Analar). Dilution with 200 ml of petroleum ether and 2 ml of D_2O followed by washing (H_2O), drying, and evaporation gave 11.3 g (91%) of crude product which was sublimed to yield 11.0 g of colorless feathery camphor-*3,3-d*$_2$, mp 177–178° (sealed capillary). Analysis by mass spectroscopy gave 83.5% d_2 and 16.5% d_1.

d-**Camphor-*3-endo-d*$_1$** (**25**).—This compound was prepared from 7.58 g (49 mmol) of camphor-*3,3-d*$_2$ by the procedure described above for the preparation of camphor-*3-exo-d*$_1$ except that the enolate was added to a solution of 10 ml of HOAc in 25 ml of water. There was obtained 7.05 g of crude product which consisted of ~70% camphor, ~25% of a slightly more polar (tlc) product, and ~5% of three still more polar compounds. The major contaminant was apparently the product **26** of addition of *n*-butyllithium to the carbonyl group of **24**. Chromatography of 1.6 g of the crude product on silica gel resulted in dehydration of this tertiary alcohol and elution of 382 mg of (probably) **28** together with camphor. Further elution gave 800



28

mg of camphor-*3-endo-d*$_1$ which was sublimed to give colorless crystals. Analysis by mass spectroscopy gave 94% d_1 and 6% d_0. From the coupling pattern of the CHOH proton in the nmr spectrum of the derived ($LiAlH_4$) isoborneol the D is almost entirely endo.

Registry No.—**4**, 34733-67-0; **6**, 34733-68-1; **9**, 34733-69-2; **10**, 10334-07-3; **15**, 34733-71-6; **16**, 34733-72-7; **24**, 34733-73-8; *d*-camphor-*9,9-d*$_2$, 34739-97-4.

Acknowledgment.—The financial assistance of the National Research Council of Canada is gratefully acknowledged.

Anodic Oxidations. VIII. The Anodic Oxidation of *N,N*-Dimethylmethanesulfonamide in Alcohols and in Acetic Acid

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Received January 27, 1972

The anodic oxidation of *N,N*-dimethylmethanesulfonamide has been studied in alcohols and in acetic acid, using quaternary ammonium fluoborates and nitrates as the supporting electrolytes. The structures of the products, *N*-alkoxymethyl-*N*-methylmethanesulfonamides and *N*-acetoxymethyl-*N*-methylmethanesulfonamide, were established by synthesis.

Compounds containing the grouping XCH_2Y, where Y is halogen, OH, OR, or O(C=O)R and X is S, O, or N, are effective electrophilic reagents, frequently used to introduce a new carbon–carbon bond in aromatic compounds or in aliphatic compounds containing reactive methylene or methine groups. Some typical reagents, with, *e.g.*, Y a halogen atom, are the chloromethylamines, the chloromethyl sulfides, the chloromethyl ethers, the chloromethyl amides, and the chloromethyl imides. When the electrophilic reagent is one in which the X above is the nitrogen of an amide group or an imide group, the reaction is an amidoalkylation reaction, and these reactions have been reviewed by Hellman[1] and by Zaugg and Martin.[2]

Many mechanisms are possible for these reactions, but the most common is the acid-catalyzed $A_{AL}1$ mechanism[3] in which the rate-determining step is the formation of the ion I. The most active reagents are

$$-XCH_2^+ \longleftrightarrow -\overset{+}{X}=CH_2$$
I

(1) H. Hellman in "Newer Methods of Preparative Organic Chemistry," Vol. II, W. Foerst, Ed., Academic Press, New York, N. Y., 1963.

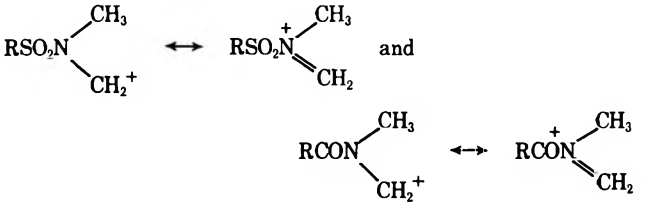
(2) H. E. Zaugg and W. B. Martin, *Org. React.*, **14**, 52 (1965).

(3) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Org. Chem.*, **31**, 133 (1966).

those in which X is the oxygen of an ether or the nitrogen of an amine. The least active are those in which X is the nitrogen of an imide, and intermediate reactivity is shown by reagents in which X is sulfur or an amide nitrogen.

The half-wave oxidation potentials for the compounds $-XCH_3$[4] parallel the reactivities of the compounds $-XCH_2Y$ discussed above. The order of increasing oxidation potential is amines < sulfides < amides. Oxidation potentials are not available for imides, but *N*-methylimides do not react under conditions where *N*,*N*-dimethylamides are successfully formyloxylated in an electrooxidation.[5]

It has been suggested[3] that the enhanced reactivity of the amine derivatives, R_2NCH_2Y, is due to the absence of both the carbonyl group and the amide resonance in the former and that, in the imides, $(RCO)_2NCH_2Y$, the additional carbonyl decreases the reactivity still further. These considerations make the anodic oxidation of an *N*,*N*-dimethylsulfonamide a subject of interest. In the anodic oxidations of an *N*,*N*-dimethylsulfonamide and an *N*,*N*-dimethylcarbonamide the product-forming intermediates are the ions shown, but the barrier to internal rotation



about the N–S bond of a sulfonamide is small in magnitude compared to the barrier to internal rotation about the N–CO bond of a carbonamide.[6] One might, therefore, expect the anodic oxidation of an *N*,*N*-dimethylsulfonamide to be more facile than the oxidation of an *N*,*N*-dimethylcarbonamide and to show oxidation behavior approaching that of an *N*,*N*-dimethylamine. In the present work the anodic oxidation of *N*,*N*-dimethylmethanesulfonamide has been studied. The oxidation products have been isolated, and their structures have been established by synthesis.

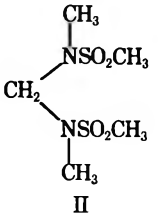
Results and Discussion

The chemistry of the sulfonamide oxidations proved to be very similar to that observed for the carbonamides. Anodic oxidation of *N*,*N*-dimethylmethanesulfonamide in methanol, ethanol, or 1-butanol, with either a quaternary ammonium nitrate or tetrafluoroborate as supporting electrolyte, resulted in the respective *N*-alkoxymethyl-*N*-methylmethanesulfonamides. These products proved to be somewhat more difficult to isolate than the corresponding products from *N*,*N*-dimethylformamide, but only because the difference in boiling point between starting material and product is much smaller in the sulfonamide case.

The structures of these *N*-alkoxymethyl-*N*-methylmethanesulfonamides were confirmed by synthesis. *N*-Methylmethanesulfonamide was treated with formaldehyde to give the hydroxymethyl derivative, which was, in turn, converted to *N*-acetoxymethyl-*N*-methylmethanesulfonamide with acetic anhydride and pyridine. Treatment of the *N*-acetoxymethyl compound with a catalytic quantity of sulfuric acid in the appropriate alcohols gave the desired *N*-alkoxymethyl compounds. It was also possible to interchange alkoxymethyl groups by treatment with acid and an alcohol. In addition, the reaction of an *N*-alkoxymethyl-*N*-methylmethanesulfonamide with anisole in the presence of acid gave a mixture of the ortho and para isomers of *N*-methyl-*N*-methoxybenzylmethanesulfonamide, both of which could be prepared independently by known reactions.

N-Acetoxymethyl-*N*-methylmethanesulfonamide is a somewhat unstable compound which decomposes, in part, during distillation at reduced pressure or within a few days on standing at room temperature, It was shown to be the product formed by electrooxidation of *N*,*N*-dimethylmethanesulfonamide in acetic acid by chemically converting the initially formed *N*-acetoxymethyl compound to a known alkoxymethyl compound and determining, by vpc analysis, the amount of this latter compound obtained.

The decomposition product of the *N*-acetoxymethyl derivative is 2,4-dimethanesulfonyl-2,4-diazapentane (II). It may also be obtained by anodic oxidation of



II

N,*N*-dimethylmethanesulfonamide in water, with ammonium fluoborate as the supporting electrolyte, or by heating *N*-methylmethanesulfonamide and paraformaldehyde in the molar ratio of 2:1 with a catalytic quantity of concentrated hydrochloric acid in a sealed tube at 120°.

Preparative electrooxidations from which the products were isolated are described in the Experimental Section. It was most convenient to do these electrolyses at constant current, a technique which permits the rapid passage of sizable amounts of charge with relatively simple equipment, even with nonaqueous solvents such as acetic acid.

With authentic samples of the oxidation products available, it was possible to study these oxidations by determining the product formed by analytical vpc rather than by isolation. The results are collected in Table I. These experiments used 140 ml of solvent, 0.05 mol of the supporting electrolyte, and 0.10 mol of the sulfonamide. The current was usually the maximum one which could conveniently be maintained constant in the cell used, and the amount of charge passed in each experiment was 0.112 faraday.

The results in Table I are very similar to results obtained in a comparable set of experiments with *N*,*N*-dimethylformamide.[7] Studies of the sulfonamide oxidation by cyclic voltammetry further confirm the

(4) For tables of the appropriate potentials, see C. K. Mann and K. K. Barnes, "Electrochemical Reactions in Nonaqueous Systems," Marcel Dekker, New York, N. Y., 1970, Chapters 9 and 12.

(5) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Org. Chem.*, **31**, 128 (1966).

(6) R. M. Moriarty, *Tetrahedron Lett.*, 509 (1964); *J. Org. Chem.*, **30**, 600 (1965).

(7) E. J. Rudd, M. Finkelstein, and S. D. Ross, *J. Org. Chem.*, **37**, 1763 (1972).

TABLE I

ANODIC OXIDATION OF *N,N*-DIMETHYLMETHANESULFONAMIDE AT CONSTANT CURRENT

Solvent	Supporting electrolyte	Current, A	Product	Registry no.	Coulombic yields, %
Methanol	Tetraethylammonium fluoborate	2.0	$CH_3SO_2N(CH_3)CH_2OCH_3$	34825-76-8	81.3
Methanol	Ammonium nitrate	2.0	$CH_3SO_2N(CH_3)CH_2OCH_3$		64.3
Ethanol	Tetra-*n*-butylammonium fluoborate	1.0	$CH_3SO_2N(CH_3)CH_2OC_2H_5$	34825-77-9	74.7
Ethanol	Tetraethylammonium nitrate	1.0	$CH_3SO_2N(CH_3)CH_2OC_2H_5$		59.1
1-Butanol	Tetra-*n*-butylammonium fluoborate	0.5	$CH_3SO_2N(CH_3)CH_2OnC_4H_9$	34825-78-0	89.3
1-Butanol	Tetraethylammonium nitrate	0.5	$CH_3SO_2N(CH_3)CH_2OnC_4H_9$		77.3
Acetic acid	Tetra-*n*-butylammonium fluoborate	1.0	$CH_3SO_2N(CH_3)CH_2OOCCH_3$	34825-79-1	53.9
Acetic acid	Tetraethylammonium nitrate	1.0	$CH_3SO_2N(CH_3)CH_2OOCCH_3$		66.1

similarity in oxidation behavior for the two amides. These measurements were carried out in acetonitrile, using 0.3 *M* tetraethylammonium perchlorate as the supporting electrolyte, a Ag/Ag^+ (0.1 *M*) reference electrode, and a platinum wire working electrode of 0.05 cm^2 area. The current–voltage curves for a solution containing 8×10^{-3} *M* *N,N*-dimethylmethanesulfonamide and 8×10^{-3} *M* tetraethylammonium nitrate are shown in Figure 1, in which two distinct oxidation peaks are to be noted. At sweep speeds below 150 mV sec^{-1} the peak potential [V *vs.* *E*(Ag/Ag^+) (0.1 *M*)] is 2.07–2.08 V for *N,N*-dimethylmethanesulfonamide, and the peak potential for the oxidation of nitrate ion occurs at a potential more than 0.5 V less anodic than that for the amide.

Still further corroboration for this similarity in oxidation behavior is afforded by competition experiments. Mixtures of the two amides (0.064 mol of each) in methanol (150 ml) were oxidized, passing 0.112 faraday of charge, with tetraethylammonium nitrate (0.05 mol) as the supporting electrolyte and with tetra-*n*-butylammonium fluoborate (0.05 mol) as the supporting electrolyte; the ratios of the two products formed, the *N*-methoxymethylformamide to the *N*-methoxymethylsufonamide, were determined. In both experiments the coulombic yield of oxidation products exceeded 95%, and the ratio of oxidation products was 1.58 with the nitrate and 1.40 with the fluoborate. This small preference for oxidation of *N,N*-dimethylformamide is consistent with its slightly lower oxidation potential.

N,N-Dimethylformamide and *N,N*-dimethylmethanesulfonamide are quite similar, both in the nature of the products formed by anodic oxidation and in the potentials at which these reactions occur. The anticipated difference in behavior between these two amides was thus not realized. The expectation was based on the relative absence of amide resonance in the sulfonamide. This would make the electrons on nitrogen more available for transfer to the electrode. Neglected, however, was the very large electron-withdrawing effect of the SO_2 group. This latter effect, larger than that due to the carbonyl group of the carbonamide, would operate in the opposite direction. In the sulfonamide case the two competing effects largely cancel one another. A better correlation with the oxidation potentials would very probably be obtained with either the ionization potentials[8,9] or the energies of the highest occupied molecular orbitals for these

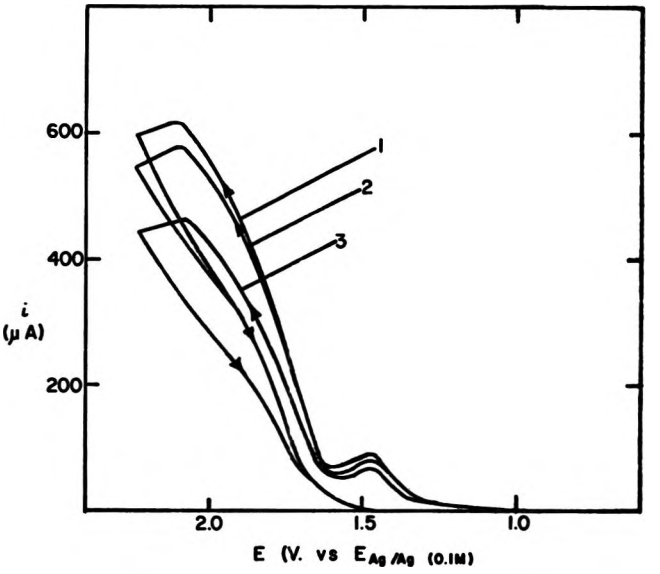
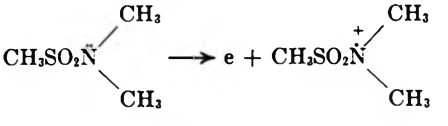


Figure 1.—Cyclic voltammetric studies in acetonitrile containing 0.3 *M* tetraethylammonium perchlorate for the electrooxidation of *N,N*-dimethylmethanesulfonamide ($\cong 8 \times 10^{-3}$ *M*) and nitrate anion ($\cong 8 \times 10^{-3}$ *M* tetraethylammonium nitrate). The sweep rates are 250 mV sec^{-1} for 1, 200 mV sec^{-1} for 2, and 125 mV sec^{-1} for 3.

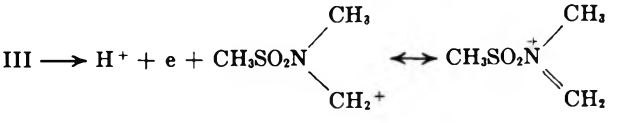
two amides.[9,10] Unfortunately, neither type of data is available.

As demonstrated previously in the case of *N,N*-dimethylformamide,[7] two mechanisms are available for the anodic oxidation of *N,N*-dimethylmethanesulfonamide. In the one, the primary reaction is an electron transfer from the sulfonamide to give a cation radical, III.



III

In a subsequent step or steps III can lose a proton and transfer an additional electron to the electrode to give the ion IV.



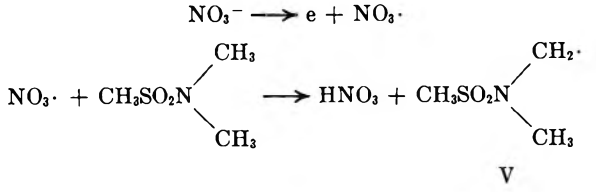
IV

(8) E. S. Pysh and N. C. Yang, *J. Amer. Chem. Soc.*, **85**, 2124 (1963).

(9) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, Chapter 7.

(10) G. J. Hoijtink, *Recl. Trav. Chim. Pays-Bas*, **77**, 555 (1958).

In the other, the initiating reaction is an electron transfer from nitrate ion to give a nitrate radical, which abstracts a hydrogen atom from the substrate to give V.



V

An additional electron transfer to the anode from V again results in the product-forming cation IV. With a nitrate salt as the supporting electrolyte, both mechanisms can operate, with the hydrogen atom abstraction mechanism becoming significant when the concentration of nitrate ion is comparable in magnitude to or larger than the concentration of the sulfonamide.

Experimental Section

Materials.—Preparations of tetraethylammonium nitrate,[11] tetraethylammonium fluoborate,[12] and tetrabutylammonium fluoborate[7] have been described.

N,N-Dimethylmethanesulfonamide[13,14] was prepared in 92% yield by treating anhydrous dimethylamine in dry benzene with methanesulfonyl chloride, bp 110° (12 mm), mp 49–51° from chloroform–hexane.

N-Methylmethanesulfonamide[15] was prepared in 66% yield by adding methanesulfonyl chloride dropwise, with stirring and cooling, to an excess of 40% aqueous methylamine. The reaction mixture was saturated with sodium chloride, and the product was extracted with methylene chloride, bp 104–107° (0.35 mm), n^{23}D 1.4514.

Preparative Electrochemical Reactions.—Two types of electrochemical preparations were run. In the first, the objective was to actually isolate the oxidation products; in the second, the objective was to determine the coulombic efficiency of the electrochemical reaction, and the products were determined analytically. The same equipment was suitable for both types of experiment. The electrolysis cell consisted of a water-jacketed, 200-ml beaker, fitted with a magnetic stirring bar, a thermometer, and a Teflon cover to which were attached two platinum electrodes, 0.025 cm thick, 2.5 cm wide, immersed to a depth of 7 cm and at a separation of 2 cm. Current was supplied by a voltage-regulated d.c. power supply. Descriptions of the reactions in the first category follow.

***N*-Methoxymethyl-*N*-methylmethanesulfonamide.**—A solution of *N,N*-dimethylmethanesulfonamide (12.3 g, 0.1 mol) and tetraethylammonium fluoborate (10.9 g, 0.05 mol) in methanol (150 ml) was electrolyzed at a constant current of 2.0 A until 0.112 faraday of charge was passed. Methanol was removed with the water pump, and ether (200 ml) was added. The fluoborate salt, which precipitated, was recovered by filtration, the ether was removed, and the residue was distilled. The crude product, 13.4 g, bp 68–73° (0.05 mm), was found to be impure by vpc. It proved difficult to separate product from starting material, and even after another distillation, the product was less than 70% pure by vpc analysis. Some additional purification was effected with a Model A-700 Aerograph Autoprep, fitted with a column, 20 ft × 0.375 in., packed with 30% SE-30 on 45/60 Chromosorb W, and maintained at a temperature of 230°. The purified product has n^{23}D 1.4453.

Anal. Calcd for $C_4H_{11}NO_3S$: C, 31.37; H, 7.24; S, 20.90. Found: C, 31.22, 30.56; H, 7.39, 7.45; S, 21.29, 21.77.

In spite of the above satisfactory results, analysis by vpc indicates that this product is only 80% pure.

***N*-Ethoxymethyl-*N*-methylmethanesulfonamide.**—A solution of *N,N*-dimethylmethanesulfonamide (24.6 g, 0.2 mol) and tetrabutylammonium fluoborate (16.5 g, 0.05 mol) in ethanol (150 ml) was electrolyzed at 1 A until 0.224 faraday of charge was passed. The work-up was the same as that described above. The crude product, 16.6 g (88% coulombic yield), had bp 116–121° (12 mm) and n^{23}D 1.4433. A sample redistilled for analysis had bp 129–130° (15 mm) and n^{22}D 1.4434.

Anal. Calcd for $C_5H_{13}NO_3S$: C, 35.91; H, 7.84; S, 19.17. Found: C, 35.53; H, 8.11; S, 19.52.

***N*-*n*-Butoxymethyl-*N*-methylmethanesulfonamide.**—A solution of *N,N*-dimethylmethanesulfonamide (24.6 g, 0.2 mol) and tetrabutylammonium fluoborate (16.5 g, 0.05 mol) in 1-butanol (140 ml) was electrolyzed at a constant current of 0.5 A until 0.224 faraday of charge was passed. The work-up described above resulted in 14.3 g (65.3% coulombic yield) of product, bp 85–91° (0.35 mm), n^{24}D 1.4438. A sample redistilled for analysis had bp 91° (0.35 mm) and n^{23}D 1.4439. Analysis by vpc indicated that this sample was 97% pure.

Anal. Calcd for $C_7H_{17}NO_3S$: C, 43.05; H, 8.77; S, 16.42. Found: C, 43.56; H, 8.99; S, 16.97.

2,4-Dimethanesulfonyl-2,4-diazapentane.—A solution of ammonium fluoborate (10.4 g, 0.1 mol) and *N,N*-dimethylmethanesulfonamide (12.3 g, 0.1 mol) in water (150 ml) was electrolyzed at 2 A until 0.20 faraday of charge was passed. The solution was saturated with sodium chloride and extracted with methylene chloride (3 × 250 ml). Removal of the methylene chloride and crystallization from acetone yielded 4.58 g of product, mp 174–177°. The aqueous layer was distilled at the water pump, and the residue was digested with acetone to yield an additional 1.32 g of product. The total yield was 5.90 g (51% coulombic yield). A sample recrystallized from acetone for analysis had mp 175–177°.

Anal. Calcd for $C_5H_{14}N_2O_4S_2$: C, 26.08; H, 6.13; N, 12.16; S, 27.79. Found: C, 26.50; H, 6.25; N, 11.93; S, 28.11.

For the experiments of the second type, in which the products formed were determined by vpc analysis but not isolated, the solutions electrolyzed contained 0.05 mol of the supporting electrolyte, 0.10 mol of *N,N*-dimethylmethanesulfonamide, and 140 ml of either acetic acid or the appropriate alcohol. The amount of charge passed was 0.112 faraday in each experiment. The results are compiled in Table I.

Since the electrooxidation products of *N,N*-dimethylmethanesulfonamide had not been prepared previously, these same products were synthesized using known chemical reactions. The preparations described below served both as proofs of structure and sources of authentic material.

***N*-Acetoxymethyl-*N*-methylmethanesulfonamide.**—A mixture of *N*-methylmethanesulfonamide (21.6 g, 0.2 mol), paraformaldehyde (6.2 g, 0.207 mol), and potassium carbonate (0.3 g) in ethanol was refluxed for 1 hr. The ethanol was removed with the water pump. Pyridine (25 ml) and acetic anhydride (40 ml) were added, and the mixture was left standing for 24 hr. The excess reagents were removed with the water pump, and the crude product was distilled at 0.04 mm, yield 19.6 g (54%), bp 100–101°, n^{22}D 1.4518. A sample redistilled for analysis had bp 97° (0.015 mm) and n^{24}D 1.4505.

Anal. Calcd for $C_5H_{11}NO_4S$: C, 33.14; H, 6.12; N, 7.73. Found: C, 32.97; H, 6.21; N, 7.94.

The residue from the first distillation above yielded, after two crystallizations from acetone, 1.0 g of 2,4-dimethanesulfonyl-2,4-diazapentane, mp 176–178°.

The *N*-acetoxymethyl-*N*-methylmethanesulfonamide is unstable at room temperature and is slowly converted on standing to 2,4-dimethanesulfonyl-2,4-diazapentane.

***N*-Ethoxymethyl-*N*-methylmethanesulfonamide.**—Concentrated sulfuric acid (1.5 ml) was added to a solution of *N*-acetoxymethyl-*N*-methylmethanesulfonamide (43 g, 0.237 mol) in ethanol (500 ml). The solution was left standing overnight. Pyridine (65 ml) was added, and the ethanol was removed by distillation. The residue was taken up in ether (1 l.), and the solution was extracted with water (2 × 100 ml). The ether solution was dried over magnesium sulfate; the ether was removed, and the crude product was distilled at 0.02 mm, yield 29.3 g (74%), bp 65°, n^{23}D 1.4429.

Anal. Calcd for $C_5H_{13}NO_3S$: C, 35.91; H, 7.84; N, 8.38. Found: C, 35.66; H, 7.88; N, 8.26.

***N*-*n*-Butoxymethyl-*N*-methylmethanesulfonamide.**—The above procedure applied to a solution of *N*-acetoxymethyl-*N*-methylmethanesulfonamide (45.3 g, 0.25 mol) in 1-butanol (500 ml) gave 23.4 g (48%) of product, bp 85–95° (0.1–0.02 mm), n^{24}D 1.4451. On redistillation this product had bp 80° (0.01 mm) and n^{23}D 1.4460. Crystallization of the residue from the

(11) S. D. Ross and M. M. Labes, *J. Amer. Chem. Soc.*, **79**, 4155 (1957).
(12) N. S. Moe, *Acta Chem. Scand.*, **19**, 1023 (1965).
(13) R. M. Moriarty, *J. Org. Chem.*, **30**, 600 (1965).
(14) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2717 (1956).
(15) B. Helferich and H. Grunert, *Ber.*, **73B**, 1131 (1940).

first distillation from acetone yielded 1.8 g of 2,4-dimethanesulfonyl-2,4-diazapentane.

N-**Methoxymethyl-*N*-methylmethanesulfonamide.**—A solution of *N*-*n*-butoxymethyl-*N*-methylmethanesulfonamide (6.1 g, 0.0313 mol) in methanol (50 ml) was treated with concentrated sulfuric acid (3 drops), and the mixture was left standing for 5 hr. The reaction mixture was dissolved in anhydrous ether (250 ml), and the solution was stirred with sodium carbonate to neutralize the acid. Filtration of the solid, removal of the solvents, and distillation at 0.01 mm yielded 3.6 g (75%) of a product, bp 52–56°, which gave a single peak on vpc.

Anal. Calcd for $C_4H_{11}NSO_3$: C, 31.37; H, 7.24; S, 20.90. Found: C, 31.27; H, 7.34; S, 21.51.

N-Methoxymethyl-*N*-methylmethanesulfonamide was also obtained in 44% yield from the reaction of *N*-acetoxymethyl-*N*-methylmethanesulfonamide with methanol.

2,4-Dimethanesulfonyl-2,4-diazapentane.—A mixture of *N*-methylmethanesulfonamide (21.6 g, 0.2 mol), paraformaldehyde (3 g, 0.1 mol), and concentrated hydrochloric acid (0.5 ml) was heated in a sealed tube at 120° for 24 hr. The yield was 15.3 g (66.5%), mp 176–178° after two crystallizations from acetone.

Anal. Calcd for $C_5H_{14}N_2O_4S_2$: C, 26.08; H, 6.13; S, 27.84. Found: C, 26.36; H, 6.24; S, 28.26.

Reaction between *N*-Ethoxymethyl-*N*-methylmethanesulfonamide and Anisole.—A solution of the sulfonamide (5 g, 0.03 mol) in anisole (30 ml) was treated with concentrated sulfuric acid (1.5 ml). After 2.5 hr the mixture was added to ether (300 ml), and the ether solution was extracted with water (2 × 100 ml). Both the aqueous extract and the ether solution gave products. The aqueous extract was taken to dryness, and the residue was crystallized from acetone, yielding 1.18 g (34.2%) of 2,4-dimethanesulfonyl-2,4-diazapentane, mp 173–176°. The ether solution was washed twice with saturated sodium bicarbonate solution and then once with water. The solution was dried over magnesium sulfate, the ether and anisole were removed by distillation, and the residue was analyzed by vpc. The products found were: *N*-methyl-*N*-*p*-methoxybenzylmethanesulfonamide, 1.43 g (20.8%); *N*-methyl-*N*-*o*-methoxybenzylmethanesulfonamide, 0.72 g (10.5%); and a third, unidentified component, 0.43 g.

N-**Methyl-*N*-*p*-methoxybenzylmethanesulfonamide.**—*N*-Methyl-*N*-*p*-methoxybenzylamine was prepared by the procedure described by Cromwell and Hoeksema,[16] except that platinum oxide was used as the catalyst for the reduction. A solution of methanesulfonyl chloride (4.7 g, 0.041 mol) in benzene (20 ml) was added dropwise, with magnetic stirring, to a solution of the above amine (12.2 g, 0.081 mol) in benzene (50 ml) in a two-necked, 250-cc, round-bottomed flask. After the addition, more benzene (50 ml) was added, and stirring was continued for 15 min. Separation of the precipitate and removal of solvent and excess reagents by distillation with the water pump gave the crude product, which was crystallized from ethyl acetate–hexane, yield 8.45 g (90%), mp 74–75°.

Anal. Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11. Found: C, 51.94; H, 6.63; N, 5.93.

N-**Methyl-*N*-*o*-methoxybenzylmethanesulfonamide.**—The above procedure gave the ortho isomer in 94% yield, mp 45–48°.

Anal. Calcd for $C_{10}H_{15}NSO_3$: C, 52.38; H, 6.59; N, 6.11. Found: C, 51.59; H, 6.50; N, 5.94.

Registry No.—*N*,*N*-Dimethylmethanesulfonamide, 918-05-8; 2,4-dimethanesulfonyl-2,4-diazapentane, 34825-80-4; *N*-methyl-*N*-*p*-methoxybenzylmethanesulfonamide, 34825-81-5; *N*-methyl-*N*-*o*-methoxybenzylmethanesulfonamide, 34825-82-6.

(16) N. H. Cromwell and H. Hoeksema, *J. Amer. Chem. Soc.*, **67**, 1658 (1945).

Effect of Activating Group on Trans Stereoselectivity of Thiolate Additions to Activated Acetylenes

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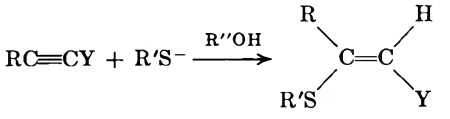
Received February 8, 1972

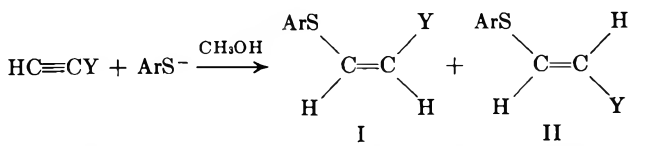
The degree of trans stereoselectivity for nucleophilic additions of arylthiols to negatively substituted acetylenic compounds of the type HC≡CY in methanol is dependent on the nature of the activating group Y, decreasing where Y is a carbonyl-containing group.

Some years ago there was noted a strong tendency for base-catalyzed additions of thiols to acetylenic compounds activated by electron-withdrawing groups to proceed in a trans fashion in protic media[1] (*e.g.*, thiolate attack at the β carbon and protonation at the α carbon occurring from opposite sides).



This "rule" of trans nucleophilic addition has since been confirmed by many workers.[2] Recently, however, several authors have reported violations of this rule; a competing cis-addition process was postulated.[3] Some of the claimed violations could be rationalized as resulting from post-isomerization of the kinetically favored trans-addition product (possessing the *Z*, or cis, configuration) to the more stable *E* (trans) isomer,[3b,c] while others could have resulted from the intermediacy of resonance-stabilized or equilibrating carbanions in aprotic solvents.[3a,d]

Work commenced in this laboratory to determine the limitations of the rule of trans-nucleophilic addition. Where violations were found, it was desirable to determine the factors promoting a competitive cis-addition



(1) W. E. Truce and J. A. Simms, *J. Amer. Chem. Soc.*, **78**, 2756 (1956).

(2) (a) W. E. Truce, *et al.*, *J. Amer. Chem. Soc.*, **79**, 5311 (1957); **81**, 5372, 5795 (1959); **83**, 4636 (1961); (b) F. Montanari, *et al.*, *Gazz. Chim. Ital.*, **87**, 1073 (1957); *Chem. Abstr.*, **52**, 9988 (1958); *Tetrahedron Lett.*, (4), 18 (1960); (c) G. Modena, *et al.*, *Ric. Sci.*, **29**, 1931 (1959); *Chem. Abstr.*, **54**, 10928 (1960); *Gazz. Chim. Ital.*, **89**, 866 (1959); *Chem. Abstr.*, **54**, 22452 (1960); (d) C. J. M. Stirling, *J. Chem. Soc., Suppl. 1*, 5856 (1964); (e) E. N. Prilezhaeva, *et al.*, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1097 (1968); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1042 (1968); (f) V. N. Petrov, *et al.*, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2180 (1966); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2109 (1966); (g) Y. Liu, *et al.*, *Hua Hsueh Hsueh Pao*, **27**, 113 (1961); *Chem. Abstr.*, **59**, 12683 (1963); *Hua Hsueh Hsueh Pao*, **30**, 283 (1964); **31**, 451 (1965).

(3) (a) F. Bohlmann, *et al.*, *Chem. Ber.*, **96**, 584 (1963); **97**, 2109 (1964); (b) M. C. Caserio, R. E. Pratt, and R. J. Holland, *J. Amer. Chem. Soc.*, **88**, 5747 (1966); (c) F. Theron and R. Vessiere, *Bull. Soc. Chim. Fr.*, 2994 (1968); (d) E. N. Prilezhaeva, *et al.*, *Quart. Rep. Sulfur Chem.*, **5**, 234 (1970); *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2217 (1967); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 2128 (1967).

TABLE I

THE REACTION OF *p*-TOLUENETHIOLATE WITH HC≡CY AND EQUILIBRATION STUDIES OF *p*-$CH_3C_6H_4SCH{=}CHY$ IN METHANOL

		Product			Equilibration Studies						
					Configuration						
		Configuration[a]		Conversion,[a] %	Initial		Final[a]			Time, hr	Temp, °C
Registry no.	Y	% Z[b]	% E[b]		% Z[b]	% E[b]	% Z[b]	% E[b]	Catalyst		
1070-71-9	C≡N	100	0	100	100	0	33	67	*p*-C_7H_7SNa	8	50
					10	90	34	66	*p*-C_7H_7SNa	3	50
13894-21-8	$SO_2C_7H_7$-*p*	100	0	65	100	0	0	100	*p*-C_7H_7SNa	144	25
937-31-5	$C_6H_4NO_2$-*p*	100	0	98	(100)	(0)	0	100	*p*-C_7H_7SNa	10	50
922-67-8	CO_2CH_3	92	8	93–96[c]	100	0	22	78	*p*-C_7H_7SNa	12	50
					0	100	23	77	*p*-C_7H_7SNa	12	50
7341-96-0	$CONH_2$	87	13	97	100	0	23	77	*p*-C_7H_7SNa	24	50
					0	100	23	77	*p*-C_7H_7SNa	24	50
1423-60-5	$COCH_3$	82	18	93	100	0	22	78	Dilute HCl	0.25	0
					0	100	21	79	Dilute HCl	0.25	0

[a] Determined by nmr analysis of the crude reaction or equilibration mixture. [b] See *J. Org. Chem.*, 35, 2853 (1970). [c] See Table II.

TABLE II

REACTION OF *p*-TOLUENETHIOLATE WITH METHYL PROPIOLATE IN METHANOL

Concn, mol/l.	Reaction time, hr	Temp, °C	Catalyst (or inhibitor)	Work-up	Product[a] % Z	% E	Conversion
0.5	2	0			91	9	[b]
0.5	46	0		Dilute HCl	92	8	93
0.05	2	0		Dilute HCl	92	8	93
0.05	2	35		Dilute HCl	93	7	96
0.05	2	25		Dilute HCl	92	8	95
0.5	2	0	α-$C_{10}H_7NHC_6H_5$	Dilute HCl	92	8	95
0.5	2	25	C_7H_7SNa		92	8	96

[a] Determined by nmr analysis of the crude reaction mixture. [b] Not determined.

process, and the extent to which such a process might be anticipated to occur. Initially, this study has examined the effects of the activating group Y. Only one solvent, methanol, was utilized at this time.

Activating groups were selected so as to provide the widest possible variation in the relative abilities to stabilize an adjacent incipient carbanion by induction or by resonance. The selections were made primarily from a compilation of $\sigma_R^-/\sigma_{I_p}^-$ values[4] and included (in increasing order of potential resonance delocalization) sulfonyl, cyano, carbomethoxy, amido, and acetyl. An additional activating group, *p*-nitrophenyl, was chosen for its ability to delocalize an adjacent negative charge in the absence of a carbonyl function.[5]

The results of sodium *p*-toluenethiolate and base-catalyzed addition of *p*-toluenethiol to the substrates ethynyl *p*-tolyl sulfone, propiolonitrile, *p*-nitrophenylacetylene, methyl propiolate, propiolamide, and butynone are summarized in Table I.

Examination of Table I indicates that there are two categories of substrates.[5a] The first group adds *p*-toluenethiolate with 100% stereoselectivity, in accordance with the rule of trans-nucleophilic addition, to give adducts of structure I and includes acetylenic compounds possessing as activating groups *p*-tolysulfonyl, cyano, and *p*-nitrophenyl. The second group adds *p*-toluenethiolate with a high degree of stereoselectivity but also permits some cis addition (both products I and II). This group includes substrates with carbomethoxy, amido, and acetyl activating groups. Thus, a carbonyl-containing function apparently allows a limited competitive cis addition in terminal acetylenic substrates.

Firm establishment of the degree of stereoselectivity of addition depended on the certainty with which post-isomerization could be eliminated as the potential source of cis-addition product II; consequently, isomerically pure trans-addition products I were subjected to the various reaction conditions and found not to isomerize. Reactions were carried out utilizing an excess of the acetylenic substrate to preclude thiolate-[2b] or thiol-[6] induced post-isomerization. The volatility of some substrates (propiolonitrile, methyl propiolate, and butynone) necessitated utilization of a relatively large excess of the acetylenic compound, which in some cases reacted to form by-product (*i.e.*, methoxide adducts). Methoxide addition was competitive in very few cases, however; conditions were selected so as to minimize this side reaction. The reliability of the results is further supported by the identical isomer distributions obtained in sodium *p*-toluenethiolate addition and in the base-catalyzed addition of *p*-toluenethiol. (See Experimental Section.)

The position of equilibrium for each isomeric pair was determined in order to establish the more stable isomer (see Table I). It was believed that the cis-addition product II should be the more stable isomer in all cases, but a previous report[7] had raised doubts concerning the relative stabilities of (*Z*)- and (*E*)-β-*p*-tolylmercaptoacrylonitrile.

The addition of *p*-toluenethiolate to methyl propiolate was the most extensively studied reaction. This addition was performed under a wide variety of conditions (see Table II) and although *p*-toluenethiolate has

(4) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 58.

(5) D. H. Hunter and D. J. Cram, *J. Amer. Chem. Soc.*, 88, 5765 (1966).

(5a) NOTE ADDED IN PROOF. Similar results and conclusions have been reported by E. N. Prilezhaeva, *et al.*, *Zh. Org. Khim.*, 7, 1349 (1971); *J. Org. Chem. USSR*, 7, 1394 (1971).

(6) P. E. Butler, W. H. Mueller, and J. J. R. Reed, *Environ. Sci. Technol.*, 1, 315 (1967).

(7) F. Scotti and E. J. Frazza, *J. Org. Chem.*, 29, 1800 (1954).

TABLE III
PHYSICAL AND NMR DATA FOR p-$CH_3C_6H_4SCH{=}CHY$

Y	Registry no.	Configuration	Mp, °C	H_α[a]	H_β[a]	J_{H-H}[b]
C≡N	34726-87-9	Z	47–48	5.29	7.20	10.5
	34726-88-0	E	c	4.90	7.36	15.5
$SO_2C_7H_7$-p	19737-97-4	Z	116–117	6.25	7.17	10.2
	34726-90-4	E	78.5–80	5.98	7.47	14.5
$C_6H_4NO_2$-p	32291-86-4	Z	97.5–99.5	6.46	6.76	11.0
	32291-88-6	E	87–89	6.40	c	15.3
CO_2CH_3	34726-93-7	Z	54–55	5.85	7.36	10.2
	34726-94-8	E	34.5–35.5	5.61	7.77	15.0
$CONH_2$	34726-95-9	Z	169.5–170.5	6.15[d]	7.13	10.0
	34726-96-0	E	130–132	5.91	7.54	15.0
$COCH_3$	34726-97-1	Z	54–55	6.32	7.18	9.8
	34726-98-2	E	60–61	5.91	7.65	15.3

[a] δ in ppm from tetramethylsilane; $CDCl_3$ solution, except as noted. [b] Coupling constant in cps. [c] Could not be determined. [d] DMSO-d_6 solution.

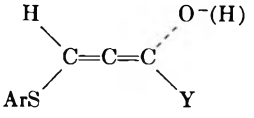
been reported to add to ethyl propiolate with 100% stereoselectivity,[2b] in no case was methyl (Z)-β-tolylmercaptoacrylate (I, Y = CO_2CH_3; from trans addition) observed isomerically pure. Inert atmosphere, presence of a free-radical inhibitor, and variation of concentration, reaction time, temperature, mode of addition (normal or inverse), and work-up conditions failed to alter significantly the product distribution of methyl (Z)- (92%) and (E)- (8%) β-p-tolylmercaptoacrylate. Control experiments on the pure Z isomer I employing catalytic methoxide, thiolate, thiol, and dilute acid proved that the E isomer was not arising from the Z product by post-isomerization.

Propiolamide and butynone were also found to afford limited amounts of cis addition to give E product II. The purified Z products I were subjected to control experiments. (Z)-β-p-Tolylmercaptoacrylamide was stable under the reaction and work-up conditions, but (Z)-4-p-tolymercapto-3-buten-2-one was unstable in acidic media, equilibrating completely in 15 min at room temperature. Consequently, in the work-up of the reaction mixture from the addition of p-toluenethiolate to butynone, the acidification of the reaction mixture was not carried out past pH 7.

Nmr was chosen as the method of analysis of the addition products. (Vapor phase chromatography was not employed, as the relatively high temperatures necessary might cause post-isomerization.[2b]) The coupling constants of cis and trans protons [J_{H-H} (cis) = 5–11, J_{H-H} (trans) = 13–18 cps][8a] and the appearance of the α proton in an otherwise clear area of the spectrum permitted qualitative distinction between the products and quantitative determination of the isomer distribution.

Nmr and melting point data for the adducts p-$CH_3C_6H_4SCH{=}CHY$ are summarized in Table III.

The activating group effect, which may result in some cis addition, has important mechanistic implications. The kinetic data of Truce and Heine,[8b] which suggested that the addition of p-toluenethiolate to phenylacetylene to give (Z)-β-p-tolylmercaptostyrene exclusively, *via* a synchronous attack of thiolate and proton abstraction, may not be applicable in systems where cis addition occurs. Several mechanisms appear possible in these systems, and, in fact, different mechanistic pathways may be utilized by different substrates. In substrates possessing a carbonyl-containing activating group, an enol(ate) intermediate is probable.



Protonation of the carbonyl oxygen might occur before protonation of the α carbon.[5a] An analogous intermediate has been proposed for the addition of ethylenimine to ethyl propiolate.[9]

The nature of the mechanism of addition to the substrate where total stereoselectivity was observed is more ambiguous. The failure of p-nitrophenylacetylene to undergo any cis addition suggests a concerted process; a carbanionic mechanism would probably involve a delocalized intermediate[5] which would protonate to give a mixture of isomers. Ethynyl p-tolyl sulfone also adds thiolate 100% stereoselectively, but the corresponding *tert*-butyl substrate permits some cis addition,[10] possibly *via* stepwise addition. Elucidation of the mechanism(s) of addition requires further investigation.

Experimental Section[11]

Starting Materials and Reagents.—p-Toluenethiol was purchased from the Eastman Organic Chemical Co., and used without further purification. Other reagents were obtained through the usual chemical supply companies and used without further purification. (Z)-β-Chloroacrylic acid and p-tolylsulfonylethyne were obtained from M. L. Gorbaty and L. D. Markley, respectively, of this laboratory; other acetylenic substrates were prepared by known procedures. Absolute methanol was "Baker Analyzed Reagent" grade.

Methyl Propiolate.—Esterification[12] of 50.0 g of propiolic acid[13] gave a 67% yield of methyl propiolate: bp 99–101.5° [lit.[12] bp 102° (742 mm)]; nmr (CCl_4) δ 3.06 (s, 1 H), 3.76 (s, 3 H).

(8) (a) C. N. Barnwell and N. Sheppard, *Mol. Phys.*, **3**, 351 (1960); (b) W. E. Truce and R. F. Heine, *J. Amer. Chem. Soc.*, **81**, 593 (1959).

(9) (a) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965); (b) W. E. Truce and D. G. Brady, *ibid.*, **31**, 3543 (1966); (c) R. Huisgen, B. Giese, and H. Huber, *Tetrahedron Lett.*, 1883 (1967).

(10) Unpublished results.

(11) All analyses were carried out by Dr. C. S. Yeh and staff of the Purdue Chemistry Microanalytical Laboratory. All melting and boiling points are uncorrected. All nmr spectra were run on a Varian A-60A with the spectrometer operating at 60 MHz, using tetramethylsilane as an internal standard.

(12) E. Ingold, *J. Chem. Soc.*, **127**, 1199 (1927).

(13) V. Wolf, *Chem. Ber.*, **86**, 736 (1963).

Propiolamide.—Methyl propiolate (21.0 g) was treated with liquid ammonia to afford a 96% yield of propiolamide: mp 58–61° (lit.[14] mp 61–62°); nmr (D_2O) δ 3.50 (s, 1 H), 4.43 (s, 2 H).

Propiolonitrile.—Propiolamide was dehydrated[15] with phosphorous pentoxide to give a 60% yield of propiolonitrile: bp 40–42° (lit.[13] bp 42.5°); nmr ($CDCl_3$) δ 2.57.

***p*-Nitrophenylacetylene.**[16]—A mixture (3.35 g) of crude (*Z*)- and (*E*)-β-bromo-*p*-nitrostyrene[17] was dehydrobrominated. The yield of *p*-nitrophenylacetylene, mp 146–148° (lit.[16] mp 148–149°), was 47%: nmr ($CDCl_3$) δ 3.37 (s, 1 H), 7.63 (d, 2 H, J = 8.0 cps, ortho aromatic protons), 8.20 (d, 2 H, J = 8.0 cps, meta aromatic protons).

Preparation of Methyl (*Z*)-β-Chloroacrylate.—Concentrated sulfuric acid (2.0 ml, 3.7 g, 0.038 mol) was added dropwise to a solution of 7.00 g (0.066 mol) of (*Z*)-β-chloroacrylic acid in 50 ml of methanol and the reaction mixture was heated at reflux for 2 hr. After cooling, it was poured into 250 ml of water. The solution was extracted with ether (3 × 150 ml) and the combined ethereal extracts were washed once with saturated sodium bicarbonate solution and dried over magnesium sulfate. The ether was distilled off at atmospheric pressure and the residual liquid was distilled under vacuum to afford 6.90 g (87.0%) of methyl (*Z*)-β-chloroacrylate, bp 68–70° (40 mm) [lit.[18] bp 79–83° (78 mm)].

Preparation of Methyl (*E*)-β-Chloroacrylate.—The procedure used was identical with that of the previous reaction, except that (*E*)-β-chloroacrylic acid (Aldrich) was substituted for the *Z* isomer. There was obtained 5.80 g (73.0%) of methyl (*E*)-β-chloroacrylate, bp 43–46° (40 mm) [lit.[18] bp 74–75° (131 mm)].

Preparation of Sodium *p*-Toluenethiolate.[19]—*p*-Toluenethiol (25.0 g, 0.198 mol) in 150 ml of toluene was treated with 4.50 g (0.195 g-atom) of sodium at reflux to give 27.1 g (94.9%) of sodium *p*-toluenethiolate.

General Procedure for the Reaction of Sodium *p*-Toluenethiolate with Activated Acetylenes.—A solution of sodium *p*-toluenethiolate in absolute methanol was added dropwise to a stirred solution of the acetylenic compound (in excess) in absolute methanol at 0° and the reaction mixture was stirred at ice-bath temperature for 2 hr. Acidification to a pH of approximately 6 with dilute hydrochloric acid and concentration *in vacuo* at room temperature afforded a residue which was taken up in carbon tetrachloride or chloroform and water. The organic phase was concentrated as before, weighed, and analyzed by nmr.

Reactions of Sodium *p*-Toluenethiolate and Methyl Propiolate.

A.—Following the procedure outlined above, 0.25 g (3.0 mmol) of methyl propiolate in 3 ml of methanol was treated with 0.29 g (2.0 mmol) of sodium *p*-toluenethiolate in 2 ml of methanol to give 0.39 g (92%) of a mixture of methyl (*Z*)- (91%) and (*E*)- (9%) β-*p*-tolylmercaptoacrylate.

B.—Utilizing the same quantities of reagents and conditions as in A, but omitting acidification in the work-up procedure, afforded 92% trans-addition product and 8% cis.

C.—The same quantities of reagents were employed but the concentrations were decreased by a factor of ten by increasing the volumes of solvent. Work-up gave 0.39 g (92%) of methyl β-*p*-tolylmercaptoacrylate (92% *Z* and 8% *E*) and 0.05 g of methyl (*Z*)- and (*E*)-β-methoxyacrylate.

D.—Utilizing the same quantities of reagents as in A, the reaction was allowed to proceed for 44 hr. Work-up gave 0.39 g (92%) of methyl (*Z*)- (92%) and (*E*)- (8%) β-*p*-tolylmercaptoacrylate and 0.19 g of methyl 3,3-dimethoxypropionate.

E.—The same quantities of reagents were used as in A. The reaction was carried out at −35°. A 96% conversion (0.40 g) to a mixture of 92% *Z* and 8% *E* adducts was obtained.

F.—Sodium *p*-toluenethiolate (0.29 g, 2.0 mmol) in 20 ml of methanol was added to methyl propiolate (0.25 g, 3.0 mmol) in 30 ml of methanol at 25°, and stirring was continued at room temperature for the normal period of time, to yield, after work-up, methyl (*Z*)- (93%) and (*E*)- (7%) β-tolylmercaptoacrylate as well as the isomeric methyl β-methoxyacrylates and methyl 3,3-dimethyoxypropionate.

G.—The same quantities of reagents and conditions were employed as in A, but the reaction was conducted under nitrogen in the presence of a catalytic amount (0.01 g, 0.045 mmol) of *N*-phenyl-1-naphthylamine. The distribution of products was 92:8 methyl (*Z*)/(*E*)-β-*p*-tolylmercaptoacrylate.

Reaction of Sodium *p*-Toluenethiolate with Ethynyl *p*-Tolyl Sulfone.—Employing the general procedure, 0.21 g (1.4 mmol) of sodium *p*-toluenethiolate in 2 ml of methanol was added to 0.27 g (1.5 mmol) of ethynyl *p*-tolyl sulfone in 3 ml of methanol to afford 0.40 g (65%) of (*Z*)-1-*p*-tolylmercapto-2-*p*-tolylsulfonylethene and 0.11 g (35%) of a 7:3 mixture of (*Z*)- and (*E*)-1-methoxy-2-*p*-tolylsulfonylethene.

Reaction of Sodium *p*-Toluenethiolate and Propiolonitrile.—A cold solution of 0.29 g (2.0 mmol) of sodium *p*-toluenethiolate in 5 ml of methanol was added to a stirred solution of 0.15 g (2.9 mmol) of propiolonitrile in 25 ml of methanol at −78°. Stirring was continued at that temperature for 1 hr, after which unreacted propiolonitrile was removed at reduced pressure. Acidification, concentration, and work-up as usual provided 0.35 g (100%) of (*Z*)-β-*p*-tolylmercaptoacrylonitrile and 0.09 g of (*Z*)-β-methoxyacrylonitrile.

Reaction of Sodium *p*-Toluenethiolate and *p*-Nitrophenylacetylene.—Sodium *p*-toluenethiolate (0.30 g, 2.0 mmol) in 2 ml of methanol was added to *p*-nitrophenylacetylene (0.31 g, 2.1 mmol) in 35 ml of methanol according to the general procedure to give, after work-up, 0.53 g (100%) of (*Z*)-β-*p*-tolylmercapto-*p*′-nitrostyrene.

Reaction of *p*-Toluenethiolate and Propiolamide.—Propiolamide (0.14 g, 2.0 mmol) in 3 ml of methanol was treated with 0.22 g (1.5 mmol) of sodium *p*-toluenethiolate in 2 ml of methanol at 0° for 4 hr to give 0.29 g (100%) of a mixture of 87% (*Z*)- and 13% (*E*)-β-*p*-tolylmercaptoacrylamide.

Reaction of Sodium *p*-Toluenethiolate and Butynone.—Butynone (0.11 g, 2.0 mmol) in 10 ml of methanol was treated at −70° with 0.15 g (1.0 mmol) of sodium *p*-toluenethiolate in 5 ml of methanol. Following the addition, stirring was continued at −45° for 3 hr. Work-up afforded 0.18 g (93%) of 82% (*Z*)- and 18% (*E*)-4-*p*-tolylmercapto-3-buten-2-one.

General Procedure for the Base-Catalyzed Reaction of *p*-Toluenethiol and Activated Acetylenes.—A methanolic solution of the thiol and a catalytic amount of base (sodium methoxide or *p*-toluenethiolate, or triethylamine) was added dropwise to a stirred solution of the acetylenic substrate in methanol at 0°, and the reaction mixture was stirred at that temperature for 2 hr. The reaction mixture was concentrated *in vacuo* at room temperature and the crude product was analyzed by nmr. The residue was taken up in chloroform or carbon tetrachloride, washed with water, concentrated, and weighed.

Thiolate-Catalyzed Reaction of *p*-Toluenethiol and Methyl Propiolate.—*p*-Toluenethiol (0.25 g, 2.0 mmol) and sodium *p*-toluenethiolate (0.01 g, 0.07 mmol) in 3 ml of methanol were added to 0.25 g (3.0 mmol) of methyl propiolate as outlined above to provide 0.42 g (96%) of methyl (*Z*)- (92%) and (*E*)- (8%) β-*p*-tolylmercaptoacrylate.

Triethylamine-Catalyzed Reaction of *p*-Toluenethiol and Ethynyl *p*-Tolyl Sulfone.—Triethylamine (0.0150 ml, 0.010 g, 0.10 mmol) was added to 0.18 g (1.4 mmol) of *p*-toluenethiol and 0.27 g (1.5 mmol) of ethynyl *p*-tolyl sulfone in 5 ml of methanol at 25°. Work-up afforded 0.38 g (72% conversion) of (*Z*)-1-*p*-tolylmercapto-2-*p*′-tolylsulfonylethene.

Thiolate-Catalyzed Reaction of *p*-Toluenethiol and Propiolonitrile.—Solutions of 0.24 g (1.9 mmol) of *p*-toluenethiol in 4 ml of methanol and 0.01 g (0.07 mmol) of sodium *p*-toluenethiolate in 2 ml of methanol were added to 0.17 g (3.3 mmol) of propiolonitrile in 6 ml of methanol at −45°. Stirring for 2 hr at that temperature and work-up as usual gave 0.17 g (51%) of (*Z*)-β-*p*-tolylmercaptoacrylonitrile and 0.12 g of *p*-toluenethiol.

Attempted Triethylamine-Catalyzed Reaction of *p*-Toluenethiol and *p*-Nitrophenylacetylene.—*p*-Nitrophenylacetylene (0.30 g, 2.0 mmol) in 30 ml of methanol was treated with 0.24 g (1.9 mmol) of *p*-toluenethiol and 0.01 g (0.10 mmol) of triethylamine in 2 ml of methanol for 10 hr. Work-up afforded only unreacted starting material.

Triethylamine-Catalyzed Reaction of *p*-Toluenethiol and Propiolamide.—Triethylamine (0.0150 ml, 0.1 mmol) was added to a solution of *p*-toluenethiol (0.24 g, 1.9 mmol) and propiolamide (0.14 g, 2.0 mmol) in 5 ml of methanol. Work-up gave

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(15) W. E. Truce and M. L. Gorbaty, *J. Org. Chem.*, **35**, 2113 (1970).

(16) S. J. Cristol, A. Begoon, W. P. Norris, and P. S. Ramey, *J. Amer. Chem. Soc.*, **76**, 4558 (1954).

(17) S. Reich and N. Chang, *Helv. Chim. Acta*, **3**, 325 (1928).

(18) A. N. Kurtz, W. E. Billups, R. B. Greenlee, R. B. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).

(19) S. I. Miller, C. E. Orzech, C. A. Welch, C. R. Ziegler, and J. I. Dickstein, *J. Amer. Chem. Soc.*, **84**, 2020 (1962).

product which was undergoing isomerization and some starting material.

Thiolate-Catalyzed Reaction of *p*-Toluenethiol and Butynone.—A cold solution of 0.24 g (1.9 mmol) of *p*-toluenethiol in 6 ml of methanol, followed by 0.01 g (0.07 mmol) of sodium *p*-toluenethiolate in 4 ml of methanol, was added to 0.20 g (3.0 mmol) of butynone in 10 ml of methanol at −45°. Work-up provided 0.38 g (96%) of 82% (*Z*)- and 18% (*E*)-4-*p*-tolylmercapto-3-buten-2-one.

Preparation of Methyl (*Z*)-β-*p*-Tolylmercaptoacrylate.—A solution of *p*-toluenethiol (1.30 g, 10.5 mmol) and sodium *p*-toluenethiolate (0.02 g, 0.1 mmol) in 8 ml of methanol was added to methyl propiolate (1.00 g, 11.9 mmol) in 12 ml of methanol according to the general procedure. Work-up in the usual fashion followed by crystallization, filtration by suction, and rinsing with a small amount of cold methanol, afforded 1.46 g of methyl (*Z*)-β-*p*-tolylmercaptoacrylate, mp 54–56°. Concentration of the mother liquor gave an additional 0.36 g of less pure product, mp 50–52.5°. The total yield was 1.82 g (82.5%).

An analytical sample, prepared by recrystallization from ether–hexane, had mp 54–55°.

Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.43; H, 5.81; S, 15.39; mol wt, 208.29. Found: C, 63.27; H, 5.91; S, 15.35; mol wt, 204.6.

Purification of Methyl (*E*)-β-*p*-Tolylmercaptoacrylate.—A mixture of methyl (*Z*)- (45%) and (*E*)- (55%) β-*p*-tolylmercaptoacrylate (0.65 g, 3.1 mmol) was dissolved in a minimal amount of hexane and chromatographed on silica gel (750 × 25 mm) using hexane–ether as eluent, in the following proportions and volumes: 10:1 (500 ml); 9:1 (500 ml); 6:1 (500 ml); 3:1 (500 ml); and 2:1 (2000 ml). Fractions (20 ml each) were collected; both isomers were eluted in fractions 137–153 and, although separation was not achieved, enrichment of the *E* isomer was observed in some fractions, which were taken up in a small amount of hexane. Crystallization occurred upon cooling; filtration by suction afforded 0.15 g of methyl (*E*)-β-*p*-tolylmercaptoacrylate, mp 34.5–35.5°.

An analytical sample, mp 35.5–36°, was prepared by sublimation at 25° (1–2 mm).

Anal. Found: C, 63.61; H, 5.67; S, 15.60; mol wt, 211.9.

Purification of (*Z*)-1-*p*-Tolylmercapto-2-*p*′-tolylsulfonylethene.—A mixture of (*Z*)-1-*p*-tolylmercapto-2-*p*′-tolylsulfonylethene and a small amount of ethynyl *p*-tolyl sulfone (0.38 g) was recrystallized from methanol to afford 0.27 g of pure (*Z*)-1-*p*-tolylmercapto-2-*p*′-tolylsulfonylethene, mp 116–117° (lit.[20] mp 114–115°).

Preparation of (*Z*)-1-*p*-Tolylmercapto-2-*p*′-tolylsulfonylethene.—(*Z*)-1-*p*-Tolylmercapto-2-*p*′-tolylsulfonylethene (0.30 g, 1.0 mmol) in 40 ml of methanol was treated at room temperature for 6 days with 0.01 g (0.07 mmol) of sodium *p*-toluenethiolate. Concentration *in vacuo* and recrystallization of the residue from methanol gave (*E*)-1-*p*-tolylmercapto-2-*p*′-tolylsulfonylethene, mp 78–80° (lit.[21] mp 92–93°).

Preparation of (*Z*)-β-*p*-Tolylmercaptoacrylonitrile.—Propiolonitrile (0.17 g, 3.3 mmol) in 3 ml of methanol was treated with *p*-toluenethiol (0.25 g, 2.0 mmol) in 2 ml of methanol for 2 hr at 0°. Concentration *in vacuo* gave 0.35 g (100%) of (*Z*)-β-*p*-tolylmercaptoacrylonitrile, mp 47–48° [lit.[7] bp 116–120° (2 mm)].

Preparation of (*E*)- and (*Z*)-β-*p*-Tolylmercaptoacrylonitrile.[22]—(*Z*)- (90%) and (*E*)- (10%) β-*p*-tolylmercaptoacrylamide (0.25 g, 1.3 mmol) in 2 ml of dry benzene was treated with 0.62 g (5.2 mmol) of thionyl chloride at reflux temperature for 7 hr. Work-up afforded 0.21 g (97%) of an amber oil composed of 90% (*E*)- and 10% (*Z*)-β-*p*-tolylmercaptoacrylonitrile which was not purified.

Purification of (*Z*)-β-*p*-Tolylmercapto-*p*′-nitrostyrene.—(*Z*)-β-*p*-Tolylmercapto-*p*′-nitrostyrene (0.53 g, 2.0 mmol) contaminated with a small amount of *p*-nitrophenylacetylene was recrystallized from ether–hexane to give light yellow (*Z*)-β-*p*-tolylmercapto-*p*′-nitrostyrene, mp 95–98°.

Preparation of an analytical sample, mp 97.5–99.5°, was achieved by recrystallization from methanol.

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82; mol wt, 271.34. Found: C, 66.60; H, 4.97; N, 5.38; S, 11.69; mol wt, 272.8.

Preparation of (*E*)-β-*p*-Tolylmercapto-*p*′-nitrostyrene.—*p*-Nitrophenylacetylene (0.30 g, 2.0 mmol) in 15 ml of methanol was treated with 0.58 g (4.0 mmol) of sodium *p*-toluenethiolate in 4 ml of methanol for 12 hr at 50°. Solvent removal *in vacuo* yielded a yellow liquid, which was taken up in chloroform and washed twice with dilute base and once with water. Solvent removal at reduced pressure afforded 0.60 g of material composed of 0.48 g (87%) of (*E*)-β-*p*-tolylmercapto-*p*′-nitrostyrene and 0.12 g of di-*p*-tolyl disulfide. Recrystallization of the former from methanol provided yellow product, mp 87–89°.

Anal. Found: C, 66.21; H, 4.94; N, 5.28; S, 12.16; mol wt, 278.

Preparation of (*Z*)-β-*p*-Tolylmercaptoacrylamide.—Propiolamide (2.00 g, 29.0 mmol) in 60 ml of methanol was treated at room temperature for 20 hr with 3.10 g (25.0 mmol) of *p*-toluenethiol and 0.43 g (3.0 mmol) of sodium *p*-toluenethiolate in 40 ml of methanol. Work-up in the usual manner afforded 5.30 g (98.5%) of crude product. Recrystallization from methanol gave pure (*Z*)-β-*p*-tolylmercaptoacrylamide, mp 166.5–168°.

An analytical sample, prepared by further recrystallization from methanol, had mp 169.5–170°.

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.54; mol wt, 193.27. Found: C, 62.13; H, 5.67; N, 7.28; S, 16.54; mol wt, 187.5.

Preparation of (*E*)-β-*p*-Tolylmercaptoacrylamide.—A solution of 0.40 g (2.1 mmol) of (*Z*)-β-*p*-tolylmercaptoacrylamide and 0.01 g (0.08 mmol) of *p*-toluenethiol was acidified with one drop of dilute hydrochloric acid and heated at 50° for 3 weeks. Concentration at reduced pressure, filtration by suction, and washing of the precipitate with ether gave 0.30 g (75%) of (*E*)-β-*p*-tolylmercaptoacrylamide, mp 128.5–130°.

An analytical sample, mp 130–132°, was prepared by recrystallization from ether–hexane.

Anal. Found: C, 62.10; H, 5.70; N, 7.23; S, 16.62; mol wt, 196.

Preparation of (*Z*)-4-*p*-Tolylmercapto-3-buten-2-one.—Butynone (0.80 g, 12.0 mmol) in 25 ml of methanol was treated successively with 1.24 g (10.0 mmol) of *p*-toluenethiol in 15 ml of methanol and 0.01 g (0.07 mmol) of sodium *p*-toluenethiolate in 2 ml of methanol at −70°. Following completion of the addition, the reaction mixture was stirred at 0° for 30 min. Work-up in the usual manner and drying over magnesium sulfate gave, after solvent removal and recrystallization, 1.49 g (73%) of (*Z*)-4-*p*-tolylmercapto-3-buten-2-one, mp 50–55°.

Preparation of an analytical sample, mp 54–55°, was accomplished by recrystallization from ether.

Anal. Calcd for $C_{11}H_{12}OS$: C, 68.89; H, 6.29; S, 16.67; mol wt, 192.29. Found: C, 68.16; H, 6.58; S, 16.90; mol wt, 189.9.

Preparation of (*E*)-4-*p*-Tolylmercapto-3-buten-2-one.—A solution of (*Z*)- and (*E*)-4-*p*-tolylmercapto-3-buten-2-one (0.75 g, 3.1 mmol) in 5 ml of methanol was acidified with one drop of dilute hydrochloric acid. Concentration *in vacuo* gave an oily yellow solid which was taken up in carbon tetrachloride and washed with water. Concentration of the organic phase gave a yellow oil, which crystallized from hexane. Filtration by suction afforded 0.30 g (38%) of (*E*)-4-*p*-tolylmercapto-3-buten-2-one, mp 60–61° (lit.[23] mp 60.5–61.5°).

General Procedure for Equilibration Studies.—In systems where equilibration studies were conducted, the normal procedure involved *p*-toluenethiolate catalysis in methanol at either room temperature or 50°. An exceptional case was the isomeric 4-*p*-tolylmercapto-3-buten-2-ones (where acid-catalyzed equilibration conditions were utilized). If both isomers were present at equilibrium, the equilibrium mixture was approached from both directions (pure *Z* and pure *E*) separately.

General Procedure for Control Experiments.—The less stable isomer of each isomeric pair of adducts was subjected to the various reaction conditions. Usually, this involved separate treatment with catalytic methoxide, acid, thiolate, and thiol in methanol at similar concentration and temperature and for the same period of time as the thiolate addition to the acetylenic substrate. Analysis was performed by nmr of the crude reaction mixture, as usual. In no case was post-isomerization of the less stable product observed under the reaction or work-up conditions.

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Registry No.—Sodium *p*-toluenethiolate, 10486-08-5.

Acknowledgments.—This work was supported by Grant No. GP 12326 from the National Science Foundation, for which we are grateful. A portion of this work was presented at the 161st National Meeting of the American Chemical Society on March 31, 1971, and was taken from the Ph.D. Thesis of G. J. W. T., Purdue University, Aug 1970.

Stereochemistry of Amido Derivatives of 3a,4,5,6-Tetrahydroindan and Related Compounds

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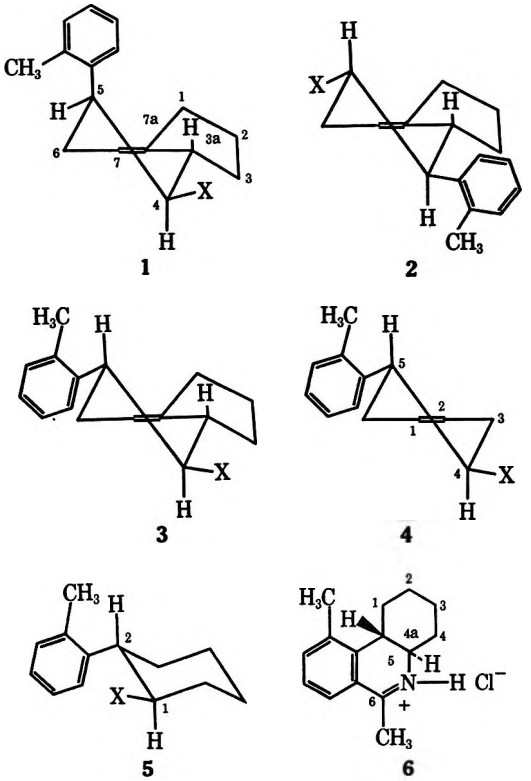
Received July 19, 1971

Three isomeric 5-*o*-tolyl-4-nitro- and 4-*o*-tolyl-5-nitro-3a,4,5,6-tetrahydroindans and 4-nitro-5-*o*-tolylcyclohexene were converted to the corresponding amines with retention of stereochemistry by reduction with iron in acetic acid. Rotational isomerism of the formamide, acetamide, and *N*-methylacetamide derivatives of the amines was studied by nmr. Two rotational isomers were seen in deuteriochloroform for all amides except the acetamides. The geometry of the major amide conformers is discussed. Of special interest from a conformational standpoint is the observation of a predominance of the half-chair conformation with the *o*-tolyl group occupying an axial orientation in the series of *cis*-4-amino-*cis*-*o*-tolyl-3a,4,5,6-tetrahydroindan and corresponding amides.

The nmr characterization of isomeric 5-*o*-tolyl-4-nitro- and 4-*o*-tolyl-5-nitro-3a,4,5,6-tetrahydroindans was reported earlier.[2] We now report the preparation of amines **1a–4a** in quantitative yields by iron in acetic acid reduction[3,4] of the corresponding nitro compounds of established stereochemistry[2,3] and an nmr investigation of rotational isomerism in derived amides of **1a–5a**. Retention of configuration at the nitro-bearing carbon during the iron in acetic acid reduction[3] is substantiated by the splitting pattern and/or width of the signal of the hydrogen on the nitrogen-bearing carbon of the resulting amine and amide derivatives. Migration of the double bond during the synthesis of the amino- and amidocyclohexenes **4** is ruled out on the basis of the integration of the olefinic hydrogens and the multiplicities and widths of the signals of the hydrogens at the functional group bearing carbons. The proof is not as unequivocal for the tetrahydroindan derivatives **1–3**, but two of the three possible products of simple migration are ruled out on similar grounds and the third, resulting in a 6,7-disubstituted 2,4,5,6,7,7a-hexahydroindene, seems an unlikely candidate from a thermodynamic stability standpoint. If any migration had occurred, mixtures would be expected.

Because of the fixed orientation of the bridgehead H-3a, only one half-chair conformation is possible for the tetrahydroindan compounds **1–3**, but boat and other flexible conformations are not ruled out. On the basis of the coupling patterns and/or widths of the signals of the hydrogens on the functional group bearing carbons (J_{aa} values are normally around 10–11 Hz, and J_{ae} and J_{ee} are usually in the neighborhood of 3.5 Hz) the nmr spectra in $CDCl_3$ indicate a time-average predominance of the conformations shown in Chart I. This is expected for all compounds of series **2–5**, where the substituents are trans and where the diequatorial conformation is preferred, but it is not as predictable for compounds of series **1**. In series **1** the spectra of **1a**, **1b**, **1d**, and **1e** are very informative. For **1a** in trichloroethylene the signal of H-4 gives a doublet of doublets, J_{43a} = 8.5 and J_{45} = 4.5 Hz, indicative of a predominance of the conformer with H-4 in axial orientation. The signal of H-5 gives a seven-peak multiplet with width of 12.4 Hz. The splitting pattern indicates $J_{56(ax)}$ = 6.2, $J_{56(eq)}$ = 1.7, and J_{54} = 4.5 Hz.

CHART I



a, X = NH_2
b, X = NHCHO
c, X = $^{+}NH_2CH_3Cl^-$
d, X = NCH_3COCH_3
e, X = $NHCOCH_3$

(1) Public Health Service Predoctoral Fellow 5-FO1-GM-34,830, 1967–1969.

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The seven-peak multiplet results from overlapping of the two inner components of what would otherwise be an eight-peak multiplet. The signal indicates a predominance of the conformer where H-5 has the equatorial orientation. For **1b** in $CDCl_3$, after deuterium exchange of the NH hydrogen, the signal of H-4 appears as a doublet of doublets, $J_{43a} = 10.0$ and $J_{45} = 4.7$ Hz, and the width of the signal of H-5 is 12 Hz, again consistent with a predominance of the conformer with H-4 axial and H-5 equatorial. For **1d** in $CDCl_3$ the signal of H-4 also gives a doublet of doublets, $J_{43a} = 11.0$ and $J_{45} = 4.6$ Hz. For **1e** the width of the signal of H-5 is again about 12 Hz and the signal of H-4 appears as a six-peak multiplet indicative of $J_{43a} \cong J_{4NH} \cong 9.7$ and $J_{45} \cong 4.7$ Hz. The NH signal appears as a broad doublet at δ 5.27, $J_{NH,4} \cong 9.7$ Hz. The data again support a predominance of the half-chair conformation with the aromatic ring occupying an axial orientation. The signals of H-5 in the spectra of 1b and **1e** appear essentially as multiplets having three fairly broad components which suggest coupling constants of slightly over 6 Hz between H-5 and pseudoaxial H-6, about 1 Hz, or less, between H-5 and equatorial H-6, and about 4.7 Hz between H-5 and H-4 as seen from the signals of H-4. Molecular models show that the dihedral angle between H-5 and equatorial H-6, in the proposed conformation, is close to 90° and explains the very small coupling constant between these hydrogens.

The nmr spectra of the formamides **1b–5b** and the four *N*-methyl acetamides investigated (**1d**, **3d**, **4d**, and **5d**) all show the presence of two rotational conformers resulting from slow rotation, on the nmr time scale, about the C–N bond of the amido group. A fairly rough approximation by integration indicates a ratio of conformers of about 3:1 in deuteriochloroform. The presence of two conformers could be detected from differences in chemical shifts of the signals of some of the following groups between the two conformers: CHO, HN, NCH_3, $ArCH_3$, PhCH, $COCH_3$, and the hydrogen on the amido-bearing carbon. It is interesting to note that rotational conformers were not detected in any of the secondary acetamides investigated, compounds **1e**, **4e**, and **5e**. This does not imply a more rapid rotation about the C–N bond but suggests a position of the equilibrium in favor of essentially only one conformer. Published data on isomerism of secondary amides[5] indicate a usual predominance of the isomer having a trans orientation of the N substituent and the R or H on the carbonyl carbon. Our results with the five formamides are in agreement with this. In all formamides the signal of the formyl hydrogen of the major isomer gives an arrow doublet, $J = 2$ Hz, while that of the minor isomer gives a coupling constant of 12 Hz between the formyl and NH hydrogens. This is consistent with a trans orientation of these two hydrogens in the minor isomers and cis in the major. Deuterium exchange of the NH hydrogen causes each of these two signals to collapse to a singlet. In deuteriochloroform the signal of the formyl hydrogen of the major isomer was always the furthest downfield and the difference was most pronounced for compounds **2b–5b**. This is as expected because in the minor isomer, having the formyl hydrogen cis to the N substituent, the formyl hydrogen comes closer to the face, and thus the shielding region, of the aromatic ring. A comparison of the chemical shifts of the hydrogen on the amido-bearing carbon (XCH) and of the tolyl methyl group ($ArCH_3$) between acetamides **1e**, **4e**, and **5e** with the respective signals of the major conformers of formamides **1b**, **4b**, and **5b** suggests that the acetamides also have the trans orientation between the acetyl methyl group and the N substituent. For the XCH signal the differences in chemical shifts between the acetamides and the major conformers of the corresponding formamides are 0.09, 0.02, and 0.0 ppm for series **1**, **4**, and **5**, respectively, and for the $ArCH_3$ signals the differences are 0.02, 0.03, and 0.02, respectively. The formamide **2b** was investigated at higher temperature in tetrachloroethylene. Merging of the corresponding signals of the two conformers occurred between 120 and 130°. The data are given in the Experimental Section. At 130° the signal of the formyl hydrogen appears as a doublet with separation of 4.4 Hz. This represents the average coupling constant between the CHO and NH hydrogens in the more rapidly rotating system. On the basis of coupling constants of 2.0 and 12.0 Hz in the major and minor frozen conformers, and of 4.4 Hz in the mobile system at elevated temperature, the calculated time-average proportions of conformers at 130° is 76% of the major and 24% of the minor. Since the calculation involves differences in widths between fairly narrow signals, small errors in measurements of signal widths can introduce fairly large errors in calculated values. At the normal operating temperature of 37° the ratio, from integration of signals, was about 4:1 in tetrachloroethylene.

The Bischler–Napieralski cyclization[6] of **5e**, by refluxing with phosphorus oxychloride in chlorobenzene, yielded the 6,10-dimethyl-4a,10b-*trans*-1,2,3,4,4a,10b-hexahydrophenanthridine (the free amine of **6**). The nmr spectrum of the product obtained from treatment of **4e** under similar conditions suggests that random migration of the double bond has occurred. In compound **6**, and the corresponding free imine, the nmr signal of the methyl group at C-6 appears as a doublet with separation of 1.5 Hz. The splitting is attributed to homoallylic coupling[7] with H-4a.

Experimental Section

The nmr spectra were recorded on a Varian A-60 spectrometer at a temperature of ~37°, unless stated otherwise, utilizing ~20% (w/v) solutions with tetramethylsilane (TMS) as the internal reference. High-temperature studies were accomplished using the Varian HR-60 spectrometer. Infrared spectra were determined using a Beckman IR-5-A infrared spectrometer. Melting points were determined on the Kofler micro hot stage (K) equipped with a factory-calibrated thermometer or on the Thomas-Hoover capillary melting point apparatus (TH). Elemental analyses were conducted by the Huffman Laboratories, Wheatridge, Colo.

Primary amines 1a, 2a, 3a, and 4a were prepared by iron and acetic acid reduction of the known parent nitro compounds[2,3] by a method described by Kornblum and coworkers[4] for the synthesis of (+)-α-phenylethylamine. Quantitative recovery of each free amine as a light orange oil from its basified reaction mixture

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was achieved by using a continuous extractor with diethyl ether as solvent. A sample of each oil taken for vpc analysis on a 10 ft × 0.125 in. column of 10% QF-1 (Fluoro Silicone) on 60/80 mesh acid washed Chromosorb W at 215° indicated that reduction was complete and that none of the parent nitro derivative was present. These four amines were not further purified but were used directly to synthesize their corresponding formamide and acetamide derivatives. Nmr of free bases (C_2Cl_4) follows: **1a**, δ 5.53 (m, 1, =CH), 3.45 (seven-peak m, 1, J = 6.2, 4.5, 1.7 Hz, PhCH), 2.68 (dd, 1, J = 8.5, 4.5 Hz, XCH), 2.44 (s, 3, $ArCH_3$); **2a**, δ 5.42 (m, 1, =CH), ~3.1 (broad m, 1, XCH), ~2.55 (partially overlapped, poorly resolved triplet, separation of ~10 Hz, PhCH), 2.33 (s, 3, $ArCH_3$); **3a**, δ 5.40 (m, 1, =CH), ~2.85 (broad m, 2, XCH and PhCH), 2.33 (s, 3, $ArCH_3$); **4a**, δ 5.53 (m, 2, =CH), ~2.98 (broad m, 2, XCH and PhCH), 2.33 (s, 3, $ArCH_3$).

Formamides 1b, 2b, 3b, and 4b were synthesized by refluxing the appropriate primary amine in redistilled 99% formic acid (10 molar equiv excess) with dry toluene in a manner essentially described by McKusick and Webster[8] for *N*-*o*-tolylformamide. When necessary the individual formamide was further purified by descending dry column chromatography[9] utilizing diethyl ether to eliminate the dark material and then further eluting with diethyl ether–acetone mixtures to recover the formamide.

cis-**4-Formamido-*cis*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan (1b)**[10] was recrystallized from benzene–*n*-hexane (73%): mp 161.4–164.3° (K); ir (KBr) 1565, 1650 (C=O), 2885 (formyl CH), 2945, and 3220 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.98 (d, <1, J = 2 Hz, CHO, major), 7.95 (d, <1, J = 12 Hz, CHO, minor), 5.62 (m, 1, =CH), 4.17 (m, <1, XCH, gives dd, J = 10 and 4.7 Hz, after deuterium exchange of the NH hydrogen), 3.65 (m, $W_{1/2}$ = 12 Hz, ArCH), 2.32 (s, 3, $ArCH_3$).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.60; H, 8.13; N, 5.49.

cis-**4-*o*-Tolyl-*trans*-5-formamido-3a,4,5,6-tetrahydroindan (2b)**[10] was recrystallized from benzene–*n*-hexane: mp 110.1–112.8° (K); ir (KBr) 1540, 1660 (C=O), 2875 (formyl CH), and 3270 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.70 (d, <1, J = 2 Hz, CHO, major), 7.48 (d, <1, = 12 Hz, CHO, minor), ~5.84 (m, <1, NH, major), ~6.30 (m, <1, NH, minor), 5.44 (m, 1, =CH), 4.43 (m, <1, W >30 Hz, XCH, major), 3.65 (m, <1, XCH, minor), 2.85 (t, <1, J ≅ 10.5 Hz, ArCH, major), 2.78 (t, <1, J ≅ 10.5 Hz, ArCH, minor), 2.32 (s, <3, $ArCH_3$ major), 2.23 (s, <3, $ArCH_3$, minor); nmr (C_2Cl_4) at 37° δ 7.22 (d,[11] CHO, major), 7.18 (d,[11] CHO, minor), 5.34 (m, 1, =CH), 4.30 (m, <1, W >30 Hz, XCH, major), 3.42 (m, <1, XCH, minor), 2.77 (t,[12] J ≅ 10 Hz, ArCH), 2.21 (s, <3, $ArCH_3$, major), 2.11 (s, <3, $ArCH_3$, minor); nmr (C_2Cl_4) at 130° δ 7.42 (d, 1, J = 4.4 Hz, CHO), 5.87 (m, 1, NH), 5.31 (m, 1, =CH), 4.05 (m, 1, W >30 Hz, XCH), 2.76 (t, 1, J = 10 Hz, ArCH), 2.19 (s, 3, $ArCH_3$).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.12; H, 8.27; N, 5.62.

cis-**4-Formamido-*trans*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan (3b)**[10] was recrystallized from benzene: mp 155.9–159.0° (K); ir (KBr) 1550, 1655 (C=O), 2860 (formyl CH), and 3200 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.77 (d, <1, J = 2 Hz, CHO, major), 7.57 (d, <1, J = 12 Hz, CHO minor), 5.80 (broad d, <1, separation ~10 Hz, NH, major), 5.49 (m, 1, =CH), 4.25 (q, J ≅ 10 Hz, XCH, major, gives essentially a triplet, J = 10 Hz, after deuterium exchange of NH hydrogen), 3.21 (m, W ≅ 27 Hz, PhCH, major), 2.31 (s, <3, $ArCH_3$, major), 2.24 (s, <3, $ArCH_3$, minor).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.48; H, 8.23; N, 5.48.

trans-**4-Formamido-5-*o*-tolylcyclohexene (4b)** was recrystallized from benzene–*n*-hexane: mp 96.8–98.5° (K); ir (KBr) 1550, 1655 (C=O), 2890 (formyl CH), and 3220 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.80 (d, <1, J = 2 Hz, CHO, major), 7.61 (d, <1, J = 12 Hz, CHO, minor), 6.11 (m, <1, NH, major), 5.77 (m, 2, =CH), 4.43 (m, <1, W ≅ 32 Hz, XCH major), 3.21 (m, W ≅ 25 Hz, ArCH, major), 2.35 (s, <3, $ArCH_3$, major), 2.27 (s, <3, $ArCH_3$, minor).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.40; H, 7.98; N, 6.51.

The *N*-methylammonium salts **1c, 3c, 4c,** and **5c** were prepared by lithium aluminum hydride reduction of the respective formamide precursors by a method essentially described by Cope and Ciganek[13] for the synthesis of *N*,*N*-dimethylcyclohexylmethylamine. Each secondary amine was then dissolved in diethyl ether and treated with a solution of concentrated hydrochloric acid in methanol.

cis-**4-*N*-Methylamino-*cis*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan hydrochloride (1c)**[10] was recrystallized from diethyl ether and absolute ethanol (63%): mp 224.0–227.0° (TH, sealed capillary); ir (KBr) 2450, 2700 cm^{-1} (NH); nmr (95% HCOOH–5% D_2O) δ 5.72 (m, 1, =CH), 3.82 (m, 1, ArCH), 3.53 (m, 1, XCH), (the signal at 3.82 is narrower than the one at 3.53 but partial overlap of the two signals precludes width measurement), 2.92 (five-peak m with separation of 2.8 Hz,[14] 3, NCH_3), 2.45 (s, 3, $ArCH_3$); nmr of free base (C_2Cl_4) δ 5.56 (m, 1, =CH), 3.51 (m, 1, W ≅ 12.5 Hz, ArCH), 2.42 (s, 3, NCH_3 or $ArCH_3$), 2.40 (s, 3, NCH_3 or $ArCH_3$). Mass spectral analysis of the molecular ion gave m/e 241.1852 (calcd for $C_{17}H_{23}N$: 241.1828). The mass spectral analysis was carried out on the hydrochloride salt. The loss of HCl is a normal fragmentation for hydrochloride salts of amines.

Anal. Calcd for $C_{17}H_{24}ClN$: C, 73.49; H, 8.71; N, 5.04. Found: C, 72.93; H, 8.70; N, 5.07.

cis-**4-*N*-Methylamino-*trans*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan hydrochloride (3c)**[10] was recrystallized from diethyl ether and absolute ethanol (81%): mp 258.5–259.0° (TH, sealed capillary); ir (KBr) 2450 and 2650 cm^{-1} (NH); nmr (95% HCOOH–5% D_2O) δ 5.86 (m, 1, =CH), 3.63 (broad m, 2, XCH and ArCH), 2.80 (five-peak m with separation of 2.8 Hz,[14] 3, NCH_3), 2.42 (s, 3, $ArCH_3$); nmr of free base (C_2Cl_4) δ 5.41 (m, 1, =CH), 3.11 (m, 1, W ≅ 26 Hz, ArCH), 2.35 (s, 3, $ArCH_3$), 2.17 (s, 3, NCH_3).

Anal.. Calcd for $C_{17}H_{24}ClN$: C, 73.49; H, 8.71; N, 5.04. Found: C, 73.43; H, 8.69; N, 5.03.

trans-**4-*N*-Methylamino-5-*o*-tolylcyclohexene hydrochloride (4c)** was recrystallized from diethyl ether and absolute methanol: mp 227.0–229.0° (TH, sealed capillary); ir (KBr) 2730 cm^{-1} (NH); nmr (95% HCOOH–5% D_2O) δ 5.87 (m, 2, =CH), 3.85 (m, 1, XCH), 3.51 (m, 1, W ≅ 27 Hz, ArCH, partially overlapped with signal at 3.85, not as broad), 2.86 (five-peak m,[14] 3, NCH_3), 2.42 (s, 3, $ArCH_3$).

Anal. Calcd for $C_{14}H_{20}ClN$: C, 70.72; H, 8.48; N, 5.89. Found: C, 70.87; H, 8.44; N, 5.90.

trans-**2-o-Tolyl-*N*-methylaminocyclohexane hydrochloride (5c)** was recrystallized from diethyl ether and absolute methanol: mp 197.7–200.2° (TH, sealed capillary); ir (KBr) 2425 and 2730 cm^{-1} (NH); nmr (95% HCOOH–5% D_2O) δ ~3.60 (m, W < 30 Hz, 1, XCH), ~3.17 (m, 1, ArCH), 2.78 (five-peak multiplet,[14] 3, NCH_3), 2.40 (s, 3, $ArCH_3$); nmr of free base (C_2Cl_4) δ ~2.61 (m, 2, XCH and ArCH), 2.32 (s, 3, $ArCH_3$), 2.15 (s, 3, NCH_3).

Anal. Calcd for $C_{14}H_{22}ClN$: C, 70.12; H, 9.25; N, 5.84. Found: C, 70.02; H, 9.17; N, 5.85.

Refluxing the respective free bases of the *N*-methylammonium salts **1c, 3c,** and **4c** with acetic anhydride in benzene afforded the *N*-methylacetamides **1d, 3d,** and **4d**. Both **1d** and **3d** were purified by dry column chromatographic techniques[9] utilizing diethyl ether as elution solvent, but neither could be crystallized. The nmr and ir of their respective oils were consistent with the expected products, however.

cis-**4-*N*-Methylacetamido-*cis*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan (1d)**[10] had ir (neat) 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.60

(8) B. C. McKusick and O. W. Webster, *Org. Syn.*, **41**, 102 (1961), footnote 2.

(9) B. Loev and M. M. Goodman, *Chem. Ind. (London)*, 2026 (1967).

(10) In the nomenclature adopted for the tetrahydroindans, the configuration of substituents (cis or trans) is related to the pseudoaxial bridgehead hydrogen on C-3a.

(11) The signals for both conformers are overlapped with the NH signal. The chemical shifts were obtained from the singlets resulting after deuterium exchange of the NH hydrogen.

(12) The components of the triplet are somewhat broad, suggesting a slight difference in chemical shift of the signal for the two conformers. The triplet sharpens at 130°.

(13) A. C. Cope and E. Ciganek, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 339.

(14) In pure formic acid the signal is a triplet, J = 5.6 Hz. In the presence of D_2O the doublet of the monodeuterated methylamminium ion is superimposed over the triplet, leading to the five-peak multiplet. Any dideuterated species will enhance the center component of the multiplet. Addition of more D_2O causes disappearance of the outer components of the multiplet to eventually give a three-peak multiplet with separation of 2.8 Hz resulting from a mixture of mono- and dideuterated species.

(m, 1, =CH), 4.60 (dd, <1, J = 11.0 and 4.6 Hz, XCH, major), 3.75 (m, >1, ArCH and XCH, minor), 2.23 (s, 3, $ArCH_3$ or NCH_3), 2.20 (s, 3, NCH_3 or $ArCH_3$), 2.17 (s, <3, $COCH_3$, minor), 2.05 (s, <3, $COCH_3$, major).

cis-4-*N*-Methylacetamido-*trans*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan (3d)[10] had ir (neat) 1640 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.43 (m, 1, =CH), 5.08 (dd, <1, J = 11.0 and 10.0 Hz, XCH, major), 3.95 (dd, <1, XCH, minor), ~3.2 (m, ~1, $W \cong 14$ Hz, ArCH), 2.59 (s, <3, NCH_3, minor), 2.54 (s, <3, NCH_3, major), 2.35 (s, ~3,[15] $ArCH_3$), 2.13 (s, ≪3, either $ArCH_3$ or $COCH_3$ from minor conformer), 1.82 (s, ~3,[15] $COCH_3$).

trans-4-*N*-Methylacetamido-5-*o*-tolylcyclohexene (4d) was recrystallized from *n*-hexane in 89% yield: mp 89.8–90.8° (K); ir (KBr) 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.75 (m, 2, =CH), 5.32 (m, <1, $W \cong 30$ Hz, XCH, major), ~4.3 (m, <1, XCH, minor), 3.21 (m, ~1, $W \cong 27$ Hz, ArCH), 2.52 (s, 3, NCH_3), 2.36 (s, ~3,[15] $ArCH_3$), 2.18 (s, ≪3,[15] either $ArCH_3$ or $COCH_3$ from minor conformer), 1.83 (s, ~3,[15] $COCH_3$).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.12; H, 8.39; N, 5.82.

Treatment of primary amines 1a and 4a with acetic anhydride in dry pyridine afforded the acetamido derivatives 1e and 4e.

cis-4-Acetamido-*cis*-5-*o*-tolyl-3a,4,5,6-tetrahydroindan (1e)[10] was recrystallized from benzene–*n*-hexane (95%): mp 199.8–202.3° (K); ir (KBr) 1545, 1645 (C=O), 3280 cm^{-1} (NH); nmr ($CDCl_3$) δ 5.61 (m, 1, =CH), 5.27 (d, 1, $J \cong 9.7$ Hz, NH), 4.08 (dt, 1, J ~ 9.6, 5.0 Hz, XCH), 3.65 (m, 1, W = 11.8 Hz, ArCH), 2.30 (s, 3, $ArCH_3$), 1.83 (s, 3, $COCH_3$). Mass spectral analysis of the molecular ion gave m/e 269.1770 (calcd for $C_{18}H_{23}NO$: 269.1778).

Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.74; H, 8.58; N, 5.28.

trans-4-Acetamido-5-*o*-tolylcyclohexene (4e) was recrystallized from benzene–*n*-hexane (96%): mp 133.3–138.1° (K); ir (KBr) 1555, 1630 (C=O), and 3250 cm^{-1} (NH); nmr ($CDCl_3$) δ 5.96 (d, 1, $J \cong 8.7$ Hz, NH), 5.77 (m, 2, =CH), 4.41 (m, 1, W = 31 Hz, XCH), 3.22 (m, 1, W = 23.8 Hz, ArCH), 2.38 (s, 3, $ArCH_3$), 1.71 (s, 3, $COCH_3$).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.41; H, 8.18; N, 6.14.

Catalytic hydrogenation of compounds 4b, 4d, and 4e utilizing 10% palladium on carbon in solutions of benzene or methanol afforded derivatives 5b, 5d, and 5e.

trans-2-*o*-Tolylformamidocyclohexane (5b) was recrystallized from benzene–*n*-hexane (98%): mp 129.2–130.0° (K); ir (KBr) 1550, 1660 (C=O), 2880 (formyl CH), and 3275 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.70 (d, <1, J = 2 Hz, CHO, major), 7.42 (d, <1, J = 12.0 Hz, CHO, minor), 6.03 (m, <1, NH, major), 4.23 (m, <1, W > 30 Hz, XCH, major), ~3.33 (m, <1, XCH, minor), 2.75 (m, ~ 1, $W \cong 28$ Hz, ArCH), 2.31 (s, <3, $ArCH_3$, major), 2.23 (s, <3, $ArCH_3$, minor).

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.44. Found: C, 77.10; H, 8.75; N, 6.53.

trans-2-*o*-Tolyl-*N*-methylacetamidocyclohexane (5d) was recrystallized from *n*-hexane–benzene (97%): mp 116.5–118.0° (K); ir (KBr) 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 5.00 (m, <1, W > 25 Hz, XCH, major), ~3.93 (m, <1, XCH, minor), ~2.9 (m, ~1, ArCH), 2.63 (s, ≪3, NCH_3, minor), 2.57 (s, <3, NCH_3, major), 2.39 (s, ~3,[15] $ArCH_3$), 1.81 (s, ~3,[15] $COCH_3$), 2.09 (s, ≪3, either $ArCH_3$ or $COCH_3$ of minor conformer). Mass spectral analysis of the molecular ion gave m/e 245.1758 (calcd for $C_{16}H_{23}NO$: 245.1778).

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.49; H, 9.00; N, 5.70.

trans-2-*o*-Tolylacetamidocyclohexane (5e) was recrystallized from benzene–*n*-hexane (98%): mp 145.4–145.9° (K); ir (KBr) 1565, 1635 (C=O), and 3280 cm^{-1} (NH); nmr ($CDCl_3$) δ 5.81 (d, 1, J = 8.7 Hz, NH), 4.23 (m, 1, W ~ 30 Hz, XCH), 2.73 (m, 1, W ~ 24 Hz, ArCH). 2.33 (s, 3, $ArCH_3$), 1.62 (s, 3, $COCH_3$).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.06. Found: C, 77.90; H, 9.10; N, 6.05.

6,10-Dimethyl-4a,10b-*trans*-1,2,3,4,4a,10b-hexahydrophenanthridine hydrochloride (6) was prepared essentially as described by Whaley and Govindachari[6] for a general synthesis of phenanthridines by refluxing a solution of 5e, phosphorus oxychloride (15 molar equiv excess), and dry chlorobenzene for 4 hr. The basified extract yielded the oil of the imine [ir (neat) 1635 cm^{-1} (C=N)], which was then treated with dry hydrogen chloride gas in benzene and recrystallized from 2-propanol to afford the salt in 29% yield: mp 222.8–225.8° (TH, sealed capillary); ir (KBr) 1665 (C=N), 2680 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.59 (m, 3, aromatic), 3.06 (d, 3, J = 1.5 Hz, C-6 methyl), 2.61 (s, 3, C-10 methyl); free imine nmr ($CDCl_3$) δ 7.16 (m, 3, aromatic), 2.30 (d, 3, J = 1.5 Hz, C-6 methyl), and 2.43 (s, 3, C-10 methyl).

Anal. Calcd for $C_{15}H_{20}ClN$: C, 72.13; H, 8.07; N, 5.61. Found: C, 72.33; H, 8.05; N, 5.49.

Registry No.—1a, 34805-94-2; 1b, 34805-95-3; 1c, 34805-96-4; 1d, 34805-97-5; 1e, 34805-98-6; 2a, 34805-99-7; 2b, 34806-00-3; 3a, 34806-01-4; 3b, 34806-02-5; 3c, 34806-03-6; 3d, 34806-04-7; 4a, 34806-05-8; 4b, 34806-06-9; 4c, 34806-07-0; 4d, 34806-08-1; 4e, 34806-09-2; 5b, 34806-10-5; 5c, 34806-11-6; 5d, 34806-12-7; 5e, 34806-13-8; 6, 34806-14-9.

Acknowledgment.—We wish to thank Mr. Bernard J. Nist for the determination of the high-temperature nmr spectra.

(15) Because these signals overlap signals of the ring methylene hydrogens the integration does not allow the assignment of the minor CH_3 signal, at δ 2.13, to the $ArCH_3$ or $COCH_3$ signals.

1-Phenyl-2-acyl-3-amino-2-pyrazolin-5-ones from 1-Phenyl-3-azidocarbonyl-2-pyrazolin-5-ones[1]

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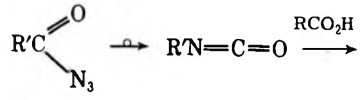
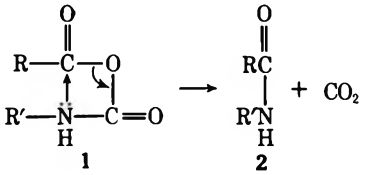
Received January 7, 1972

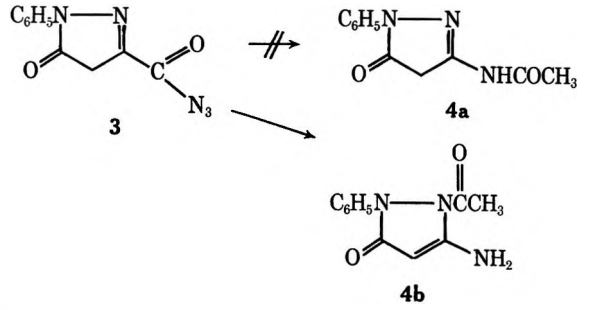
The Curtius reaction of 1-phenyl-3-azidocarbonyl-2-pyrazolin-5-one (**3**) in glacial acetic acid leads to 1-phenyl-2-acetyl-3-amino-3-pyrazolin-5-one (**4b**) rather than the expected 1-phenyl-3-acetamido-2-pyrazolin-5-one.

The Curtius reaction, the conversion of a carboxylic acid to an amine *via* the acid azide and isocyanate, has been used extensively in synthetic organic chemistry. When an acylamine is the desired product, this frequently may be obtained directly by rearranging the azide in an anhydrous acid.[2] It has been proposed[2] that this rearrangement proceeds *via* the mixed anhydride **1** which forms the acylamine **2** with loss of carbon dioxide.



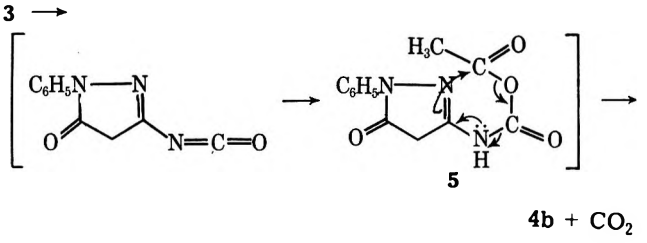


However, when this reaction sequence was attempted with 1-phenyl-3-azidocarbonyl-2-pyrazolin-5-one (**3**) in glacial acetic acid, 1-phenyl-3-acetamido-2-pyrazolin-5-one (**4a**),[3] which would be expected by analogy to the conversion of **1** to **2**, was not obtained. The major product of the reaction of **3** with glacial acetic acid is a new monoacetyl derivative, which I have shown to be 1-phenyl-2-acetyl-3-amino-3-pyrazolin-5-one (**4b**).



Comparison with authentic samples by thin layer chromatography (silica gel with ethyl acetate as eluent) showed the presence of small amounts of 1-phenyl-3-acetamido-2-pyrazolin-5-one (**4a**) and 1-phenyl-3-amino-2-pyrazolin-5-one.

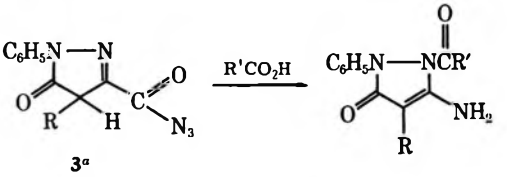
Apparently, in the proposed intermediate mixed anhydride[4] **5**, two nitrogen atoms are capable of nucleophilic attack on the acid carbonyl—the exocyclic nitrogen at position 3 and the 2 nitrogen of the ring. Attack by the exocyclic nitrogen to give compound **4a** would require a four-membered ring in the transition state (as in **1**). Attack by the ring nitrogen involves a six-membered ring, and would lead directly to the observed product **4b**.



Other pyrazolone–acid combinations gave products which were assigned analogous structures (Table I)

TABLE I

1-PHENYL-2-ACYL-3-AMINO-3-PYRAZOLIN-5-ONES



R	R'	Registry no. of product	Mp, °C	Acid
H	H	34804-11-0	185 dec	Formic
H	CH_3	34804-12-1	188–190	Acetic
H	CH_2CH_3	34804-13-2	200–203	Propionic
OC_6H_5	CH_3	34804-14-3	209–211	Acetic
p-$OC_6H_4CH_3$	CH_3	34804-15-4	185–187	Acetic

[a] Registry numbers: 34804-09-6 (R = OC_6H_5), 34804-10-9 (R = *p*-$OC_6H_4CH_3$).

on the basis of the similarity of their nmr and infrared spectra to those of **4b**.

The assignment of structure **4b** to the reaction product is based on chemical properties, infrared and nuclear magnetic resonance spectroscopy, and high-resolution mass spectrometry.

Of the four possible structures for the monoacetyl compound (**4a**, **4b**, **4c**, and **4d**), only the 3-acetyl derivative, **4a**, is known.[3] Synthetic routes to **4c** and **4d** could not be devised, nor could an alternative route to **4b**. Comparison with a sample of **4a**, prepared by the literature method,[3] ruled out this structure.

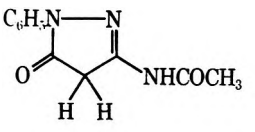
The presence of the 1-phenyl-3-amino-2-pyrazolin-5-one[3] nucleus was confirmed by hydrolysis of **4b** to this compound. The ease of hydrolysis of **4b** (2% aqueous sodium hydroxide, 10 min at room temperature) is consistent with a compound containing a 2-acetyl or 5-*O*-acetyl group (**4b** or **4d**) rather than a

(1) R. W. Hendess, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, No. 89.

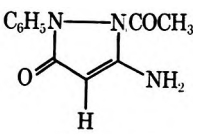
(2) P. A. S. Smith, *Org. React.*, **3**, 377 (1946).

(3) A. Weissberger and H. D. Porter, *J. Amer. Chem. Soc.*, **64**, 2133 (1942).

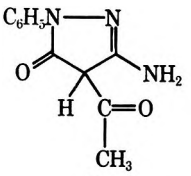
(4) The proposed intermediate isocyanate could not be isolated or synthesized independently.



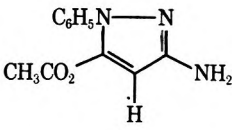
4a



4b



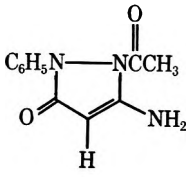
4c



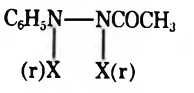
4d

3-*N*- or 4-acetyl group (**4a** or **4c**). (For example, 1-phenyl-3-acetamido-5-acetoxypyrazole[3] is hydrolyzed only as far as **4a**, and 1-phenyl-3-methyl-4-acetyl-2-pyrazolin-5-one[5,6] is stable under similar conditions.)

High-resolution mass spectrometry provided the most conclusive evidence for acetylation of **4b** (M = $C_{11}H_{11}N_3O_2$, mol wt 217) in the 2 position.[7] A strong peak at *m/e* 150.0794 (M − C_3HNO), which corresponds to fragment **6a**, is most significant. The gen-



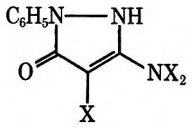
4b



6a, X = H
b, X = D

eration of this fragment from **4b** can be envisioned as arising from cleavage of the 2–3 and 1–5 bonds of the pyrazolone with rearrangement (indicated by r) of hydrogen (or deuterium, see below). This fragment **6** would be difficult to rationalize if the pyrazolone were acylated at a position other than the 2 nitrogen.

Among the other fragments observed in the mass spectrum of **4b** was a parent molecular ion and a fragment peak at *m/e* 175.0748 (M − C_2H_2O). This peak is attributed to fragment **7a** formed by loss of $COCH_2$



7a, X = H
b, X = D

from **4b** with rearrangement of a hydrogen from the acetyl to the ring nitrogen. The loss of the acetyl group is consistent with the presence of $NCOCH_3$, but not with $CCOCH_3$.

When the sample was allowed to exchange with deuterium oxide in the heated inlet system,[7] three deuterium atoms were introduced into the parent molecular ion (see also the discussion of the nmr spectrum, below). This sample gave deuterated fragments corresponding to those above; the M − C_3HNO fragment **6** contained two deuterium atoms and the M − C_2H_2O fragment **7** three deuterium atoms.

(5) F. Stoltz, *J. Prakt. Chem.*, **55**, 145 (1897).
(6) A. Weissberger and H. D. Porter, *J. Amer. Chem. Soc.*, **65**, 1495 (1943).
(7) G. P. Happ and D. P. Maier, personal communication.

The nmr spectrum of **4b** exhibited a singlet at τ 8.00, corresponding to the methyl of the acetyl group, and a singlet at τ 5.47 assigned to the single hydrogen at C-4 on the basis of its slow exchange with deuterium oxide. The resonance peak of the two amino protons (which also exchanged with deuterium oxide) was located under those of the aromatic protons centered at τ 2.67.

Experimental Section

Diethyl α-(*p*-Tolyloxy)oxalacetate.—The preparation of this compound was analogous to that of α-phenoxyoxalacetate,[8] precaution being taken to prevent contact of the compound with ground glass[9] during distillation.

1-Phenyl-3-ethoxycarbonyl-4-(*p*-tolyloxy)-2-pyrazolin-5-one.—To a solution of 596.6 g of diethyl α-(*p*-tolyloxy)oxalacetate in 600 ml of dimethylformamide was added a solution of 216.3 g of phenylhydrazine in 400 ml of dimethylformamide. After the solution had been heated on a steam bath for 2 hr, it was cooled and 4 l. of water was added. The syrup which formed solidified on standing overnight. The solid was washed with water in a Waring Blendor and dried. After repeated washings of this yellow solid with warm methylcyclohexane in a Waring Blendor, 300 g (44%) of the product was obtained as a tan powder. A portion was recrystallized from acetonitrile to give a white solid: mp 145–146°; nmr ($CDCl_3$) τ 9.08 (t, J = 7 Hz, 3 H) and 6.03 (q, J = 7 Hz, 2 H), ethyl group, 7.82 (s, 3 H), methyl of the tolyl group, a complex multiplet centered at 2.92 of the nine aromatic protons, and the acidic H at −0.40 (s).

Similarly prepared was 1-phenyl-3-ethoxycarbonyl-4-phenoxy-2-pyrazolin-5-one, mp 169–171°.

1-Phenyl-3-azidocarbonyl-2-pyrazolin-5-one (**3**).—This compound was prepared from 1-phenyl-3-ethoxycarbonyl-2-pyrazolin-5-one *via* the carboxhydrazide according to the procedure of Weissberger and Porter.[3]

A similar procedure was used to prepare 1-phenyl-3-azidocarbonyl-4-(*p*-tolyloxy)-2-pyrazolin-5-one, decomposing at 127°, and 1-phenyl-3-azidocarbonyl-4-phenoxy-2-pyrazolin-5-one, decomposing at 125°, both showing absorption due to the azide at 2160 cm^{-1}.

1-Phenyl-2-acetyl-3-amino-3-pyrazolin-5-one (**4b**).—A stirred suspension of 11.5 g of **3** in 100 ml of glacial acetic acid was warmed slowly on a steam bath. Evolution of gas began at *ca.* 70°. After being heated for 1.5 hr, the solution was cooled and diluted with 400 ml of water. A small amount of tar which separated was removed and discarded. After dilution of the filtrate to 1 l. with water, the product was extracted with 3 × 250 ml of ethyl acetate. The extracts were combined, washed with water, and evaporated to a syrup, which was crystallized from 30 ml of acetonitrile to give 3.2 g (29%) of 1-phenyl-2-acetyl-3-amino-3-pyrazolin-5-one. Recrystallization from acetonitrile (charcoal) gave an analytical sample, mp 188–190°. The properties and spectra of this compound are discussed above.

Anal. Calcd for $C_{11}H_{11}N_3O_2$ (217.23): C, 60.8; H, 5.4; N, 19.4. Found: C, 60.8; H, 5.1; N, 19.6.

Similarly prepared were 1-phenyl-2-propionyl-3-amino-3-pyrazolin-5-one (16%), mp 200–203°, nmr (DMSO-d_6) τ 9.13 (t, J = 7 Hz, 3 H) and 7.70 (q, J = 7 Hz, 2 H), ethyl group, 5.46 (s, 1 H), hydrogen on C-4, 2.66 (m, 5 H), phenyl group, and 2.27 (s) of the amine; 1-phenyl-2-acetyl-3-amino-4-(*p*-tolyloxy)-3-pyrazolin-5-one (57%), mp 185–187°, nmr ($CDCl_3$) τ 7.98 (s, 3 H), methyl group of the acetyl, 7.76 (s, 3 H), methyl of the tolyl group, and a multiplet of 11 H due to the nine aromatic and two amino hydrogens; 1-phenyl-2-formyl-3-amino-3-pyrazolin-5-one (10%), mp 185° dec; and 1-phenyl-2-acetyl-3-amino-4-phenoxy-3-pyrazolin-5-one (29%), mp 209–211°.

Elemental analyses of all compounds were satisfactory.

Registry No.—**3**, 34804-05-2; **4a**, 2311-90-2; **4b**, 34804-07-4; 1-phenyl-3-ethoxycarbonyl-4-(*p*-tolyloxy)-2-pyrazolin-5-one, 34804-16-5; 1-phenyl-3-ethoxycarbonyl-4-phenoxy-2-pyrazolin-5-one, 34804-17-6.

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(9) W. E. Bachmann, W. Cole, and A. L. Wilds, *ibid.*, **62**, 824 (1940).

Reactions of 2-Acyl-3(2*H*)-benzofuranones with Hydrazines and Diamines

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Received January 28, 1972

2-Acetyl-3(2*H*)-benzofuranone (**1a**) reacts with hydrazine to yield 2-(1-hydrazino-1-hydroxyethyl)-3(2*H*)-benzofuranone (**2**), the α-azine of 2-acetyl-3(2*H*)-benzofuranone (**4**) or 3(2*H*)-benzofuranone hydrazone depending upon the conditions, whereas 2-benzoyl- and 2-(2,4-dimethylbenzoyl)-3(2*H*)-benzofuranones (**1b** and **1c**) give 3-phenyl- and 3-(2,4-xylyl)-1*H*-benzofuro[3,2-*c*]pyrazoles (**5a** and **5b**), respectively. Phenylhydrazine reacts with acylbenzofuranones **1** to give the corresponding α-phenylhydrazones (**6a–c**) or the corresponding 3-substituted 1-phenyl-1*H*-benzofuro[3,2-*c*]pyrazoles (**7a–c**). Treatment of compounds **1a** and **1b** with ethylenediamine affords the corresponding substituted 2,2′-[ethylenebis(nitriloalkylidene)]bis-3(2*H*)-benzofuranones (**8a** and **8b**), instead of the expected 5-substituted 2,3-dihydrobenzofuro[3,2-*e*][1,4]diazepines. 1,8-Naphthalenediamine reacts with compounds **1** in the presence of *p*-toluenesulfonic acid to give 2-substituted perimidine *p*-toluenesulfonates (**9a–c**).

Our interest in the reactions of 2-acyl-1,3-indandiones with hydrazine[1] and other diamines[2,3] prompted us to investigate the reactions of the structurally related 2-acyl-3(2H)-benzofuranones (**1a–c**) with various diamines.

As previously reported, 2-acyl-1,3-indandiones react with hydrazine to form monohydrazones.[1] In the present study of the reaction of acylbenzofuranones with hydrazine, we were unable to isolate the corresponding hydrazones. Instead various products were obtained depending upon the reaction conditions and the structure of the acyl group.

Ethanolic solution of equimolar amounts of 2-acetyl-3(2*H*)-benzofuranone (**1a**) and hydrazine stirred at room temperature gave a 1:1 addition product, 2-(1-hydrazino-1-hydroxyethyl)-3(2*H*)-benzofuranone (**2**). Under the same conditions the aroyl derivatives **1b** and **1c** were recovered unchanged. Structure **2** is based on the elemental analyses, the ir spectrum, and the method of preparation, which is analogous to that used by Braun[4] to prepare the 1:1 addition product from 2-phenylacetyl-1,3-indandione and hydrazine. All attempts to form the corresponding monohydrazone **3** from the addition product **2** were unsuccessful. Treatment of **2** with ethanolic solutions of hydrochloric acid at room temperature or at refluxing temperature without acid reversed the reaction and compound **1a** was recovered.

Slow addition of hydrazine to a refluxing ethanolic solution of an equimolar amount of **1a**, so that the reaction took place essentially in the presence of an excess of **1a**, gave the α-azine of 2-acetyl-3(2*H*)-benzofuranone (**4**) in 55% yield. The aroylbenzofuranones **1b** and **1c** failed to give the corresponding azines.

Reversed addition of the reactants, compound **1a** to a refluxing ethanolic solution of excess hydrazine, yielded 3(2*H*)-benzofuranone hydrazone. The structure of this hydrazone is supported by elemental analyses and spectral data. Under the same conditions compounds **1b** and **1c** did not give this hydrazone. However, when acetic acid was added to the reaction mixture, 3(2*H*)-benzofuranone hydrazone was formed. Examples of deacylation of 2-acyl-3(2*H*)-benzofuranones are reported in the literature.[5] In this reaction, addition of **1** to excess hydrazine, the azine **4** was never obtained. This can be attributed to the fact that azine **4** reacts with excess hydrazine to give the hydrazone of 3(2*H*)-benzofuranone.

In refluxing acetic acid acetylbenzofuranone **1a** reacted with hydrazine, giving azine **4** in almost quantitative yield, whereas the aroylbenzofuranones **1b** and **1c** yielded the corresponding 3-substituted 1*H*-benzofuro[3,2-c]pyrazoles **5a** and **5b**.

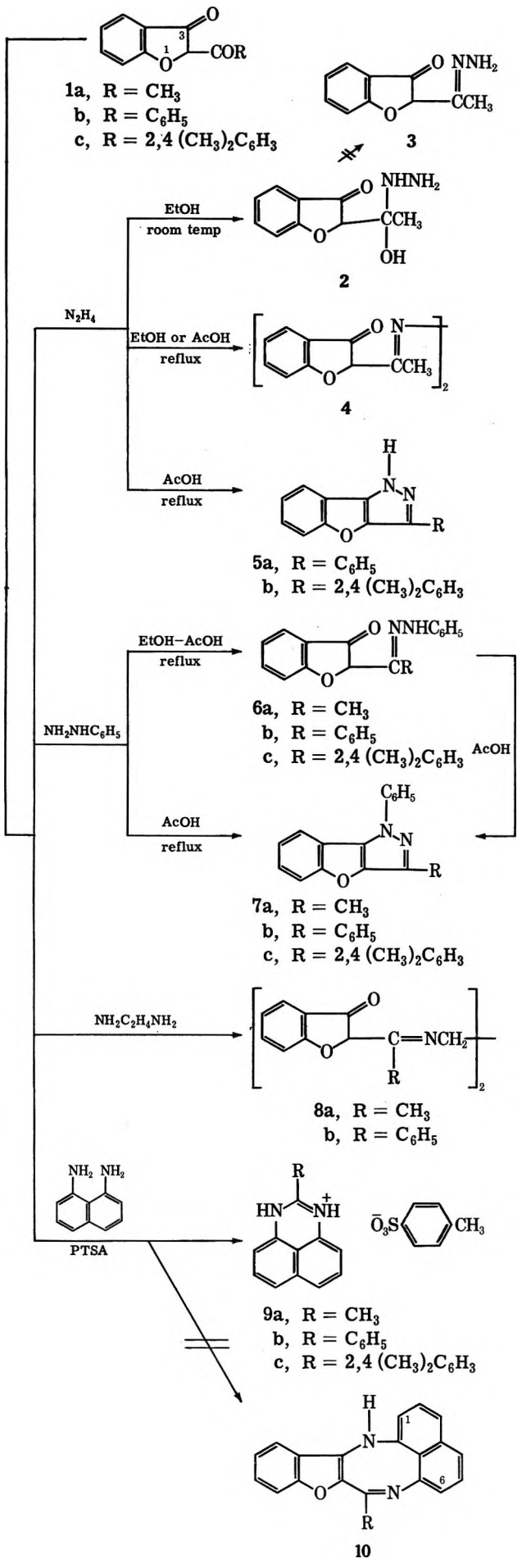
Treatment of phenylhydrazine with 2-acyl-3(2*H*)-benzofuranones (**1a–c**) in refluxing ethanol–acetic acid mixtures gave the corresponding monophenylhydrazones (**6a–c**). The assignment of the hydrazono group on the side chain is based on the mass spectra of these compounds and on the similarities of their chemical properties with those of the known α-hydrazones of 2-acyl-1,3-indandiones.[1]

Phenylhydrazones **6a–c** when heated at reflux in acetic acid cyclized to give 3-substituted 1-phenyl-1*H*-phenylbenzofuro[3,2-*c*]pyrazoles (**7a–c**). The structures of these compounds are based on elemental analyses and spectral data. The benzofuropyrazoles **7a–c** were also obtained directly from the acylbenzofuranones **1a–c** and phenylhydrazine by refluxing in acetic acid.

In a previous paper we reported that treatment of 2-benzoyl-1,3-indandione with ethylenediamine in the presence of formic acid gave 5-phenyl-2,3-dihydro-6*H*-indeno[1,2-*e*][1,4]diazepin-6-one.[2] Attempts to form the 5-substituted 2,3-dihydrobenzofuro[3,2-*e*][1,4]diazepines by treating the acylbenzofuranones **1a** and **1b** with ethylenediamine in the presence of formic acid failed. The products isolated were 2,2′-[ethylenebis(nitriloethylidyne)]- and 2,2′-[ethylenebis(nitrilobenzylidyne)]bis-3(2*H*)-benzofuranones (**8a** and **8b**, respectively). Under the same conditions compound **1c** did not react, the starting material being recovered. The structures of these compounds are based on elemental analyses and spectral data. In addition, attempts to prepare 6-substituted 11*H*-benzo[*b*]benzofuro[3,2-*e*][1,4]diazepines from acylbenzofuranones **1** and *o*-phenylenediamine under the conditions used by Mosher and Piesch to prepare benzoindenodiazepinones[6] failed.

The reaction of the acylbenzofuranones **1a–c** with 1,8-naphthalenediamine in the presence of *p*-toluenesulfonic acid was investigated as a possible route to eight-membered heterocyclic compounds. It was

(1) R. A. Braun and W. A. Mosher, *J. Amer. Chem. Soc.*, **80**, 2749 (1958).
(2) W. A. Mosher and S. Piesch, *J. Org. Chem.*, **35**, 1026 (1970).
(3) W. A. Mosher and T. E. Banks, *ibid.*, **36**, 1477 (1971).
(4) R. A. Braun, University Microfilms, Ann Arbor, Mich., L. C. Card No. Mic 58-5283, 104 pp; *Diss. Abstr.*, **19**, 953 (1958).
(5) R. Bryant and D. L. Haslam, *J. Chem. Soc.*, 1345 (1967).
(6) W. A. Mosher and S. Piesch, *J. Org. Chem.*, **35**, 2109 (1970).



found that this reaction proceeds similarly to that already reported by this laboratory between 2-acyl-1,3-indandiones and 1,8-naphthalenediamine[3] giving 2-substituted perimidine *p*-toluenesulfonates (**9a–c**) instead of 8-substituted 14*H*-benzofuro[3,2-*f*]naphtho-[1,8-*bc*][1,5]diazocines (**10**). It is believed that the mechanism of this reaction is the same as that proposed by Mosher and Banks[3] for the formation of 2-substituted perimidines from 2-acyl-1,3-indandiones. However, we failed to isolate the expected by-product, 3(2*H*)-benzofuranone.

Experimental Section[7]

2-Acyl-3(2*H*)-benzofuranones (**1a–c**) were prepared according to known methods.[8,9] 2-(2,4-Dimethylbenzoyl)-3(2*H*)-benzofuranone (**1c**) is not reported in the literature. It was obtained in 38% yield from methyl salicylate and 2-chloro-2′,4′-dimethylacetophenone as light yellow crystals: mp 88–90°; nmr δ 6.8–7.6 (m, 7 H), 2.0–2.1 (m, 6 H); mass spectrum *m/e* 266, 249, 234, 205, 133.

Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.69; H, 5.26; N, 18.05. Found: C, 76.73; H, 5.04; N, 18.09.

2-(1-Hydrazino-1-hydroxyethyl)-3(2*H*)-benzofuranone (**2**).—A mixture of hydrazine (0.16 g, 5 mmol) and 2-acetyl-3(2*H*)-benzofuranone (**1a**) (0.9 g, 5 mmol) in ethanol (50 ml) was stirred at room temperature for 1 hr. The precipitate was collected by filtration to give 0.66 g (62%) of **2** as a white powder: mp >300°; ir 3300–3280, 3200–3180, and 1630–1620 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.67; H, 5.71; N, 13.27.

A solution of **2** in ethanol stirred at reflux for 1 hr gave **1a**, mp 90–91° alone and in mixture with **1a** prepared as in ref 8. Compound **1a** was obtained also when a solution of **2** in ethanol containing a few drops of hydrochloric acid was stirred at room temperature for 1 hr.

α-Azine of 2-Acetyl-3(2*H*)-benzofuranone (**4**).—A solution of hydrazine (0.08 g, 2.5 mmol) in ethanol (25 ml) was added dropwise to a refluxing solution of **1a** (0.45 g, 2.5 mmol) in ethanol (25 ml). The mixture was refluxed for an additional 2 hr and cooled, and the precipitate was collected by filtration to give 0.25 g (55%) of **4** as bright red needles;[10] mp 250–251°; ir 1640, 1600–1590, and 1520–1500 cm^{-1}. No bands at 3500–3100 cm^{-1} were observed.

Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.98; H, 4.51; N, 7.92.

A 90% yield of azine **4** (mp 250–251° alone and in mixture with the azine prepared as described above) was obtained when a solution of acetylbenzofuranone **1a** (3.6 g, 20 mmol) and hydrazine (1.3 g, 40 mmol) in acetic acid (25 ml) was heated at reflux for 3 hr.

3(2*H*)-Benzofuranone Hydrazone from 1a.—A solution of **1a** (0.45 g, 2.5 mmol) in ethanol (25 ml) was added dropwise to a refluxing solution of hydrazine (0.32 g, 10 mmol) in ethanol (25 ml). The mixture was refluxed for an additional 1.5 hr, cooled, and chromatographed on neutral alumina (chloroform as the eluent) to give 94 mg (25%) of 3(2*H*)-benzofuranone hydrazone as a yellow solid. A sample was crystallized from chloroform–hexane mixtures to yield pale yellow platelets: mp 105–106°;

(7) Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer spectrophotometer, Models 137 and 421. Unless otherwise specified, they were taken as Nujol mulls between sodium chloride plates. The nuclear magnetic resonance spectra were obtained on a Varian Associates spectrometer, Model A-60A, using DMSO-d_6 as the solvent, unless otherwise noted. Chemical shifts are reported as δ values (parts per million) relative to TMS as an internal standard. Mass spectra were recorded on a CEC 21/110B spectrometer. Elemental analyses were performed by M-H-W Laboratories, Garden City, Mich., by Micro Analysis, Inc., Marshallton Del., and by Dr. A. Bernhardt, Microanalytisches Laboratorium in Max Planck Institute für Kohlenforschung, Germany.

(8) T. A. Geissman and A. Armen, *J. Amer. Chem. Soc.*, **77**, 1623 (1955).

(9) R. Bryant and D. L. Haslam, *J. Chem. Soc.*, 2361 (1965).

(10) The red color can be attributed to the conjugation of the enol form as in the analogous sulfur compound, the azine of 2-acetylbenzo[*b*]thiophen-3(2*H*)-one, which is reported to be red: W. J. Barry and E. W. McClelland, *J. Chem. Soc.*, 472 (1935).

ir 3100, 3000, and 1600 cm^{-1}; nmr ($CDCl_3$) δ 6.7–7.7 (m, 4, aromatic H), 4.9 (s, broad, 2 H), and 5.0 (sharp, 2 H). The mass spectrum shows a molecular ion peak at *m/e* 148.

Anal. Calcd for $C_8H_8N_2O$: C, 63.91; H, 5.18; N, 17.70. Found: C, 63.83; H, 5.10; N, 17.50.

3(2*H*)-Benzofuranone Hydrazone from 1b and from 1c.—A solution of the appropriate acylbenzofuranone (10 mmol) in ethanol (50 ml) was added dropwise to a refluxing solution of hydrazine (excess) in ethanol (50 ml) and then acetic acid (2 drops) was added. The mixture was refluxed for an additional 0.5 hr and worked up as described above for the hydrazone from **1a**. A 70% yield of 3(2*H*)-benzofuranone hydrazone was obtained as pale yellow platelets from chloroform–hexane, mp (alone and in mixture with the hydrazone obtained from **1a**) 105–106°.

3(2*H*)-Benzofuranone Hydrazone from Azine 4.—A mixture of azine **4** (0.5 g, 0.29 mmol) and hydrazine (20 ml), stirred at room temperature for 1 hr, gave a red solution, which gradually became pale yellow. After removal of the excess hydrazine under reduced pressure, the residue was chromatographed on neutral alumina (chloroform as the eluent) to give 160 mg (38%) of 3(2*H*)-benzofuranone hydrazone, mp 105–106° alone and in mixture with the hydrazone obtained as described above. The yield increased to 56% when the above mixture of azine **4** and hydrazine was heated at reflux for 15 min.

3-Phenyl-1*H* benzofuro[3,2-*c*]pyrazole (5a).—Hydrazine (0.65 g, 20 mmol) was added to a solution of **1b** (2.38 g, 10 mmol) in acetic acid (50 ml) and the mixture was refluxed for 24 hr. The acid was removed *in vacuo* and the residue was chromatographed on alumina (ethanol as the eluent) to give 1.52 g (65%) of **5a** as buff crystals: mp 217–219°; ir (KBr) 3230, 1600–1610 cm^{-1}; nmr δ 7.1–7.8 (m, 9 H); mass spectrum *m/e* 234, 176, 151, 132, 117, 103, 77.

Anal. Calcd for $C_{15}H_{10}N_2O$: C, 76.92; H, 4.27; N, 11.96. Found: C, 76.80; H, 4.47; N, 11.70.

3-(2,4-Xylyl)-1H-benzofuro[3,2-*c*]pyrazole (5b) was obtained as a light yellow powder, mp 162–163°, in 9% yield from **1c** and hydrazine following the procedure above described for compound **5a**. The ir spectrum is similar to that of **5a**; nmr δ 6.7–7.8 (m, 7 H), 2.0–2.1 (s, 6 H); mol wt, 262 (mass spectrum).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.86; H, 5.34; N, 10.69. Found: C, 77.60; H, 5.62; N, 10.53.

2-Acetyl-3(2*H*)-benzofuranone α-Phenylhydrazone (6a).—Phenylhydrazine (1.1 g, 10 mmol) was added to a solution of **1a** (1.8 g, 10 mmol) in ethanol (50 ml) and acetic acid (0.5 ml) and the mixture was heated at reflux for 12 hr. The solvent was removed *in vacuo* and the residue was chromatographed on alumina (chloroform as the eluent) to give 1.2 g (45%) of **6a** as a yellow solid, mp 135–140°. A sample was recrystallized from petroleum ether (bp 30–60°)–ether to yield pale yellow crystals: mp 147–148°; ir (KBr) 3400–3350, 1600–1595 cm^{-1}; nmr δ 7.0–7.4 (m, 9 H), 3.3 (s, 1 H), and 1.7 (s, 3 H). The mass spectrum shows a molecular ion at *m/e* 266 and major fragments at *m/e* 235, 196, 159, 133, 120, 105, 93, and 77. This compound gave a positive Tollens test.[1,11]

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.07; H, 5.31; N, 10.33.

2-Benzoyl-3(2*H*)-benzofuranone α-Phenylhydrazone (6b).—A mixture of **1b** (2.38 g, 10 mmol), phenylhydrazine (1.1 g, 10 mmol), and acetic acid (2 ml) in ethanol (50 ml) was heated at reflux for 12 hr. The solvent was removed *in vacuo* and the residue was worked up as described under **6a** and gave 1.7 g (54%) of **6b**. Recrystallization from petroleum ether–ether gave yellow crystals: mp 220–221°; ir (KBr) 3350–3390, 1600–1610 cm^{-1}; the mass spectrum shows a molecular ion peak at *m/e* 328 and a prominent peak at *m/e* 195, which probably is the fragment $C_6H_5C{=}NNHC_6H_5^+$. This compound gave a positive Tollens test.[1,11]

Anal. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.83; H, 4.88; N, 8.54. Found: C, 77.12; H, 4.61; N, 8.47.

2-(2,4-Dimethylbenzoyl)-3(2*H*)-benzofuranone α-phenylhydrazone (6c) was obtained as yellow crystals, mp 227–229°, in 16% yield from **1c** and phenylhydrazine following the procedure above described for **6b**. The ir spectrum is similar to that of **6b**; nmr δ 6.7–7.8 (m, 12 H), 3.4 (s, 1 H), and 2.0–2.1 (s, 6 H); the mass spectrum shows a prominent peak at *m/e* 223 probably due to the fragment $C_6H_3(CH_3)_2C{=}NNHC_6H_5^+$. Fragment $C_6H_3(CH_3)_2CO$ (*m/e* 133) was absent.

Anal. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.65; H, 5.59; N, 7.82. Found: C, 77.43; H, 5.68; N, 7.59.

3-Methyl-1-phenyl-1*H*-benzofuro[3,2-*c*]pyrazole (7a).—Phenylhydrazine (0.54 g, 5 mmol) was added to a refluxing solution of **1a** (0.9 g, 5 mmol) in acetic acid (25 ml). The dark red mixture was refluxed for an additional 0.5 hr, the acetic acid was removed *in vacuo*, and the residue was chromatographed on alumina (chloroform as the eluent) to give 0.16 g (13%) of **7a** as pale yellow crystals: mp 71–72° (petroleum ether); ir 1600 1595 cm^{-1}; nmr δ 7.3–8.0 (m, 9 H), 2.5 (s, 3 H); the mass spectrum shows the required molecular ion and major peaks at *m/e* 233, 222, 206, 195, 179, 152, 146, 124, 105, 77, and 51.

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.21; H, 5.07; N, 11.15.

1,3-Diphenyl-1*H*-benzofuro[3,2-*c*]pyrazole (7b) was obtained as pale yellow crystals, mp 155–157° (ether–hexane), in 76% yield from **1b** and phenylhydrazine following the procedure above described for **7a** (refluxing time 48 hr and chloroform–methanol as eluent).

Anal. Calcd for $C_{21}H_{14}N_2O$: C, 81.29; H, 4.52; N, 9.03. Found: C, 81.15; H, 4.53; N, 8.76.

1-Phenyl-3-(2,4-xylyl)-1*H*-benzofuro[3,2-*c*]pyrazole (7c) was obtained as pale yellow crystals, mp 173–175° (glyme), in 14% yield from **1c** and phenylhydrazine following the procedure above described for **7b** (refluxing time 72 hr).

Anal. Calcd for $C_{23}H_{18}N_2O$: C, 82.74; H, 4.17; N, 8.34. Found: C, 82.41; H, 4.29; N, 8.30.

The above three compounds **7a**, **7b**, and **7c** were also obtained by refluxing the corresponding α-phenylhydrazones **6a**, **6b**, and **6c** in acetic acid for 12, 48, and 72 hr, respectively. The yields were 32% for **7a**, 83% for **7b**, and 17% for **7c**.

2,2′-[Ethylenebis(nitriloethylidyne)]bis-3(2*H*)-benzofuranone (8a).—Ethylenediamine (0.3 g, 5 mmol) was added dropwise to a solution of **1a** (0.9 g, 5 mmol) in ethanol (50 ml). Formic acid (0.5 ml) was added and the mixture was heated at reflux for 1 hr. The solvent was removed *in vacuo* and the residue was chromatographed on alumina (chloroform as eluent) to give 70 mg (7.5%) of **8a**: mp 217–219°; ir 1640–1645 and 1550–1560 cm^{-1}; nmr δ 7.1–7.9 (m, 8 H), 3.5–3.8 (broad peak, 4H), 2.6 (s, 2 H), and 2.4 (s, 6 H).

Anal. Calcd for $C_{22}H_{20}N_2O_4$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.69; H, 5.81; N, 7.31.

2,2′-[Ethylenebis(nitrilobenzylidyne)]bis-3(2*H*)-benzofuranone (8b) was obtained as yellow crystals, mp >300° (methanol), in 16% yield from **1b** and ethylenediamine following the procedure above described for **8c** (refluxing time 72 hr and elution with methanol instead of chloroform). The ir spectrum is similar to that of **8a**; nmr δ 7.1–7.9 (m, 18 H), 3.5–3.7 (broad, 4H), 2.7 (s, 2 H); mol wt, 500 (mass spectrum).

Anal. Calcd for $C_{32}H_{24}N_2O_4$: C, 76.80; H, 4.79; N, 5.60. Found: C, 76.64; H, 4.71; N, 5.76.

Under the same conditions compound **1c** did not react with ethylenediamine. The starting material was recovered.

Reaction of 2-Acyl-3(2*H*)-benzofuranones with 1,8-Naphthalenediamine.—A solution of the appropriate 2-acyl-3(2*H*)-benzofuranone (20 mmol) in ethanol (100 ml) was added dropwise over 0.5 hr to a refluxing solution of 1,8-naphthalenediamine (4.5 g, 28 mmol) and *p*-toluenesulfonic acid (4.0 g, 20 mmol) in ethanol (200 ml). The mixture was refluxed for an additional 24 hr and concentrated to half volume *in vacuo*, and the precipitate was collected by filtration. Compound **1a** gave 5.5 g (77%) of 2-methylperimidine *p*-toluenesulfonate, identical (mixture melting point and ir spectrum) with an authentic sample,[3] and compound **1b** gave 3.3 g (29%) of 2-phenylperimidine *p*-toluenesulfonate, also identical with an authentic sample.[3] Compound **1c** gave 1.4 g (11%) of 2-(2,4-xylyl)perimidine *p*-toluenesulfonate, mp 250–252°, as brown crystals.

Anal. Calcd for $C_{26}H_{24}N_2SO_3$: C, 70.27; H, 5.41; N, 10.81. Found: C, 70.02; H, 5.35; N, 10.64.

Several attempts to isolate the expected by-product, the 3(2*H*)-benzofuranone, from the reaction mixture failed.

Registry No.—**1c**, 34823-84-2; **2**, 34839-58-2; **4**, 34823-85-3; **5a**, 34823-86-4; **5b**, 34823-87-5; **6a**, 34823-88-6; **6b**, 34823-89-7; **6c**, 34823-90-0; **7a**,

(11) S. P. Mulliken, "Identification of Pure Organic Compounds," Vol. 2, Wiley, New York, N. Y., 1916, p. 29.

34823-91-1; **7b**, 34823-92-2; **7c**, 34823-93-3; **8a**, 34823-94-4; **8b**, 34823-95-5; **9c**, 34823-96-6; 3(2*H*)-benzofuranone hydrazone, 34823-97-7.

Acknowledgment.—We gratefully acknowledge the valuable assistance of Dr. Mario F. Sartori in connection with this research.

Synthesis and Reactions of 3-Diazo-1,4-diphenyl-4-hydroxy-2-butanone

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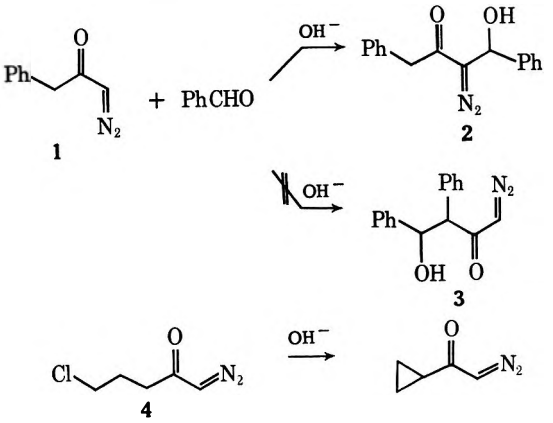
Received January 11, 1972

1-Diazo-3-phenyl-2-propanone (1) underwent aldol condensation with benzaldehyde at the diazo carbon to give 3-diazo-1,4-diphenyl-4-hydroxy-2-butanone (2) in 63% yield. Irradiation of 2 in benzene or methanol below 50° gave 1,4-diphenyl-1,3-butanedione (5) in 50% yield. Pyrolysis of 2 in refluxing chlorobenzene gave 40% of 5. Treatment of 2 with hydrogen chloride in ether gave 20% of the dione 5 and 31% of 3-chloro-1,4-diphenyl-4-hydroxy-2-butanone (6). Similarly, when treated with hydrogen bromide in ether, 2 gave 10% of the dione 5 and 45% of 3-bromo-1,4-diphenyl-4-hydroxy-2-butanone (10). The structures of 5 and 10 rest on the physical data and their reduction to 2-chloro-1,4-diphenyl-1,3-butanediol (8) and 2-bromo-1,4-diphenyl-1,3-butanediol (11), respectively.

Under appropriate conditions diazomethyl ketones undergo normal base-catalyzed reactions without the destruction of the $-COCN_2-$ moiety.[1,2] For example, base-catalyzed intramolecular aldol and Dieckman-type condensation reactions have been shown to take place at the diazo carbon of some diazomethyl ketones.[1] Normal base-catalyzed intramolecular alkylation can also apparently occur at the α-methylene carbon of a suitable diazomethyl ketone.[2] Similar intermolecular condensation reactions of diazomethyl ketones, however, have not been investigated.

We wish to report here the first example of a normal base-catalyzed intermolecular condensation reaction of a diazomethyl ketone of the type RCH_2COCHN_2, which has two potential condensation sites. Successful condensation of 1-diazo-3-phenyl-2-propanone (1) with benzaldehyde resulted in exclusive reaction at the diazo carbon to give 3-diazo-1,4-diphenyl-4-hydroxy-2-butanone (2). The photochemical, thermal, and acid-catalyzed decompositions of this novel α-diazo-β-hydroxy ketone 2 were also investigated.

Synthesis of 2.—Treatment of a dilute, ethanolic solution of the diazo ketone 1 and an excess of benzaldehyde with 2% sodium hydroxide solution at room temperature resulted in an immediate development of a red color characteristic of diazo ketone decomposition.[3] When the solution was held at -5 to 0° and then treated with base, no such color developed but the aldol reaction product was formed. Extraction of the reaction solution with carbon tetrachloride and chromatography of the concentrated extract on alumina gave, besides unreacted starting materials, a deep yellow oil which crystallized to give 3-diazo-1,4-diphenyl-4-hydroxy-2-butanone (2) in 63% yield. The infrared spectrum of 2 showed bands at 4.78 and 6.08 μ, confirming retention of the diazo ketone moiety, and a band at 2.94 μ supported the presence of a hydroxyl group. The nmr spectrum of a pure and dry sample of 2 in carbon tetrachloride revealed a doublet at δ 7.21 and a singlet at δ 3.68 due to ten phenyl and two methylene protons, respectively. The one-proton doublets at δ 5.91 (J = 4 Hz), and 4.3 (J = 4 Hz) were attributed to the methine and the hydroxyl protons, respectively. Exchange of the hydroxyl proton with deuterium oxide, as judged by the disappearance of the δ 4.3 peak and the collapse of the δ 5.91 peak to a singlet, confirmed this assignment. No evidence for the formation of the aldol product 3 which would have resulted from condensation at the α-methylene carbon was obtained by nmr spectroscopic examination of various chromatographic fractions. The remainder of the unrecovered starting material apparently decomposed during the reaction or the work-up. We cannot, however, eliminate the possible formation of a small amount of 3.



The fact that 1 condenses with benzaldehyde largely at the diazo carbon contrasts with the intramolecular cyclization of 5-chloro-1-diazo-2-pentanone (4) to give cyclopropyldiazomethyl ketone.[2] The azomethine protons of both 1 and 4 were shown to be more acidic than the respective methylene protons by the addition of a drop of deuterium oxide containing a catalytic amount of sodium carbonate to a carbon tetrachloride solution of 1 or 4. In both cases the azomethine peak was rapidly and completely removed from the nmr spectra. The methylene peaks in both cases remained unaffected. The cyclization of 4 to give cyclopropyldiazomethyl ketone demonstrates the ease of formation of a three-membered ring over a five-membered ring, probably due to a more favorable entropy of activation for the former process.[4] The intramolecular alkylation in

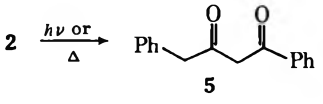
(1) T. L. Burkoth, *Tetrahedron Lett.*, 5049 (1969).
(2) N. F. Woolsey and D. D. Hammargren, *ibid.*, 2087 (1970).
(3) P. Yates and D. G. Farnum, *J. Amer. Chem. Soc.*, **85**, 2967 (1963).
(4) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 198.

addition is irreversible and thus probably rate controlled. Formation of 2 takes place under reversible conditions and probably reflects thermodynamic control of the condensation.

Reactions.—Until recently no α-diazo-β-hydroxy ketones were known.[5] We were interested in determining to what extent the adjacent hydroxyl group alters or becomes involved in the reactions of the diazo group. To this end three types of reactions of hydroxydiazo ketone 2 were investigated: pyrolysis, photolysis, and reactions with hydrogen halides.

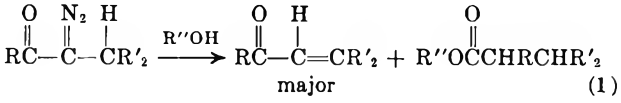
Pyrolysis.—Pyrolysis of 2 in refluxing chlorobenzene and subsequent evaporation of the solvent gave a yellow oil from which 1,4-diphenyl-1,3-butanedione (5) was isolated, *via* its copper salt, in a 40% yield. The remaining material was an intractable oil from which no further pure material could be obtained.

Photolysis.—Photolysis of 2 in benzene or methanolic solution gave dione 5 in 49 and 52% yields, respectively. Thin layer chromatography of the crude photoproduct in each case also revealed the presence of another minor product. A number of efforts, using various separation techniques, were made to obtain this portion of the photoproduct but all of them proved unrewarding. The yields of the dione 5 are considered minimal because its recovery from the reaction mixture proved difficult and was invariably accompanied by decomposition.



5

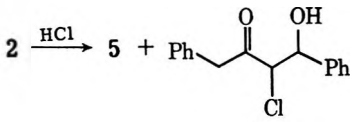
The reactions of a similar type of diazo ketone with a carbon–hydrogen bond adjacent to the diazo carbon but without the hydroxy group have been studied under pyrolytic and photolytic conditions.[6] The exclusive or the major product in these reactions resulted from an apparent 1,2-hydride shift to form an α,β-unsaturated ketone; the Wolff rearrangement product was formed in small amounts in some cases (reaction 1). In view of the moderate yields of the



major (1)

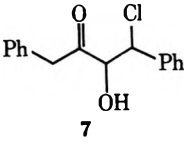
dione 5 and the incomplete characterization of the reaction mixture, it would be difficult to eliminate Wolff rearrangement as a reaction path. No evidence for a β-lactone or ester, however, could be adduced from the spectra of the crude reaction mixture; therefore, the Wolff rearrangement must certainly be a minor reaction path. Thus, the presence of a hydroxy group α to the diazo group does not change the general reactivity observed for diazoalkyl ketones.

Hydrogen Halide.—Treatment of a solution of diazo ketone 2 in ether with dry hydrogen chloride gas, evaporation of the solvent, and preparative tlc of the concentrate gave a 20% yield of dione 5 and a 31% yield of 3-chloro-1,4-diphenyl-4-hydroxy-2-butanone (6).



6

The ir spectrum of 6 contained bands at 2.93 and 5.88 μ for the hydroxyl and the keto groups, respectively. The nmr spectrum, besides a multiplet at δ 7.18 and a singlet at δ 3.77 due to ten phenyl and two methylene protons, respectively, revealed a rough quartet at δ 4.86 (J = 5, J' = 8 Hz) attributed to a benzylic methine proton, and doublets at δ 4.24 (J' = 8 Hz) and 3.30 (J = 5 Hz) assigned to the methine proton α to the keto group and hydroxyl proton, respectively. When the nmr sample was treated with D_2O, the doublet at δ 3.30 disappeared and the quartet at δ 4.86 collapsed to a doublet, confirming these assignments. It is not possible to assign structure 6 to the chloro hydroxy ketone exclusively on the basis of ir and nmr spectra, because the isomeric structure 7 is also compatible with the spectral data. Evidence in favor of



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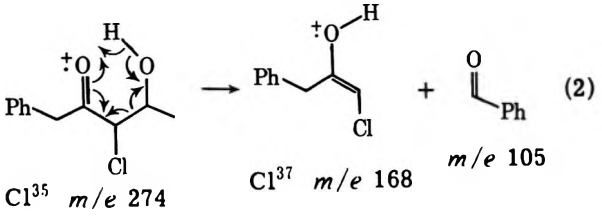
structure 6 came from the mass spectra of the chloro compound, which, in addition to an m/e 274 (M^+) and other peaks, had important peaks at m/e 168 and 170 in *ca.* 3:1 ratio, indicating the presence of ^{35}Cl and ^{37}Cl in the ions, respectively. McLafferty rearrangement[7] of 6 readily accounts for these peaks (reaction 2) but a reasonable cleavage of 7 to give the observed halogen containing fragments is not possible.

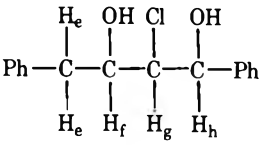


Cl^{35} m/e 274 Cl^{37} m/e 168 m/e 105 (2)

Unambiguous proof for the assignment of the structure 6 to the HCl reaction product was obtained from the nmr spectrum of the reduction product of 6 with $LiAlH_4$. $LiAlH_4$ reduction of 6 gave a 46% yield of 3-chloro-1,4-diphenyl-1,3-butanediol (8). The ir spectrum showed no carbonyl peak and the compound gave a negative borax test for a 1,2-diol. The nmr spectrum of 8 revealed a ten-proton multiplet at δ 7.27, a rough one-proton multiplet at δ 4.98, a two-proton multiplet at δ 3.97, a rough one-proton doublet at δ 3.57, and a three-proton multiplet at δ 2.84. On addition of a drop of deuterium oxide, the multiplet at δ 4.98 became a sharp doublet, the doublet at δ 3.57 disappeared, and the multiplet at δ 2.84 integrated for two protons. This deuterium exchange established three things: (a) the peak at δ 3.57 was due to a

(5) T. Severin and H. Lercher, *Ber.*, **103**, 2148 (1970).
(6) V. Franzen, *Justus Liebigs Ann. Chem.*, **602**, 199 (1957).
(7) V. W. McLafferty, *Anal. Chem.*, **31**, 82 (1959).

hydroxyl proton; (b) the second hydroxyl proton was under the multiplet at δ 2.84; and (c) the peak at δ 4.98 was due to a proton which was on a carbon bearing a hydroxyl group. The last point confirmed the structure of the reduced product as **8** and, therefore, of the structure of the starting chlorohydroxy ketone as **6**.



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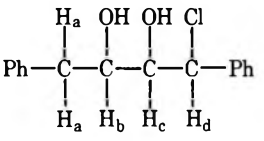


9

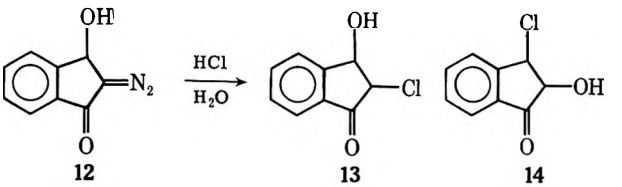
Structure **9**, which would be expected from the reduction of **7**, would have two protons on carbon atoms bearing a hydroxyl group, *i.e.*, protons H_b and H_c. The nmr spectrum of **9** in deuterium oxide would be expected to show multiplet for the proton H_b, since it would be coupled to the methylene protons H_{aa} as well as to the methine proton H_c. Similarly, H_c would be expected to give a multiplet (a quartet, or a triplet) because it would be coupled to the two neighboring methine protons H_b and H_d. The proton appearing at δ 4.98 which must be coupled to a hydroxyl group, however, was only a doublet and, therefore, could not be due to either H_b or H_c. This excluded the 1,2-diol **9** from consideration as the possible structure for the reduction product and, therefore, eliminated structure **7** as the possible structure for the chlorohydroxy ketone.

Structure **8**, the product which would be expected from the reduction of **6**, would also have two protons on carbon bearing a hydroxyl group, *i.e.*, protons H_f and H_h. Once again, H_f would be expected to give a multiplet, since it would be coupled to the methylene protons H_{ee} as well as to the methine proton H_g. H_f could, therefore, absorb at either δ 2.84 or δ 3.97 (probably the latter) but cannot be the cause of the doublet at δ 4.98. However, the proton H_h is coupled only to the methine proton H_g and would be expected to give a doublet after deuteration of the alcohol. The doublet at δ 4.98 must be, therefore, due to proton H_h. This firmly established the structure **8** for the reduced product and, therefore, structure **6** for the chlorohydroxy ketone.

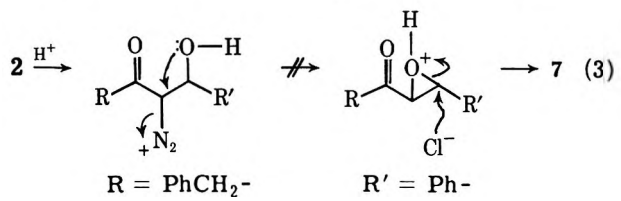
An exactly comparable set of reactions was carried out with the hydroxydiazo ketone **2** and anhydrous hydrogen bromide in ether to give 3-bromo-1,4-diphenyl-4-hydroxy-2-butane (**10**) in 45% yield and the dione **5** in 10% yield. $LiAlH_4$ reduction of **10** gave 2-bromo-1,4-diphenyl-1,3-butanediol (**11**). The ir, nmr, and mass spectral data in this series of compounds (see Experimental Section) was entirely consistent with the structures assigned in the chlorohydroxy ketone series.

Treatment of **12** with aqueous hydrochloric acid solution has been reported[5] to give **13**, although the evidence for this structure is not compelling. An nmr structure determination suffers from an inability to distinguish **13** from **14**. In this as well as our series this type of product could have arisen from anchimerically assisted loss of nitrogen by the adjacent hydroxyl group from a diazonium intermediate to form an intermediate or transient epoxide (reaction 3). Acidic opening of the expoxide would favor formation of **7**. Since **7** was not formed, however, we feel confident in eliminating this reaction path and in concluding that the intramolecular hydroxyl group cannot compete with chloride or bromide ion for the intermediate diazonium ion.

The hydride shift which evidently is necessary to form the dione **5** in acid need not be assisted by the hydroxyl group because α,β-unsaturated ketones are formed on hydrogen halide treatment of alkyl diazo ketones.[8] It is not clear why 1,3-indandione is not formed from **12** on acid treatment. The aqueous conditions of this reaction or some stereochemical factor could be involved, and these and other possibilities are under investigation.



12 **13** **14**



R = $PhCH_2$- R′ = Ph-

Experimental Section

Irradiations were carried out with a 550-W Hanovia 673A-36 medium pressure mercury-vapor arc lamp in a Pyrex reaction vessel equipped with a Pyrex, water cooled, immersion well, a nitrogen inlet, and a magnetic stirrer. Analytical tlc was performed with silica gel HF-254 or aluminum oxide H (Merck). Melting points were determined on a Köfler hot stage and are uncorrected.

The infrared (ir) spectra were determined on a Beckman IR-12 spectrometer. The nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer using TMS as an internal reference. The mass spectra were obtained on a CEC 491 mass spectrometer at 70 eV.

3-Diazo-1,4-diphenyl-4-hydroxy-2-butanone (**2**).—To an ice cold, stirred solution of 1.0 g (6.0 mmol) of 1-diazo-3-phenyl-2-propanone[9] (**1**) in 60 ml of redistilled ethanol (0.10 *M*) and 3 ml of benzaldehyde was added 0.1 g of sodium hydroxide in 5 ml of water. After 30 min of stirring, during which time the solution acquired a golden yellow color, another 0.1 g of sodium hydroxide in 5 ml of water and 3 ml of benzaldehyde were added. The solution was stirred for 2 hr more and then poured into 150 ml of cold water and finally extracted with three 100-ml portions of carbon tetrachloride. After evaporation of most of the solvent, the yellow extract was placed on a chromatography column (24 mm by 34 cm) packed with basic alumina (Fisher, 100 g) in carbon tetrachloride and eluted with carbon tetrachloride (150 ml), benzene (150 ml), and finally ethanol (300 ml). Removal of the solvent from the ethanol fraction afforded 1.4 g of yellow oil, which was crystallized in cold ether–pentane to give 1.2 g (65%) of 3-diazo-1,4-diphenyl-4-hydroxy-2-butanone (**2**) as yellow crystals: mp 56–57°; nmr (CCl_4) δ 7.21 (m, 10 H, 2 Ph), 5.91 (d, 1 H, J = 4 Hz, CHOH), 4.20 (d, 1 H, J = 4 Hz, CHOH), 3.68 ppm (s, 2 H, CH_2); nmr (CCl_4–D_2O) δ 7.20 (d, 10 H, 2 Ph), 5.88 (s, 1 H, CHOD), 3.66 ppm (s, 2 H, CH_2); ir (KBr) 2.94 (w, OH), 4.78 (s, CHN_2), 6.08 μ (s, CO). *Anal.* Calcd for $C_{16}H_{14}N_2O_2$: C, 72.20; H, 5.26; N, 10.52. Found: C, 72.30; H, 5.31; N, 10.40.

Irradiation. A. In Benzene.—A solution of 500 mg (1.9 mmol) of the hydroxydiazo ketone **2** in 150 ml of benzene was

(8) E. M. Avaro and J. Levisalles, *Bull. Soc. Chim. Fr.*, 735 (1967).
(9) A. Platner and H. Heusser, *Helv. Chim. Acta*, **28**, 1046 (1945).

purged with nitrogen for 30 min and then irradiated through Pyrex for 75 min. Removal of the solvent under reduced pressure gave a yellow oil which was dissolved in 4 ml of methanol, poured into 20 ml of a hot saturated solution of aqueous copper acetate, and left overnight. Filtration gave green flakes of the copper salt of 1,4-diphenyl-1,3-butanedione which were washed with cold ether and dried, mp 198–200° (lit.[10] mp 200–201°). The copper salt was placed in a 125-ml separatory funnel together with 10 ml of ether and was shaken with 20-ml portions of 20% sulfuric acid until decomposition was complete and two homogeneous phases were present. The ether layer was dried over Drierite, filtered, and evaporated to give 220 mg (49%) of 1,4-diphenyl-1,3-butanedione (**5**) as yellow crystals: mp 52–53° (lit.[10] mp 52°); nmr (CCl_4) δ 15.50 (s, 1 H, CHOH), 7.75 and 7.25 (m, 10 H, 2 Ph), 6.02 (s, 1 H, CHOH), 3.59 ppm (s, 2 H, CH_2CO); ir ($CHCl_3$) 3.64 (broad m, OH), 6.41 μ (broad s, CO).

B. In Methanol.—Irradiation of 500 mg (1.9 mmol) of the diazo ketone **2** in 150 ml of methanol for 75 min followed by the same work-up procedure as above gave 235 mg (52%) of the dione **5**, mp 52–53°.

Pyrolysis of 2.—A stirred solution of 500 mg (1.9 mmol) of the diazo ketone **2** in 20 ml of redistilled chlorobenzene under a reflux condenser was heated rapidly in a preheated oil bath maintained at 170°. After about 60 sec, vigorous evolution of nitrogen occurred and was complete in approximately 5 min. Treatment of the yellow oil, formed on evaporation of the solvent, with a hot saturated aqueous solution of copper acetate and decomposition of the precipitated copper salt in a similar fashion as in the photolysis reactions gave 200 mg (40%) of the dione **5**, mp 52–53°.

3-Chloro-1,4-diphenyl-4-hydroxy-2-butanone (6).—Dry hydrogen chloride gas was bubbled through a stirred solution of 500 mg (1.9 mmol) of hydroxy diazo ketone **2** in 60 ml of anhydrous ether. After 10 min, the light yellow reaction solution was washed with three 20-ml portions of 2% sodium bicarbonate solution. Removal of the solvent afforded a light yellow oil which was subjected to preparative thin layer chromatography on silica gel developed with chloroform. Removal of the spot with R_f 0.69, extraction with ether, and subsequent evaporation of the solvent yielded 220 mg of a light orange liquid which crystallized in ether–pentane to give 90 mg (20%) of brown crystals of dione **5**, mp 52–53°. Similarly, recovery of the spot with R_f 0.45 gave 230 mg of a brown oil which crystallized in ether–pentane to give 160 mg (31%) of 3-chloro-1,4-diphenyl-4-hydroxy-2-butanone (**6**) as white crystals: mp 51–52°; nmr (CCl_4) δ 7.18 (m, 10 H, 2 Ph), 4.86 (q, 1 H, J = 5, J' = 8 Hz, CHOH), 4.24 (d, 1 H, J' = 8 Hz, CHCl), 3.77 (s, 2 H, CH_2), 3.30 ppm (d, 1 H, J = 5 Hz, CHOH); ir (KBr) 2.93 (w, OH), 5.88 μ (s, CO); mass spectrum (70 eV, 90°) m/e (rel intensity) 276 (0.19), 274 (0.44), 170 (5), 168 (18), 119 (10), 107 (8), 106 (23), 105 (28), 92 (10), 91 (100), 78 (19), 77 (48), 65 (24), 51 (30), 50 (16), 39 (21). *Anal.* Calcd for $C_{16}H_{15}ClO_2$: C, 69.96; H, 5.46; Cl, 12.93. Found: C, 69.76; H, 5.51; Cl, 13.05.

3-Bromo-1,4-diphenyl-4-hydroxy-2-butanone (10).—Following the same procedure as for the preparation of **6**, treatment of 500 mg (1.9 mmol) of hydroxy diazo ketone **2** with hydrogen bromide gas gave on work-up a light yellow oil which was dissolved in 2 ml of ether and 10 ml of pentane and cooled in a refrigerator for 48 hr to give 280 mg (45%) of 3-bromo-1,4-diphenyl-4-hydroxy-2-butanone (**10**) as white crystals: mp 56–57°; nmr (CCl_4) δ 7.19 (m, 10 H, 2 Ph), 4.95 (q, 1 H, J = 5, J' = 8 Hz, CHOH), 4.32 (d, 1 H, J' = 8 Hz, CHBr), 3.85 (s, 2 H, CH_2), 3.40 ppm (d, 1 H, J = 5 Hz, CHOH); ir (KBr) 2.94 (w, OH), 5.93 μ (s, CO); mass spectrum (70 eV, 90°) m/e (rel intensity) 320 (0.4), 318 (0.4), 239 (8), 214 (13), 212 (12), 147 (11), 133 (15), 131 (19), 119 (8), 107 (19), 106 (17), 105 (19), 103 (13), 92 (14), 91 (100), 75 (11), 73 (30), 65 (20), 51 (19), 39 (11). *Anal.* Calcd for $C_{16}H_{15}BrO_2$: C, 60.23; H, 4.70; Br, 25.04. Found: C, 60.42; H, 4.51; Br, 25.29.

Work-up of the remainder of the reaction mixture by the copper salt method gave 30 mg (10%) of the dione **5**, mp 52–53°.

2-Chloro-1,4-diphenyl-1,3-butanediol (8).—A solution of 100 mg (0.36 mmol) of chloro hydroxy ketone **6** in 5 ml of anhydrous ether was added dropwise to a stirred suspension of 40 mg of $LiAlH_4$ in 10 ml of anhydrous ether. After stirring for 1 hr, excess $LiAlH_4$ was decomposed with 3 ml of ethyl acetate, and the reaction mixture was filtered to remove inorganic salts. The filtrate, which still contained a small amount of inorganic salts, was stripped of the solvent and the residue was extracted with ether. Evaporation of the solvent from the extract gave a colorless, viscous oil which was crystallized from ether–pentane to give 46 mg (46%) of 2-chloro-1,4-diphenyl-1,3-butanediol (**8**): mp 88–89°; nmr ($CDCl_3$) δ 7.27 (m, 10 H, 2 Ph), 4.98 (m, 1 H, CHOHPh), 3.97 (m, 2 H), 3.57 (d, 1 H, J = 5 Hz, OH), 2.84 ppm (m, 3 H); nmr ($CDCl_3$–D_2O) δ 7.27 (m, 10 H, 2 Ph), 4.98 (d, 1 H, J = 5 Hz), 3.97 (m, 2 H), 2.84 ppm (m, 2 H). *Anal.* Calcd for $C_{16}H_{17}ClO_2$: C, 69.43; H, 6.15; Cl, 12.84. Found: C, 69.35; H, 6.10; Cl, 13.02.

2-Bromo-1,4-diphenyl-1,3-butanediol (11).—The $LiAlH_4$ reduction of 100 mg (0.31 mmol) of **10** was carried out in the same manner as for **6** to yield 42 mg (42%) of 2-bromo-1,4-diphenyl-1,3-butanediol (**11**): mp 106–107°; nmr ($CDCl_3$) δ 7.28 (m, 10 H, 2 Ph), 5.10 (m, 1 H, CHOHPh), 4.05 (m, 2 H), 3.40 (d, 1 H, J = 5 Hz, OH), 2.85 ppm (m, 3 H); nmr ($CDCl_3$–D_2O) 7.28 (m, 10 H, 2 Ph), 5.10 (d, 1 H, J = 5 Hz, CHOHPh), 4.05 (m, 2 H), 2.85 ppm (m, 2 H). *Anal.* Calcd for $C_{16}H_{17}BrO_2$: C, 59.85; H, 5.29; Br, 24.91. Found: C, 60.13; H, 5.58; Br, 24.90.

Registry No.—**2**, 34737-54-7; **5**, 3442-15-7; **6**, 34737-56-9; **8**, 34737-57-0; **10**, 34737-58-1; **11**, 34737-59-2.

Acknowledgment.—We are indebted to the National Science Foundation (Grant GP-28407) for financial aid in the purchase of the mass spectrometer.

(10) L. I. Smith and R. E. Kelly, *J. Amer. Chem. Soc.*, **74**, 3300 (1952).

The Oxidation of Ortho-Substituted Azobenzenes as Followed by Tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium Proton Magnetic Resonance Spectral Clarification. Regioselective Routes to Azoxybenzenes[1]

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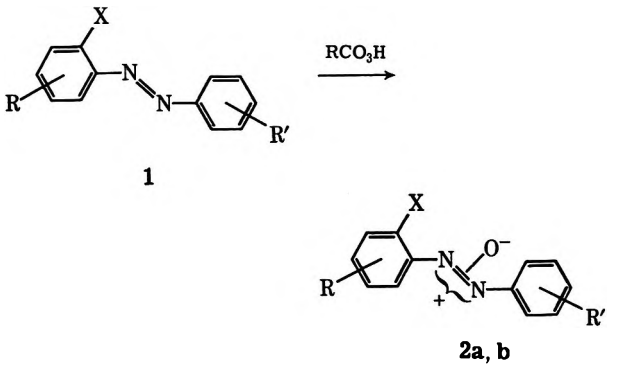
Received December 22, 1971

The ratio of isomeric azoxybenzenes produced *via* the peracetic acid oxidation of *o*- ($-CH_3$, $-OCH_3$, $-Cl$, $-CO_2H$, $-CO_2CH_3$, $-OAc$, and $-OH$) azobenzenes has been examined directly using $Eu(fod)_3$ to separate isomeric pmr signals. With the exception of the hydroxyl group, which favored oxidation of the nitrogen adjacent to the ortho-substituted benzenoid ring, all other substituents favor oxidation of the nonadjacent nitrogen with varying degrees of regioselectivity. Oxidation of azobenzene-2-carboxylic acids gave azoxybenzene-2-carboxylic acids which were >98% isomerically pure. Decarboxylation of these azoxybenzene-2-carboxylic acids proceeded readily and completed a convenient, two-step, regioselective entry into the azoxybenzenes. The differences provided by $-CO_2H$ and $-CO_2CH_3$ are discussed with regard to the role of internal hydrogen bonding.

The peracid oxidation of unsymmetrical azobenzenes (**1**) generally proceeds to yield a mixture of azoxybenzene isomers (**2a,b**). With no ortho substituent (**1**,



1 **2a, b**

X = H), the ratio of azoxybenzene isomers is generally[2] close to 1:1. With the exception of a report[3] examining the influence of simultaneous (2,2′) ortho substitution, the effect of ortho substituents upon the oxidation of azobenzenes has not been well studied,[4] particularly with regard to quantitative measurements of the minor azoxybenzene isomer formed. The apparent simplicity of this problem is offset by the inherent difficulties associated with analysis[5] by column chromatography or fractional recrystallization followed by chemical degradation to known compounds.

The importance of developing room temperature nematic systems for display[6] and spectroscopic[7] applications coupled with the ability of some azoxybenzene mixtures[2b,8,9] to form excellent low-temperature nematic mesophases prompted us to develop[9] a rapid analytical technique utilizing the lanthanide pmr shifting agent, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium[10] [$Eu(fod)_3$], for analysis of isomeric azoxybenzene mixtures. This ability to observe accurate azoxybenzene isomeric distributions *via* a direct method prompted us to examine the azoxybenzene isomeric distribution produced in the oxidation of azobenzenes possessing single ortho substituents. The ortho substituents were selected from those expected to depress[11,12] crystalline–mesomorphic transitions without destruction[12] of mesomorphic behavior.

The azobenzenes were all synthesized by two basic methods involving amine–nitroso[13] or phenol–diazonium[14] condensations. The oxidations were conducted in acetic acid at 25° using 90% hydrogen peroxide and a catalytic amount of sulfuric acid. The azoxybenzene isomer ratios were shown to be stable to these conditions for >20 hr. Purification of the crude products was accomplished without disturbing the isomeric distributions. Yields of azoxybenzenes were generally >85% of theoretical. Prior to analysis with $Eu(fod)_3$, phenols and acids were converted to acetates and esters.

The magnitude and direction of the regioselectivity of oxidation was measured by pmr analysis using $Eu(fod)_3$ to separate coincidental or closely coincidental isomeric resonances. These results are summarized in Table I. For ease of quantitative analysis, the azobenzenes were chosen to provide azoxybenzene mix-

(1) Presented in part at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971.

(2) (a) C. S. Hahn and H. H. Jaffé, *J. Amer. Chem. Soc.*, **84**, 949 (1962); (b) R. Steinstrasser and L. Pohl, *Tetrahedron Lett.*, 1921 (1971).

(3) V. M. Dzimoko and K. A. Dunaevskaya, *Zh. Obshch. Khim.*, **31**, 3385 (1961).

(4) For a convenient summary of early work in this area, see K. H. Schundehutte, "Methoden der Organische Chemie," Georg Thieme Verlag, Stuttgart, 1965, p 745.

(5) The individual isomers of azoxybenzene mixtures possess remarkably similar ir, uv, nmr, and glpc parameters. In any case, degradation to known compounds is usually required for rigorous identification.

(6) G. H. Heilmeier and J. E. Goldmacher, *Proc. IEEE*, **57**, 34 (1969).

(7) Nmr and esr: (a) C. T. Yim and F. R. Gilson, *Can. J. Chem.*, **47**, 1057 (1969); (b) P. Diehl and C. L. Khetrapal, *Mol. Phys.*, **15**, 633 (1968); (c) A. Saupé, *Angew. Chem., Int. Ed. Engl.*, **7**, 97 (1968); (d) C. F. Schwerdtferger and P. Diehl, *Mol. Phys.*, **17**, 417 (1969). Ir and uv: (e) R. A. Levenson, H. B. Gray and G. P. Ceasar, *J. Amer. Chem. Soc.*, **92**, 3653 (1970).

(8) H. Kelker, E. Scheule, R. Hatz, and W. Bartsch, *Angew. Chem., Int. Ed. Engl.*, **9**, 962 (1970).

(9) R. E. Rondeau, M. A. Berwick, R. N. Steppel, and M. P. Servé, *J. Amer. Chem. Soc.*, **94**, 1096 (1972).

(10) R. E. Rondeau and R. E. Sievers, *ibid.*, **93**, 1552 (1971).

(11) (a) Available reports[11b] indicate that ortho substitution imparts a less favorable crystal lattice packing relative to the unsubstituted analog. (b) For examples, see W. Kast in "Landolt-Börnstein," 6th ed, Vol. II, Springer-Verlag, West Berlin, 1960, Part 2a.

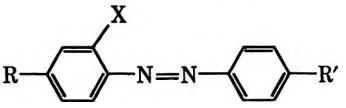
(12) (a) No azoxybenzenes in this study were expected to show mesomorphism, although the ortho substituents of interest to us were those which could ultimately be incorporated into mesomorphic compounds. Large, bulky substituents would destroy[12b] mesomorphic behavior even through greater regioselectivity might be expected from their usage. (b) G. W. Gray, "Molecular Structure and the Properties of Liquid Crystals," Academic Press, New York, N. Y., 1962.

(13) H. D. Anspon, "Organic Syntheses," Collect Vol. III, Wiley, New York, N. Y., 1943, p 711.

(14) J. L. Hartwell and L. Fieser, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 145.

TABLE I

OXIDATION OF AZOBENZENES



Compd	X	R	R'	Nitrogen oxidized, N_α[a]:N_β	Relative pmr shifting relationships[b]
3a	CH_3	H	H	1:15	$S_{N\alpha} > S_{N\beta}$ (2,2'-methyl)
3b	H	4-CH_3	H	1:1.1[c]	
4a	Cl	H	4-CH_3	1:24	$S_{N\beta} > S_{N\alpha}$ (4,4'-methyl)[d]
4b	H	4-Cl	4-CH_3	1:1.1[c]	
5a	OCH_3	H	H	1:8.3	$S_{N\alpha} > S_{N\beta}$ (2,2'-methoxy)
5b	H	4-OCH_3	H	1:1.2[c]	
6a	CO_2CH_3	H	H	1:5.7	$S_{N\beta} > S_{N\alpha}$ (2,2'-carbomethoxy)
6b	H	4-CO_2CH_3	H	1:1.4[c]	
7	CO_2H	H	H	1:18	
8a	CO_2CH_3	H	4-Cl	1:5.0	$S_{N\beta} > S_{N\alpha}$ (2,2'-carbomethoxy)
8b	H	4-CO_2Et	4-Cl	1:1.0	
9	CO_2H	H	4-Cl	1:20	
10	CO_2CH_3	H	4-OCH_3	1:3.8	$S_{N\beta} > S_{N\alpha}$ (2,2'-carbomethoxy)
11	CH_3	H	2-CO_2CH_3	1:3.2	
12	OH	5-CH_3	H	2.6:1	
13	OC(=O)CH_3	5-CH_3	H	1:9.3	$S_{N\beta} > S_{N\alpha}$ (2,2'-acetoxy)

[a] N_α is the nitrogen attached to the X-substituted ring. [b] Shifts are downfield except as indicated. Relative shifting relationships are measured as the slope (S) of the induced pmr shift of the N_α or N_β isomer *vs.* concentration of added Eu(fod)$_3$. The protons used for the comparison are indicated in parenthesis. [c] No regioselectivity implied. [d] The methyl protons of the N_α isomer are shifted slightly upfield.

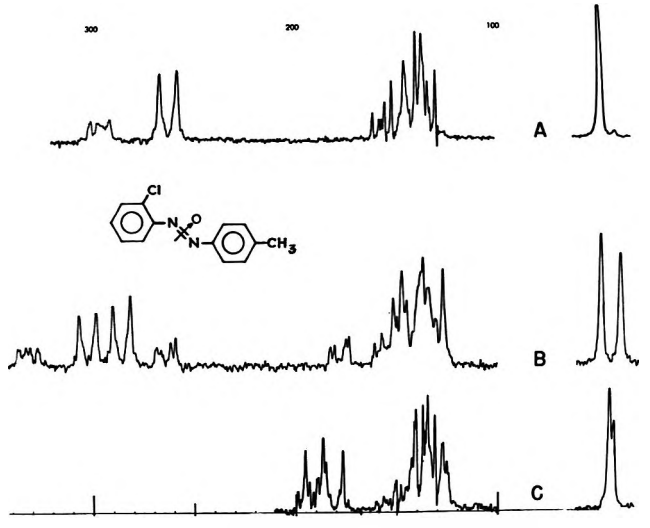


Figure 1.—Spectral clarification of the 2- and 2'-chloro-4'- and -4-methylazoxybenzenes. Pmr spectra in 0.5 ml of CCl_4 with added TMS (500-Hz sweep; methyls offset 100 Hz; aromatics offset 300 Hz): A, oxidized 2-chloro-4'-methylazobenzene mixture (25.5 mg) with 35.1 mg of added Eu(fod)$_3$; B, solution C with 42.0 mg of added Eu(fod)$_3$; C, mixture of 13.4 mg of 4-methyl and 14.9 mg of 4'-methyl isomers with no Eu(fod)$_3$.

tures which possessed, or could be converted to derivatives which possessed, singlet resonances. In most cases, a methyl function giving a singlet pmr signal was used. Structural assignments based upon lanthanide shifting patterns have been established only for 4,4'-substituted azoxybenzenes[9] in which the lanthanide interaction is at the azoxy oxygen and in which at least one of the para substituents bears a hydrogen. In instances where the coordination site was other than the central linkage, as with acetoxy and carbomethoxy azoxybenzene esters, or no para substituents bearing hydrogen were present, new rules relating shifting patterns to stereochemistry were required.[15] This was accomplished *via* synthesis of both isomers by known regiospecific methods, followed by Eu(fod)$_3$ pmr comparison of known mixtures with the mixtures obtained by oxidation of the azobenzenes. Figure 1 illustrates this process for the 2- and 2'-chloro-4'- (and -4-) azoxybenzenes.[16] In cases in which only one of the azoxybenzene isomers could be synthesized by known methods, the Eu(fod)$_3$ pmr shifting patterns were first observed and subsequently related to structure after degradation to known compounds. For example, 2'-carbomethoxy-4-methylazoxybenzene, which was obtained as the minor isomer upon oxidation of the corresponding azobenzene, was accessible in low yields through direct synthesis,[17] but the structure of the major isomer required confirmation by decarboxylation to 4'-methylazoxybenzene. Structural assignments of the oxidation products of **12** and **13** were made on the basis of the interrelationships of the major isomers obtained from each: *i.e.*, conversion by acetylation of the major product of phenol oxidation, 2'-hydroxy-5'-methylazoxybenzene, to the minor product of acetoxy oxidation, 2'-acetoxy-5'-methylazoxybenzene, and conversion by deacetylation of the major product of acetoxy oxidation, 2-acetoxy-5-methylazoxybenzene, to the minor product of phenol oxidation, 2-hydroxyl-5-methylazoxybenzene.

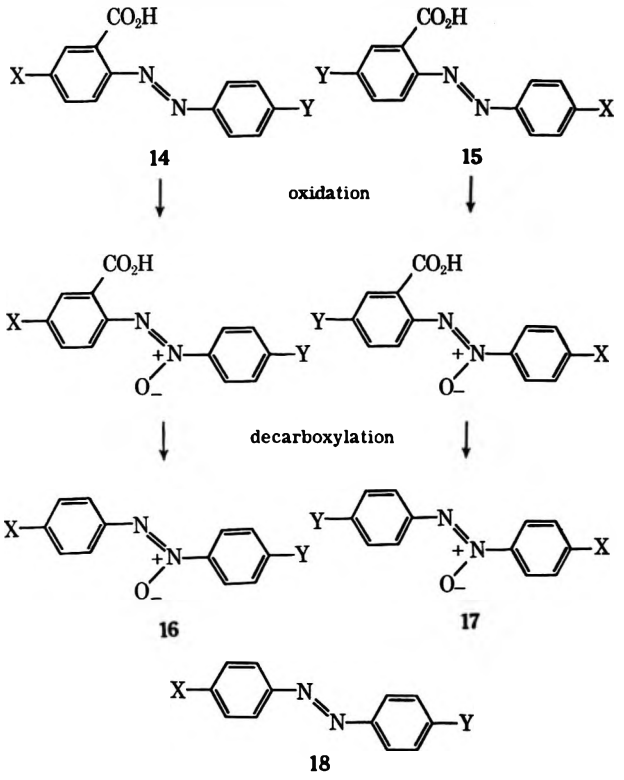
(15) (a) The pmr shifting associated with lanthanide reagents is a function[9,15b-e] of the strength of the interaction, proton distance, and angle to the lanthanide interaction site, as well as the nature of the lanthanide employed. (b) C. C. Hinckley, M. R. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, **93**, 2417 (1971), and references cited therein. (c) B. L. Shapiro, J. R. Hlubecek, G. R. Sullivan, and L. F. Johnson, *ibid.*, **93**, 3281 (1971). (d) T. H. Siddal, *Chem. Commun.*, 452 (1971). (e) G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, **93**, 5914 (1971).

(16) (a) The nomenclature[16b] is used which utilizes primed numbers to refer to substituents on the benzenoid nucleus adjacent to the N–O linkage. (b) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, 231 (1970).

(17) L. C. Behr, E. G. Alley, and O. Levand, *J. Org. Chem.*, **27**, 65 (1962), and references cited therein.

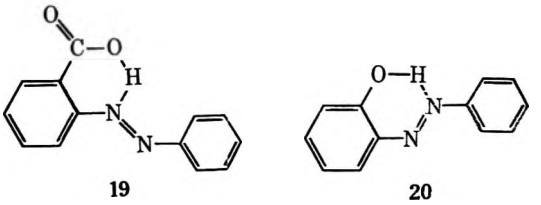
Two excellent, and totally distinct, regiospecific routes to azoxybenzenes have been reported. The first[17] involves vigorous oxidation of an intermediate indazole oxide followed by decarboxylation; the second[18] proceeds by the reaction of Grignard reagents with arylnitrosohydroxylamine derivatives. The first method proceeded poorly through the oxidation step in some instances,[19] and the second was limited by the need to employ a Grignard in the synthetic scheme. The results in Table I suggested an attractive alternative synthesis. Oxidation of the azobenzene-2-carboxylic acids **14** and **15** [(X = H, Y = $-CH_3$, $-Cl$, $-NO_2$ or $-OCH_3$, and X = $-CH_3$, $-Cl$, $-NO_2$ or $-OCH_3$, Y = H) Scheme I] gave highly crystalline azoxybenzene-2-carboxylic acid mixtures with a 14–20:1 preference for oxidation of the nitrogen nonadjacent (N_β) to the benzenoid ring possessing the 2-carboxylic acid moiety. The intermediate azoxybenzene-2-carboxylic acids (obtained with >98% isomeric integrity by one recrystallization of the crude oxidation product) underwent decarboxylation under the same conditions reported[17] for azoxybenzene-2′-carboxylic acid derivatives. Optimum purification of the final product required a simple column chromatographic separation of the azoxybenzenes **16** or **17** from the azobenzene **18**, which was formed in low yields by partial reduction of the azoxy linkage under the decarboxylation conditions.

SCHEME I
REGIOSELECTIVE SYNTHESES OF AZOXYBENZENES



With the exception of the hydroxyl group, the principle influence of the ortho substituent was, not unexpectedly, to direct oxidation to the nitrogen furthest removed (N_β) from the ortho-substituted benzenoid ring. This was attributed primarily to inductive and steric effects, since resonance contributions appeared to be of little consequence as shown by the control oxidations of **3b**, **4b**, **5b**, **6b**, and **8b**. More interesting, however, were the relative magnitudes of this N_β selectivity. The N_β selectivity imparted by the 2-carboxylic acid function was two to three times greater than that associated with the corresponding 2-carbomethoxy group, which is the larger substituent. While we cannot rigorously exclude the possibility that this is due to an increased steric N_β selectivity provided by solvent coordination[20] with azobenzene-2-carboxylic acid, internal hydrogen bonding appeared to offer a more logical explanation.

Azobenzene-2-carboxylic acids **19** should be capable of forming an internal hydrogen bond, a phenomenon which has been established[21] for 2-hydroxyazobenzenes **20**. The overall result of this internal hydrogen



bonding should be both to shield the nitrogen involved and decrease its nucleophilicity, and thereby lower[22] the probability of oxidation at that site. Such an argument implies that peracetic acid oxidation of 2-hydroxyazobenzenes could show an increased N_α oxidation selectivity. The only report pertinent to this conclusion examined the oxidation of 2-hydroxy 2′-substituted azobenzenes.[3] In these examples, the observed exclusive oxidation of the nitrogen adjacent to the 2-hydroxyl function may be due to either an internal hydrogen bonding effect promoting N_α oxidation or the expected N_β directing influence of the other 2′ substituent or both. Accordingly, we reexamined the original report[23] of the oxidation of 2-hydroxy-5-methylazobenzene (**12**) and indeed found a slight reversal of the expected N_β oxidation pattern.

Experimental Section[24,25]

General.—Tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium [Eu(fod)$_3$] was synthesized according to known procedures.[26] The oxidizing solution was composed of acetic acid, 90% hydrogen peroxide, and concentrated sulfuric acid in a volume ratio of 100:15:0.5. All oxidations were conducted in a thermostated reaction vessel rigidly maintained at 25°. Glpc was accomplished on a Varian Series 1200 instrument using a 6 ft × 0.250 in. diameter aluminum column packed with 3% SE-30 on 100/120 mesh Aeropak 30. The pmr spectra were recorded with a Varian HA601L spectrometer operating in

(18) T. E. Stevens, *J. Org. Chem.*, **29**, 311 (1964).
(19) Particularly with hydroxyl or benzyl substituents.
(20) The ortho position of the acid function should hinder coordination.
(21) (a) W. R. Brode, J. H. Gould, and G. M. Wyman, *J. Amer. Chem. Soc.*, **74**, 4641 (1952); (b) L. M. Reeves, *Can. J. Chem.*, **38**, 748 (1960).
(22) Reduction of electron density at a specific nitrogen hampers[2-4] its oxidation.
(23) D. Bigiani and R. Poggl, *Gazz. Chim. Ital.*, **54**, 114 (1924).
(24) Melting points are uncorrected. Elemental analyses are by J. Kern, Air Force Materials Laboratory, Wright-Patterson AFB, Dayton, Ohio.
(25) Eu(fod)$_3$ pmr shifting behavior of other azoxybenzene isomeric pairs 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-72-2409. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.
(26) G. S. Springer, D. W. Mark, and R. E. Sievers, *Inorg. Chem.*, **6**, 1105 (1967).

the frequency sweep mode. The unknown azoxybenzenes, which are cited without experimental preparations, were made according to the procedure detailed for 2'-methylazoxybenzene.

2'-Methylazoxybenzene.—*N*-2-Methylphenyl-*N'*-tosyloxydiimide *N*-oxide[27] (6.1 g, 0.02 mol) was dissolved in 50 ml of methylene chloride and cooled in an ice–water bath while phenylmagnesium bromide [Grignard prepared from bromobenzene (3.2 g, 0.02 mol) and magnesium (0.69 g, 0.03 g-atom) in 30 ml of dry tetrahydrofuran] solution was added through a fritted glass filter to remove unreacted magnesium. The solution was stirred at room temperature for 18 hr. An additional 100 ml of methylene chloride was then added, and the methylene chloride was extracted with 10% hydrochloric acid and 10% sodium hydroxide and dried ($MgSO_4$). Glpc analysis indicated the presence of a complex mixture of products from which the desired azoxybenzene was isolated after concentration and column chromatography on 100 g of neutral alumina (activity I) using petroleum ether (bp 30–60°)–ether (95:5) as solvent, yielding 0.57 g (14%) of a yellow oil: bp 124–125° (1 mm);[28] ir (neat) 3060, 1470, 763, and 685 cm^{-1}; uv max (cyclohexane) 228 nm (ϵ 8830) and 303 (13,300); nmr (CCl_4) δ ~6.50 and 5.66 (m, 9, aromatic protons) and 2.44 ppm (s, 3, $-CH_3$). *Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.55; H, 5.62; N, 13.46.

Oxidation of 2-Methylazobenzene.—2-Methylazobenzene[29] (1.96 g, 0.01 mol) was added to 75 ml of the oxidizing solution and stirred for 18 hr. The yellow solution was then poured onto ice–water and extracted into ether, and the ether was extracted with 10% sodium hydroxide, then dried ($MgSO_4$), concentrated, and quickly chromatographed on 100 g of neutral alumina (activity I) using petroleum ether–ether (95:5), yielding 1.83 g (86%) of a yellow liquid, bp 123–126° (1 mm).[28] Eu(fcd)$_3$ pmr analysis prior to distillation indicated that the major isomer predominated by 15:1, a ratio which was not altered upon rechromatography under the same conditions. The pmr absorbances associated with the major isomer were enhanced upon the addition of known 2-methylazoxybenzene: bp 128–130° (1.2 mm);[28] ir (neat) 3090, 1480, 763, and 685 cm^{-1}; uv max (cyclohexane) 243 nm (ϵ 9270), 256 (shoulder, 7910), and 332 (10,100); nmr (CCl_4) δ ~6.50 and 5.66 (m, 9, aromatic protons) and 2.40 ppm (s, 3, $-CH_3$). *Anal.* Calcd for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.32; H, 5.66; N, 13.38.

2-Chloro-4'-methylazobenzene.—2-Chloronitrosobenzene[30] (5.00 g, 0.035 mol) was dissolved in 50 ml of glacial acetic acid by gentle heating and added to 4-methylaniline (3.85 g, 0.035 mol) previously dissolved in 10 ml of glacial acetic acid. The solution was heated on a steam bath for 0.5 hr and allowed to stand at room temperature for 12 hr. The solution was then poured onto water and the resulting orange solid was collected by filtration. The crude product was dissolved in a minimal amount of ether and chromatographed on 100 g of neutral alumina (activity I) using pentane–ether (4:1), yielding 5.9 g (73%) of a product which, when recrystallized from 35 ml of hexane, gave orange needles: mp 43.5–44.0°; ir (KBr) 1630, 1060, 830, and 760 cm^{-1}; uv max (cyclohexane) 238 nm (ϵ 13,000), 333 18,500) and 456 (541); nmr (CCl_4) δ ~5.83 (m, 8, aromatic protons) and 2.43 ppm (s, 3, $-CH_3$). *Anal.* Calcd for $C_{13}H_{11}N_2Cl$: C, 67.68; H, 4.81; N, 12.14; Cl, 15.37. Found: C, 67.94; H, 4.71; N, 12.25; Cl, 15.47.

Oxidation of 2-Chloro-4'-methylazobenzene.—2-Chloro-4'-methylazobenzene (1.16 g, 0.005 mol) was dissolved in 100 ml of oxidizing solution and stirred for 18 hr. Work-up of the yellow solution was identical with the procedure for the oxidation of 2-methylazobenzene, yielding 1.1 g (89%) of a light yellow solid. Nuclear magnetic resonance (in CCl_4) (confer Figure 1, spectrum A) indicated that the major isomer predominated by 24:1 and underwent a pmr shifting behavior with added Eu(fod)$_3$ different from that observed for 2'-chloro-4-methylazoxybenzene: mp 63–64°; ir (KBr) 1470, 1340, 910, and 760 cm^{-1}; uv max (cyclohexane) 233 nm (ϵ 10,700) and 310 (16,700); nmr (CCl_4) δ ~6.45 and 5.58 (m, 8, aromatic protons) and 2.36 ppm (s, 3, $-CH_3$). *Anal.* Calcd for $C_{13}H_{11}N_2OCl$: C, 63.29; H, 4.49; N, 11.36; Cl, 14.37. Found: C, 63.22; H, 4.49; N, 11.50; Cl, 14.51.

2-Chloro-4'-methylazoxybenzene.—Two recrystallizations of the oxidized 2-chloro-4'-methylazobenzene gave 2-chloro-4'-methylazoxybenzene as yellow needles: mp 67.5–68.0°; ir (KBr) 1690, 1450, 915, and 755 cm^{-1}; uv max (cyclohexane) 242 nm (ϵ 9660), 273 (9080), and 328 (1200); nmr (CCl_4) δ ~6.58 and 5.58 (m, 8, aromatic protons) and 2.42 ppm (s, 3, $-CH_3$). *Anal.* Calcd for $C_{13}H_{11}N_2OCl$: C, 63.29; H, 4.49; N, 11.36; Cl, 14.37. Found: C, 63.08; H, 4.59; H, 11.54; Cl, 14.62.

Azobenzene-2-carboxylic Acids. 4'-Methylazobenzene-2-carboxylic Acid.—The general procedure is illustrated by the preparation of 4'-methylazobenzene-2-carboxylic acid. 4-Methylnitrosobenzene[30] (6.05 g, 0.05 mol) was dissolved in 25 ml of acetic acid by gentle heating and added to 2-carbomethoxyaniline (7.55 g, 0.05 mol) previously dissolved in 25 ml of acetic acid. The solution was heated on a steam bath for 45 min and allowed to stand at room temperature for 12 hr. The solution was then poured onto water and extracted into ether, and the ether was dried ($MgSO_4$) and removed under vacuum. Chromatography of the residue on ~100 g of neutral alumina (activity II) with petroleum ether–ether (2:1) gave 9.2 g (70%) of a red oil, bp 155–158° (0.03 mm). The red oil (4.57 g, 0.018 mol) was dissolved in 100 ml of ethanol, and 10 g of sodium hydroxide in 100 ml of water was added. The mixture was refluxed for 12 hr and added to 300 ml of ice–water, and the solids were suction filtered and discarded. The resulting orange filtrate was extracted with ether and the aqueous phase was neutralized with concentrated hydrochloric acid. The crude, suspended solids were filtered and recrystallized from ethanol–hexane, yielding 3.5 g (82% based on ester) of orange-yellow needles: mp 118.5–119.0°; ir (KBr) 2760 (broad), 1740, 835, 776, and 683 cm^{-1}; uv max (methanol) 230 nm (ϵ 13,600), 327 (19,200), and 435 (689); nmr ($DCCl_3$) δ ~6.0 (m, 9, aromatic protons and $-CO_2H$) and 2.42 ppm (s, 3, $-CH_3$). *Anal.* Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.00; H, 5.08; N, 11.72.

Oxidation of Azobenzene-2-carboxylic Acids. 4'-Chloroazoxybenzene-2-carboxylic Acid.—The general procedure is illustrated by the oxidation of 4'-chloroazobenzene-2-carboxylic acid. 4'-Chloroazobenzene-2-carboxylic acid (5.20 g, 0.02 mol) was added to 200 ml of the oxidizing solution and stirred for 12 hr. The yellow solution was then poured onto ice–water and stirred for 3 hr, the resultant solid suction was filtered and dissolved in ether, and the ether was dried ($MgSO_4$) and removed under reduced pressure to give 5.10 g (92%) of a yellow powder, which was homogenized with mortar and pestle. A small fraction of the powder (~250 mg) was treated with diazomethane; the resulting analysis of the esters by the Eu(fod)$_3$ pmr spectral clarification technique indicated that the major isomer predominated by 20:1. Recrystallization from ethanol–water gave 4'-chloroazoxybenzene-2-carboxylic acid as yellow crystals: mp 151–152°; ir (KBr) 2900 (broad), 1740, 1475, 840, and 761 cm^{-1}; uv max (methanol) 256 nm (ϵ 12,100) and 324 (9900); nmr ($DCCl_3$) δ 8.17 (broad singlet, 1, $-CO_2H$), ~6.50 and 5.83 (m, 8, aromatic protons). *Anal.* Calcd for $C_{13}H_9N_2O_3Cl$: C, 56.43; H, 3.28; N, 10.13; Cl, 12.82. Found: C, 56.45; H, 3.36; N, 10.13; Cl, 12.77.

Decarboxylation of 4-Methylazoxybenzene-2-carboxylic Acid and 4'-Methylazoxybenzene-2-carboxylic Acid.—4-Methylazoxybenzene-2-carboxylic acid (0.71 g, 2.8 mol) was added to 50 ml of pyridine and powdered copper (~1.5 g) along with a crystal of cupric acetate. The mixture was stirred magnetically at reflux and monitored periodically by glpc. When the ratio of 4-methylazobenzene to azoxybenzene product was 0.16:1.00 (~12 hr) the mixture was added to 200 ml of 10% hydrochloric acid and extracted with ether. The ether was extracted with additional 10% hydrochloric acid and 10% sodium hydroxide, dried ($MgSO_4$), and concentrated under reduced pressure. Column chromatography on 100 g of neutral alumina (activity I) with pentane–ether (20:1) yielded first the 4-methylazobenzene and then a yellow-white powder identified as 4- or 4'-methylazoxybenzene. Pmr analysis with Eu(fod)$_3$ indicated <5% of the minor isomer to be present. Recrystallization from hexane gave 0.36 g (61%) of 4-methylazoxybenzene, mp 50.5–51.0° (lit.[18] mp 50°). Decarboxylation of 4'-methylazoxybenzene-2-carboxylic acid under the same conditions gave 4'-methylazoxybenzene, mp 63.5–64.0° (lit.[2a] mp 65°), in 72% yield.

Oxidation of 2-Acetoxy-5-methylazobenzene.—2-Acetoxy-5-methylazobenzene (2.54 g, 0.01 mol) was dissolved in 100 ml of

(27) Synthesized according to the method of Stevens.[18]

(28) S. Oae, T. Fukumoto, and M. Yamagami, *Bull. Chem. Soc. Jap.*, **36**, 601 (1963), report bp 127–129° (2 mm) for an undetermined mixture of 2- and 2'-methylazoxybenzene.

(29) J. Burns, H. McCombie, and H. A. Scarborough, *J. Chem. Soc.*, 2928 (1928).

(30) R. E. Lutz and M. R. Lytton, *J. Org. Chem.*, **2**, 773 (1939).

oxidizing solution and stirred for 18 hr. The yellow solution was poured onto ice–water and stirred for an additional 3 hr, the resultant solid was filtered and dissolved in ether, the ether was dried ($MgSO_4$), and the sample was concentrated under reduced pressure. The concentrated solution was chromatographed on 100 g of Florisil with hexane–ether (1:1) yielding 2.21 g (82%) of a yellow-white solid. The individual azoxybenzene isomers were partially separable *via* glpc (205°, the minor azoxyacetate preceding the major isomer), in this instance indicating that no fractionation of the mixture had occurred under the conditions of chromatography. Both glpc and $Eu(fod)_3$ pmr analysis indicated that the major isomer predominated by 9.3:1.

2-Acetoxy-5-methylazoxybenzene.—Two recrystallizations from hexane–ethanol of the oxidized 2-acetoxy-5-methylazobenzene mixture gave the major isomer, 2-acetoxy-5-methylazoxybenzene, as pale yellow needles: mp 76.5–77.0°; ir (KBr) 1760, 1225, 1193, 774, and 684 cm^{-1}; uv max (methanol) 243 nm (ϵ 10,600) and 324 (11,200); nmr (CCl_4) δ ~6.50 and 5.57 (m, 8, aromatic protons), 2.38 (s, 3, C-5 $-CH_3$), and 2.21 ppm (s, 3, $-COCH_3$). *Anal.* Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.37. Found: C, 66.48; H, 5.26; N, 10.33.

2-Hydroxyl-5-methylazoxybenzene.—2-Acetoxy-5-methylazoxybenzene (2.70 g, 0.01 mol) was dissolved in 100 ml of ethanol–water (1:1), and 15 g of potassium hydroxide was added. The solution was refluxed for 30 min, acidified with 10% hydrochloric acid, and poured onto 300 ml of ice–water. After stirring overnight, the crude product was suction filtered and dissolved in ether, and the ether was dried ($MgSO_4$) and removed under vacuum. Recrystallization from hexane–ethanol gave 1.8 g (79%) of yellow-orange needles, mp 72.5–73.0° (lit.[23] mp 74°).

Oxidation of 2-Hydroxyl-5-methylazobenzene.—2-Hydroxy-5-methylazobenzene[21] (2.12 g, 0.01 mol) was dissolved in 100 ml of the oxidizing solution and stirred for 24 hr. The yellow-orange solution was then poured onto ice–water and stirred for 3 hr at room temperature. The resultant crude solid was collected by suction filtration and dissolved in ether, and the ether was dried ($MgSO_4$) and removed under vacuum, yielding 1.9 g (90%) of a yellow-orange solid. The individual azoxybenzene isomers were partially separable *via* glpc (195°, the major azoxyphenol preceding the minor isomer). Conversion of the crude azoxyphenols to the acetates by treatment with pyridine–acetic anhydride as detailed for 2′-acetoxy-5′-methylazoxybenzene, and glpc (205°, the major azoxyacetate preceding the minor isomer) coupled with $Eu(fod)_3$ pmr spectral clarification, indicated that the major azoxyphenol isomer predominated by 2.6:1.

2′-Hydroxy-5′-methylazoxybenzene.—Two recrystallizations from hexane–ethanol of the oxidized 2-hydroxy-5-methylazobenzene mixture gave the major isomer, 2′-hydroxy-5′-methylazoxybenzene, as yellow needles, mp 124.5–125.0° (lit.[23] mp 125°).

2′-Acetoxy-5′-methylazoxybenzene.—2′-Hydroxy-5′-methylazoxybenzene (1.06 g, 0.005 mol) was dissolved in 30 ml of pyridine, and 3 ml of acetic anhydride was added. The solution was stirred for 1 hr, poured onto 300 ml of hydrochloric acid (20%) at 0°, and extracted into ether, and the ether was dried ($MgSO_4$) and concentrated under reduced pressure. The concentrated solution was chromatographed on 50 g of Florisil using pentane–ether (1:1) and the product corresponding to the yellow band was collected, yielding 0.9 g (67%) of a viscous yellow oil which resisted crystallization. Distillation in a microstill at 0.5 mm with a pot temperature of 165° gave a clear yellow oil: ir (neat) 1780, 1205, 769, and 688 cm^{-1}; uv max (methanol) 230 nm (ϵ 10,500) and 310 (14,500); nmr (CCl_4) δ ~6.50 and 5.57 (m, 8, aromatic protons), 2.38 (s, 3, C-5 $-CH_3$) and 2.16 ppm (s, 3, $COCH_3$). *Anal.* Calcd for $C_{15}H_{14}N_2O_3$: C, 66.66; H, 5.22; N, 10.37. Found: C, 66.63; H, 5.25; N, 10.54. Glpc (205°) and $Eu(fod)_3$ treatment of this azoxyacetate revealed it to be isomerically pure and to possess glpc and $Eu(fod)_3$ behavior identical with those of the minor azoxyacetate formed from the oxidation of 2-acetoxy-5-methylazoxybenzene.

Registry No.—$Eu(fod)_3$, 17631-68-4; 2′-methylazoxybenzene, 34810-71-4; 2-methylazoxybenzene, 34810-72-5; 2-chloro-4′-methylazobenzene, 34810-73-6; 2′-chloro-4-methylazoxybenzene, 34810-74-7; 2-chloro-4′-methylazoxybenzene, 34810-75-8; 4′-methylazobenzene-2-carboxylic acid, 13304-23-9; 4′-chloroazoxybenzene-2-carboxylic acid, 34810-77-0; 2-acetoxy-5-methylazoxybenzene, 34810-78-1; 2′-acetoxy-5′-methylazoxybenzene, 34810-79-2.

Thermal Decomposition of Methyl and Phenyl Triphenylmethylazocarboxylates[1a,b]

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Received January 4, 1972

Products from the decomposition of methyl and phenyl triphenylmethylazocarboxylates at 60° in benzene or cumene are reported. These and other results indicate that these tritylazocarboxylates decompose to trityl radicals, nitrogen, and the corresponding alkoxycarbonyl radicals (ROC̈=O) which can escape from a solvent cage and couple with other radicals before decarboxylating or decarbonylating. These alkoxycarbonyl radicals seem to be relatively unreactive radicals since no evidence for the addition into benzene or the abstraction of the α-hydrogen atom of cumene by these radicals was obtained.

Several reports of a class of free radicals which we prefer to call alkoxycarbonyl radicals (ROC̈=O) have been published.[2-15] The most detailed remarks on alkoxycarbonyl radicals came from decomposition studies of ethyl and benzyl *tert*-butyl monoperoxyoxalates as well as di-*tert*-butyl monoperoxyoxalate.[5,6] These studies demonstrated that alkoxycarbonyl radicals were stable enough to escape from the solvent cage to be trapped by molecules of solvent such as benzene or cumene or by molecules of a scavenger such as galvinoxyl, and to abstract a hydrogen atom from some active hydrogen atom donating species such as cumene.

(1) (a) This research was partially supported by Public Health Service Grant GM 13799 from the National Institute of General Medical Sciences and Grant 3219-A from the Petroleum Research Fund administered by the American Chemical Society. We thank these organizations for their support. (b) Based on work by D. E. Z. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Iowa State University. (c) Alfred P. Sloan Research Fellow, 1970–1972.

(2) R. Stolle and W. Reichert, *J. Prakt. Chem.*, **123**, 82 (1929).

(3) W. H. Urry and E. S. Huyser, *J. Amer. Chem. Soc.*, **75**, 4876 (1953).

(4) A. D. Petrov, G. I. Nikishin, and V. D. Vorob'ev, *Fette, Seifen, Anstrichm.*, **59**, 1023 (1957); *Chem. Abstr.*, **53**, 1127*i* (1959).

(5) P. D. Bartlett and R. E. Pincock, *J. Amer. Chem. Soc.*, **82**, 1769 (1960).

(6) P. D. Bartlett, B. A. Gontarev, and H. Sakurai, *ibid.* **84**, 3101 (1962).

(7) J. C. J. Thynne and P. Gray, *Trans. Faraday Soc.*, **59**, 1149 (1963), and references cited therein.

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(10) Y. Shigemitsu, T. Tominaga, T. Shimodaira, and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **39**, 2463 (1966).

(11) W. S. Trahanovsky, J. A. Lawson, and D. E. Zabel, *J. Org. Chem.*, **32**, 2287 (1967).

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(13) M. J. Yee Quee and J. C. J. Thynne, *Ber. Bunsenges. Phys. Chem.*, **72**, 211 (1968).

(14) D. Griller and B. P. Roberts, *J. Chem. Soc. D*, 1035 (1971).

(15) T. Sakikibara and Y. Odaira, *J. Org. Chem.*, **36**, 3644 (1971).

It was also noted that only 17% of the ethoxycarbonyl radicals escaping the solvent cage decarboxylated before being trapped, while 87–98% of the *tert*-butoxycarbonyl radicals escaping the solvent cage decarboxylated; therefore, the greater the stability of the alkyl radical (R·) formed, the greater will be the rate of decarboxylation of the alkoxycarbonyl radical (ROC(=O)·).

Just as phenylazotriphenylmethane heated at 40–70° in solution has proved to be a convenient source for phenyl radicals,[16,17] triphenylmethylazocarboxylate (tritylazocarboxylate) esters (**1**) appear to be a useful system for the generation of alkoxycarbonyl radicals under mild conditions.

As expected, the carbon–nitrogen bond between the trityl and azo groups is easily cleaved at low temperatures to produce a stable trityl radical (**2**), and a nitrogen molecule is quickly or perhaps simultaneously formed, leaving the alkoxycarbonyl radical (**3**).

$$\underset{\mathbf{1}}{Ph_3CN{=}NC(=O)OR} \longrightarrow \underset{\mathbf{2}}{Ph_3C\cdot} + N_2 + \underset{\mathbf{3}}{\cdot C(=O)OR}$$

Results

During the decomposition of methyl tritylazocarboxylate (**1a**) in benzene at 60°, the evolved gas was collected and analyzed for carbon dioxide and carbon monoxide. Conventional gas analysis[18] detected the presence of no carbon dioxide and it was calculated that a maximum of 2.1 mol % of carbon monoxide could have been produced. The remainder of the evolved gas was assumed to be nitrogen, an expected product of this decomposition.

The major nonvolatile products arising from the decomposition of **1a** in benzene at 60° under a nitrogen atmosphere were separated by tlc. The products that were identified and their yields are presented in Table I.

TABLE I
DECOMPOSITION PRODUCTS FROM METHYL TRITYLAZOCARBOXYLATE (**1a**)

Compd	Mol/mol of ester Run 1[a]	Run 2[b]	Run 3[c]
Triphenylmethane (**4**)	0.21	0.20	0.20
Methyl triphenylacetate (**5a**)	0.24	0.26	0.28
Methyl 4-benzhydrylbenzoate (**6a**)	0.11	0.18	0.14
Methyl 4-carbomethoxytriphenylacetate (**7a**)	0.065	0.035	0.036

[a] Isolated yields from decomposition in benzene at 60°; original amount of ester was 12.1 mmol. [b] Decomposed in benzene at 60° and analyzed by glpc using benzil as an internal standard; original amount of ester was 0.0606 mmol. [c] Decomposed in cumene at 60° and analyzed by glpc using benzil as an internal standard; original amount of ester was 0.0681 mmol.

Also presented in Table I are the yields of the major products of the decomposition in benzene and cumene as calculated from glpc data. No measurable quantities of methyl formate, methyl benzoate, dimethyl oxalate, dimethyl carbonate, or methyl 2-phenylisobutyrate were detected.

The half-life for the decomposition of **1a** in benzene at 60° was calculated to be *ca.* 20 min based on the disappearance of the methoxy group of **1a** as followed by nmr spectroscopy.

Similar product studies were carried out on the decomposition of phenyl tritylazocarboxylate (**1b**) in benzene at 75°. No carbon dioxide and a maximum of 2.2 mol % of carbon monoxide were observed. The yields of the major nonvolatile products which were isolated and identified are presented in Table II. No measurable quantities of phenyl formate, phenyl benzoate, diphenyl oxalate, or diphenyl carbonate were noted.

TABLE II
DECOMPOSITION PRODUCTS FROM PHENYL TRITYLAZOCARBOXYLATE (**1b**)[a]

Compd	Mol/mol of ester
Triphenylmethane (**4**)	0.18
Phenyl triphenylacetate (**5b**)	0.11
Phenyl 4-benzhydrylbenzoate (**6b**)	0.16
Mixture[b]	0.11
4,4′-Dicarbophenoxytriphenylmethane (**8b**)	0.032

[a] Isolated yields from decomposition in benzene at 75°; original amount of ester was 11.6 mmol. [b] Mixture contained **5b** and **6b**.

The presence of trityl radicals (**2**) in the crude reaction products from both **1a** and **1b** was detected by esr spectroscopy.

Discussion

Although more than 95% of the theoretical amount of nitrogen was eliminated from both tritylaozcarboxylates in benzene in about 3 hr, no decarboxylation and at best only a small amount (2–3 mol %) of decarbonylation of the methoxycarbonyl (**3a**) or phenoxycarbonyl (**3b**) radicals could have occurred, since no carbon dioxide was found and only a small amount of carbon monoxide could have been produced. Calculations of bond dissociation energies indicate that decarboxylation, not decarbonylation, of the methoxycarbonyl radical should occur.[19] In fact, the calculations indicate that the decarboxylation is an exothermic reaction whereas the decarbonylation is an endothermic reaction. Most assuredly, then, the decomposition of the tritylazocarboxylates at 60–75° produced a high yield of the alkoxycarbonyl radicals.

All of the products that contain the alkoxycarbonyl group can be explained by coupling reactions of the alkoxycarbonyl radical with a trityl or substituted trityl radical. Coupling of triarylmethyl radicals at the para positions has been reported.[20] Since no benzoates, formates, or 2-phenylisobutyrates were detected, there is no evidence for addition into the aromatic systems or hydrogen abstraction reactions, even from cumene, by the alkoxycarbonyl radicals.

Coupling of two methoxycarbonyl or two phenoxycarbonyl radicals to produce an oxalate is a possible reaction pathway, but no oxalates were noted among the decomposition products.

(16) R. F. Bridger and G. A. Russell, *J. Amer. Chem. Soc.*, **85**, 3754 (1963).
(17) S. G. Cohen and C. H. Wang, *ibid.*, **75**, 5504 (1953).
(18) L. M. Dennis and M. L. Nichols, "Gas Analysis," Macmillan, New York, N. Y., 1929.
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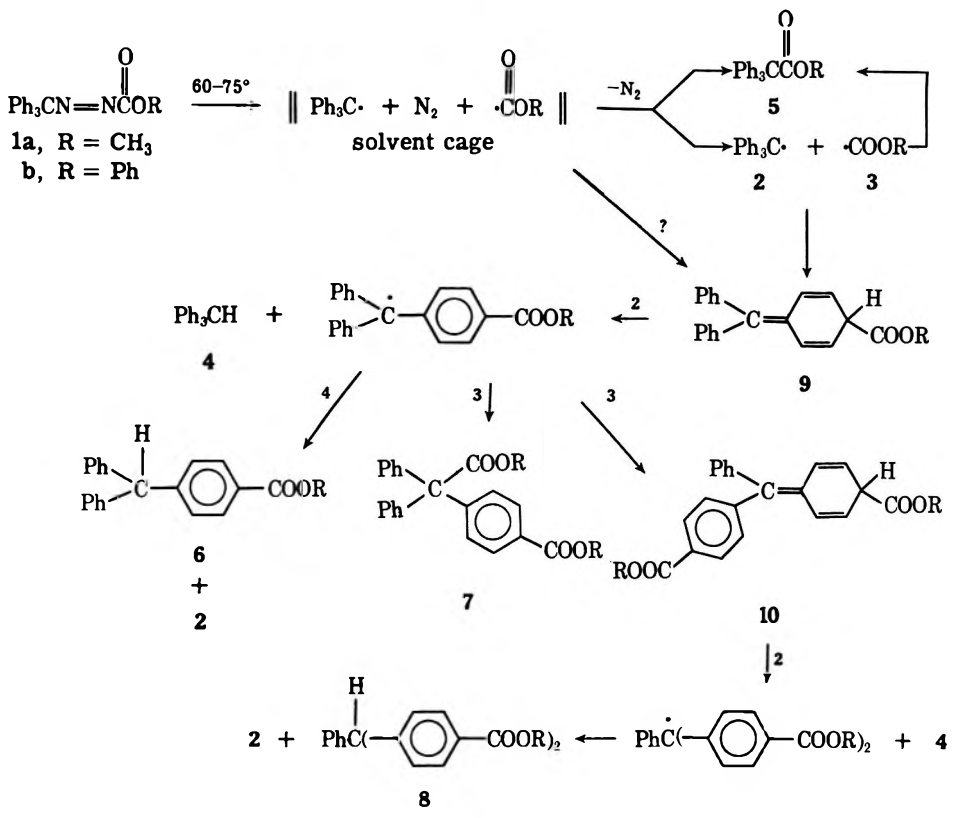
SCHEME I



Just how much of the triphenylacetate (**5**) is a result of cage recombination of radicals and how much is formed by an intermolecular coupling reaction is not known. Formation of the other products, 4-benzhydrylbenzoates (**6**) and the diester compounds **7** and **8**, can occur only if the alkoxycarbonyl radicals survive long enough to choose their point of attack on the trityl or substituted trityl radical. Indeed, the diester products can arise only if alkoxycarbonyl radicals escape from the solvent cage and are free in solution.

On the basis of the products isolated and identified, 63–68% of the trityl groups and 42–48% of the methoxycarbonyl groups from the decomposition of **1a** and 60% of the trityl groups and 42% of the phenoxycarbonyl groups from the decomposition of **1b** can be directly accounted for. In addition, a total of five other compounds (0.1–0.3 g each) from both decompositions containing trityl and/or alkoxycarbonyl groups were isolated but could not be conclusively identified. The number and nature of the decomposition products were further complicated by the reaction of oxygen with the excess trityl radicals after decomposition of **1** was complete, so that at least 20 distinct bands for each decomposition could be seen on the tlc plates.

The formation of considerable amounts of triphenylmethane (**4**) in these decompositions implies that the trityl radical is abstracting a hydrogen atom from another substituted triarylmethane or from some other species which readily donates a hydrogen atom.

In Scheme I, we present the most likely routes to the products that were identified. This scheme suggests that other tri- and tetracarboalkoxy compounds and compounds which contain ortho carboalkoxy groups should also form and thus readily accounts for the complex mixture of unidentified compounds that we observed.

Bartlett and Pincock observed ethyl benzoate, formate, and phenyldimethylacetate in their study,[5] but we did not observe similar products in our study. It is possible that in our system the concentration of the very stable trityl radicals was high enough to rapidly trap the alkoxycarbonyl radicals before they had a chance to undergo other reactions to a significant extent.

Alternatively, the ethyl benzoate that was obtained from the decomposition of ethyl *tert*-butyl monoperoxyoxalate in benzene could come from the coupling of an ethoxycarbonyl radical with a phenyl radical. The decomposition of ethyl *tert*-butyl monoperoxyoxalate produces, in addition to the ethoxycarbonyl radical, a *tert*-butoxy radical which can further cleave to give acetone and a methyl radical. The methyl radicals could attack benzene to give rise to phenyl radicals, whereas the very stable trityl radicals, produced from the decomposition of the tritylazocarboxylate, would not lead to phenyl radicals. Along the same lines, the ethyl formate produced from the decomposition of the monoperoxyoxalate in cumene could come from the ethoxycarbonyl radical abstracting a hydrogen atom from some other source besides cumene. In cumene, the *tert*-butoxy radical readily abstracts the α hydrogen atom of cumene to give a cumyl radical.[21] Possibly the ethoxycarbonyl radical abstracts a hydrogen atom from the cumyl radical to give the formate as well as coupling with it to give ethyl phenyldimethylacetate.

Our failure to detect oxalates in the product mixture from either tritylazocarboxylate could indicate that the coupling of two alkoxycarbonyl radicals is relatively slow due to an unfavorable polar effect or that the alk-

(21) C. Walling and B. B. Jacknow, *J. Amer. Chem. Soc.*, **82**, 6108 (1960), and references cited therein.

oxycarbonyl radicals are rapidly taken up by the high concentration of trityl radicals. Some reactions which consume alkoxycarbonyl radicals but not trityl radicals must be occurring, since trityl radicals were detected at the end of the reaction by esr spectroscopy. These reactions, however, must lead to products which were not identified.

It has recently been suggested that the photolysis of carbomethoxymercury compounds produces methoxycarbonyl radicals.[15] If this is true, then those methoxycarbonyl radicals must be produced in an excited state, since the products of the photolysis require that the methoxycarbonyl radicals must rapidly decarbonylate, a finding which is inconsistent with the results in this paper and previous reports.[5-7,14,19]

In conclusion, then, the tritylazocarboxylates seem to be a convenient means of generating alkoxycarbonyl radicals, which are relatively unreactive radicals that do not readily decarboxylate, decarbonylate, add into benzene rings, or abstract hydrogen atoms from cumene.

Experimental Section

Methods and Materials.—Most equipment and methods have been previously described.[22] Esr spectra were measured using a Varian Associates V-4500 spectrometer with a 100-kHz field modulation and a 9-in. magnet regulated by a Fieldial control. For glpc analysis, a 6 ft × 0.25 in. 15% SE-30 on 60/80 mesh Chromosorb P column at 125–265° was used. Glpc peak areas were measured with a planimeter.

Methyl carbazate was prepared by the method of Diels[23] and recrystallized from hexane–dichloromethane: yield 89.5%; mp 67–69° (lit.[23] mp 73°); ir ($CHCl_3$) 3425 (m), 1720 (vs), 1628 (m), 1479 (s), 1355 (w), 1265 (s), and 1057 cm^{-1} (m); nmr ($CDCl_3$) δ 6.9 (very broad s, 1), 3.90 (broad s, 2), and 3.70 (s, 3).

Methyl 3-Tritylcarbazate.—Using a variation of the method of Carpino, Terry, and Crowley,[24] 11.43 g (41.1 mmol) of trityl chloride in 20 ml of benzene was added dropwise to 3.7 g (41.1 mmol) of methyl carbazate in 25 ml of pyridine. After standing for 1 hr at room temperature the pyridinium chloride formed was removed by extracting the reaction mixture with an equal volume of water. Dichloromethane was added to the organic layer to increase the solubility of methyl 3-tritylcarbazate. The organic layer was dried ($MgSO_4$), filtered, and concentrated. The residue was recrystallized from hexane–dichloromethane twice to yield 10.8 g (79%) of white crystals: mp 175–177°; ir ($CHCl_3$) 3335 (w), 2990 (b w), 1725 (bs), 1590 (w), 1487 (s), 1442 (s), 1355 (m), 1243 (m), 1157 (s), and 905 cm^{-1} (m); nmr ($CDCl_3$) δ 7.6–7.9 (m, 15), 5.56 (s, 1), 4.47 (broad s, 1), and 3.50 (s, 3).

Anal. Calcd for $C_{21}H_{20}N_2O_2$: C, 75.91; H, 6.02; N, 8.43. Found: C, 76.11; H, 6.12; N, 8.39.

Methyl tritylazocarboxylate (1a) was prepared by the method of Carpino, Terry, and Crowley,[24] by oxidation of 8.37 g (25.2 mmol) of methyl 3-tritylcarbazate with 4.50 g (25.2 mmol) of freshly recrystallized *N*-bromosuccinimide (NBS). The yellow solid left after work-up was recrystallized from pentane–dichloromethane to yield 7.56 g (91%) of 1a, mp 98–100° with decomposition (yellow and orange crystals were obtained and the orange crystals were converted to the yellow crystals with explosive violence at *ca* 90°). Both kinds of crystals were examined by nmr and no solvent of crystallization was found): ir ($CHCl_3$) 1765 (vs), 1595 (w), 1489 (w), 1440 (m), 1250 (b s), 1026 (w), 1003 (w), 949 (w), 898 (w), and 885 cm^{-1} (w); nmr ($CDCl_3$) δ 7.20 (m, 15) and 3.86 (s, 3).

Phenyl carbazate was prepared by the method of Diels.[18] The water formed during the reaction was drawn off, and the organic layer was dried ($MgSO_4$), filtered, and concentrated to about half of the original volume. Anhydrous ether was added until all of the phenyl carbazate was precipitated. The phenol by-product remained soluble in the ether–dichloromethane. The product was collected by filtration and recrystallized from hexane–dichloromethane: yield 58%; mp 103–104° (lit.[25] mp 105°); ir ($CHCl_3$) 3430 (w), 1736 (vs), 1628 (m), 1593 (w), 1465 (vs), 1350 (w), 1250 (m), 1163 (m), 1067 (w), 1026 (m), 1005 (w), and 910 cm^{-1} (w); nmr ($CDCl_3$) δ 7.23 (m, 5), 6.65 (very broad s, 1), and 3.86 (broad s, 2).

Phenyl 3-tritylcarbazate was prepared by the method used to prepare methyl 3-tritylcarbazate and recrystallized from hexane–dichloromethane: yield 78%; mp 161–162°; ir ($CHCl_3$) 3330 (m), 2970 (b w), 1750 (b vs), 1595 (m), 1487 (vs), 1444 (s), 1423 (s), 1352 (m), 1152 (s), 1130 (s), 1100 (m), 1025 (m), 1000 (m), 940 (m), and 905 cm^{-1} (m); nmr ($CDCl_3$) δ 7.30 (m, 20), 5.92 (s, 1), and 4.53 (broad s, 1).

Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.32; H, 5.92; N, 6.95.

Phenyl tritylazocarboxylate (1b) was prepared by the method of Carpino, *et al.*,[24] by oxidation of 6.65 g (16.9 mmol) of phenyl 3-tritylcarbazate with 3.00 g (16.9 mmol) of freshly recrystallized NBS. After work-up the yellow solid residue was recrystallized from pentane–dichloromethane to produce 4.67 g (71%) of 1b: mp 105–106° with decomposition; ir ($CHCl_3$) 1778 (vs), 1590 (m), 1490 (s), 1446 (m), 1170 (m), 1156 (m), 1080 (w), 1067 (w), 1025 (w), and 1005 cm^{-1} (w); nmr ($CDCl_3$) δ 7.26 (m).

Determination of the Rate of Decomposition of Methyl Tritylazocarboxylate (1a).—Nitrogen was bubbled for 3 min through a solution of 0.0203 g (0.067 mmol) of 1a dissolved in 0.5 ml of benzene in an nmr tube. The solution was heated at 60° under nitrogen. The decomposition was followed by observing the disappearance of the methyl absorption at δ 3.86 in the nmr spectrum. The integrated areas of the signal were 114, 44, and 5 after 0, 30, and 300 min, respectively. The value at 300 min was used as the infinity point.

Analysis of the Gases Evolved[18] during the Thermal Decomposition of Methyl Tritylazocarboxylate (1a) **in Benzene.**—The total volume of the system (flask, condenser, and capillary tubing) in which the decomposition was carried out was 42 ml. The system was flushed with nitrogen for 45 min before 4.02 g (12.2 mmol) of 1a dissolved in enough benzene to make 24 ml of solution was added to the flask. After nitrogen was bubbled through the solution for 20 min, the solution was heated at 60° for 3 hr and the gas evolved was collected under a beaker submerged in a water tank. The collected gas was placed in a funnel submerged in a large water tank and approximately 100 ml of the gas was transferred to a 100-ml gas buret. The gas was then transferred to a Hemple pipette containing 30% aqueous potassium hydroxide to remove carbon dioxide; the remaining gas was transferred back to the gas buret; and the new volume was recorded. This transfer was repeated until no further decrease in volume was noted. Transfer of the gas to another Hemple pipette containing freshly prepared ammoniacal cuprous chloride removed carbon monoxide; the residual gas was returned to the gas buret; and the residual volume was recorded. This transfer was repeated until no further decrease in volume was noted. The residual gas was assumed to be nitrogen. The pertinent data are recorded in Table III.

Examination of the Decomposition of Methyl Tritylazocarboxylate (1a) **by Esr.**—An esr tube containing a deoxygenated solution of 20 mg (0.06 mmol) of 1a in 0.2 ml of benzene under a nitrogen atmosphere was heated at 60° for 2 hr. After three dilutions with deoxygenated benzene, the esr spectrum could be measured and was identical with that published[26] for the trityl radical.

Separation and Identification of the Nonvolatile Decomposition Products from Methyl Tritylazocarboxylate (1a) **in Benzene.**—The benzene was removed from the benzene solution of nongaseous products obtained from the decomposition of the 4.02 g (12.2 mmol) of 1a used for the gas analysis experiment. The crude products were dissolved in *ca*. 25 ml of dichloromethane and applied with a syringe to seven 8 × 20 cm glass plates coated with a 1-mm thickness of silica gel $PF_{254+366}$ (E. Merck, Darmstadt). The plates were developed with hexane, 50% hexane–50% benzene, and benzene, a total of 20 times per plate. Each plate was divided into four bands (at least 20 bands were visible); each band was vacuumed into a Soxhlet thimble and extracted with *ca*. 250 ml of ethyl acetate for 7 hr in a Soxhlet extractor. The ethyl acetate was removed under aspirator pressure.

(22) W. S. Trahanovsky and M. P. Doyle, *J. Org. Chem.*, **32**, 146 (1967).

(23) O. Diels, *Chem. Ber.*, **47**, 2187 (1914).

(24) L. A. Carpino, P. H. Terry, and P. J. Crowley, *J. Org. Chem.*, **26**, 4336 (1961).

(25) E. Merck, Patent Kl. 12o. Nr. 285800; *Chem. Zentrallbl.*, **86**, II, 508 (1915).

(26) H. S. Jarrett and G. J. Sloan, *J. Chem. Phys.*, **22**, 1783 (1954).

TABLE III

ANALYSIS OF GASES PRODUCED BY DECOMPOSITION OF METHYL TRITYLAZOCARBOXYLATE (1a) AND PHENYL TRITYLAZOCARBOXYLATE (1b)

Gas	Pressure, mm[a]	Volume, ml[b,c]
From Methyl Tritylazocarboxylate		
Carbon dioxide	714	0.00
Carbon monoxide	714	2.00[d,e]
Nitrogen	714	90.00[e]
From Phenyl Tritylazocarboxylate		
Carbon dioxide	713	0.10
Carbon monoxide	713	2.20[d,e]
Nitrogen	713	96.50[e]

[a] Barometer and water vapor corrections have been applied; temperature was 298° K. [b] Total volume collected was 295 ml from 1a and 280 ml from 1b. [c] Volume of the sample analyzed was 92.00 ml for 1a and 98.80 ml for 1b. [d] Maximum volume of carbon monoxide present. [e] Final volume after treatment with ammoniacal cuprous chloride was 101 ml for 1a and *ca.* 108 ml for 1b due to the presence of ammonia vapor which was not removed; correction for volume of ammonia was estimated to be 11 ml for 1a since addition of a small amount of hydrochloric acid to the water in the leveling bulb for 1b removed the ammonia and reduced the volume by 11 ml.

Band 1 yielded 0.62 g (2.54 mmol or 21 mol %) of triphenylmethane (4), mp 92–94°. Melting point, glpc retention time, and nmr and ir spectra were identical with those of authentic 4.

When band 2 (1.43 g) was treated with hot hexane, most of the solid did not dissolve. This material, when recrystallized from a mixture of hexane–dichloromethane, gave 0.87 g (2.88 mmol or 24 mol %) of a crystalline compound which had the same melting point (182–184°), glpc retention time, nmr spectrum, and ir spectrum as authentic methyl triphenylacetate (5a) prepared by a different route.[27]

When the hot hexane solution was allowed to cool, 0.41 g (1.36 mmol or 11 mol %) of methyl 4-benzhydrylbenzoate (6a) crystallized: mp 78–79° (lit.[28] mp 78–79°); ir ($CHCl_3$) 1716 (vs), 1610 (m), 1600 (m), 1492 (m), 1450 (m), 1435 (m), 1413 (w), 1277 (vs), 1115 (s), 1105 (s), 1075 (w), 1017 (m), 967 (w), and 880 cm^{-1} (w); nmr ($CDCl_3$) δ 7.95 (d, 2, J = 8 Hz), 7.21 (m, 12), 5.57 (s, 1), and 3.85 (s, 3).

Band 4 (0.56 g) contained small amounts of many compounds and was not further examined. Band 3 (0.83 g) was again dissolved in dichloromethane, applied to three 8 × 20 cm plates coated with a 1-mm thickness of silica gel, developed in 50% hexane–50% benzene 15 times, and divided into 5 bands. Each of the new bands was extracted with ethyl acetate, and the ethyl acetate was removed under aspirator pressure.

From band 3′ was recrystallized 0.24 g (0.80 mmol or 6.5 mol %) of methyl 4-carbomethoxytriphenylacetate (7a): mp 133–134°; ir ($CHCl_3$) 1718 (vs), 1607 (w), 1492 (w), 1433 (m), 1315 (m), 1277 (vs), 1110 (s), and 1010 cm^{-1} (m); nmr ($CDCl_3$) δ 7.95 (d, 2, J = 8 Hz), 7.23 (m, 12), 3.87 (s, 3), and 3.77 (s, 3); mass spectrum parent ion at m/e 360.

Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.39; H, 5.50.

Bands 1′ (0.08 g), 4′ (0.26 g), and 5′ (0.07 g) did not yield crystalline materials and could not be identified. Band 2′ (0.11 g) yielded a crystalline material for which no complete structural assignment could be made.

Analysis of Thermal Decomposition Products from Methyl Tritylazocarboxylate (1a) by Glpc.—Samples of 0.0200 g (0.0606 mmol) of 1a in 0.31 g (4.0 mmol) of benzene (run 1) and 0.0225 g (0.0681 mmol) of 1a in 0.41 g (3.4 mmol) of purified cumene[29] (run 2) were degassed three times each and sealed under vacuum (0.1 mm). After heating at 60° for 9 and 7.5 hr, respectively, the tubes were opened, and benzil was added as an internal standard. The glpc peak areas of the only detectable products are given in Table IV. No methyl formate, methyl benzoate, dimethyl oxalate, dimethyl carbonate, or methyl 2-phenylisobutyrate were observed.

TABLE IV

PRODUCTS FROM THE THERMAL DECOMPOSITION OF METHYL TRITYLAZOCARBOXYLATE (1a)

Compd	Area of Glpc Peak— Run 1[a]	Run 2[b]
Triphenylmethane (4)	0.46	2.43
Benzil[c]	2.03	9.70
Methyl triphenylacetate (5a)	0.70	3.91
Methyl 4-benzhydrylbenzoate (6a)	0.49	1.91
Methyl 4-carbomethoxytriphenylacetate (7a)	0.10	0.55

[a] In benzene as solvent. [b] In cumene as solvent. [c] Internal standard; 0.0610 mmol added to both runs.

Analysis of the Gases Evolved[18] during the Thermal Decomposition of Phenyl Tritylazocarboxylate (1b) in Benzene.—After deoxygenation of 4.54 g (11.6 mmol) of 1b the decomposition was brought about by heating the solution at 75° for 3 hr, the gas evolved being collected under a beaker submerged in a water tank. Conventional gas analysis as previously described for 1a was performed and the data are tabulated in Table III.

Examination of the Decomposition of Phenyl Tritylazocarboxylate (1b) by Esr.—A deoxygenated solution of 8 mg (0.02 mmol) of 1b in 0.2 ml of benzene was heated in an esr tube under a nitrogen atmosphere at 75° for 2 hr. The esr spectrum observed was identical with that of the trityl radical.[26]

Separation and Identification of the Nonvolatile Decomposition Products from Phenyl Tritylazocarboxylate (1b) in Benzene.—The nongaseous products obtained from the decomposition of 4.54 g (11.6 mmol) of 1b were separated and isolated, as previously described for the decomposition products of 1a.

From band 1, 0.52 g (2.13 mmol or 18 mol %) of triphenylmethane (4) was isolated, mp 92–94°. Authentic 4 had the same melting point, glpc retention time, and nmr and ir spectra as band 1.

The material from band 2 was recrystallized from hexane to yield 0.48 g (1.32 mmol or 11 mol %) of phenyl triphenylacetate (5b), mp 124–125°. The melting point, glpc retention time, and nmr and ir spectra were identical with those of 5b prepared by a different route.[30]

Band 3 by nmr analysis contained a mixture of 5b and phenyl 4-benzhydrylbenzoate (6b) (see discussion of band 4) amounting to 0.45 g (1.24 mmol or 11 mol %).

Upon recrystallization of band 4 from hexane, 0.69 g (1.90 mmol or 16 mol %) of 6b was obtained: mp 125–126°; ir ($CHCl_3$) 1725 (vs), 1595 (m), 1493 (s), 1445 (w), 1408 (w), 1263 (vs), 1160 (s), 1073 (s), 1017 (m), 1000 (w), 913 (w), and 878 cm^{-1} (w); nmr ($CDCl_3$) δ 8.15 (d, 2, J = 8 Hz), 7.23 (m, 17), and 5.63 (s, 1); mass spectrum parent ion at m/e 364.

Anal. Calcd for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.35; H, 5.74.

Band 6 (0.35 g) was a mixture of many highly colored bands; no further separation was attempted. Band 5 (0.94 g) was redissolved in dichloromethane, applied to three 8 × 20 cm plates coated with a 1-mm thickness of silica gel, developed in 50% hexane–50% benzene 15 times, and divided into five bands. Each of these new bands was extracted with ethyl acetate, and the ethyl acetate was removed from each band by rotary evaporation.

From band 3′ was isolated by recrystallization from hexane–dichloromethane 0.18 g (0.372 mmol or 3.2 mol %) of 4,4′-dicarbophenoxytriphenylmethane (8b): mp 151–153°; ir ($CHCl_3$) 3010 (w), 1733 (vs), 1610 (m), 1595 (m), 1495 (s), 1415 (m), 1265 (vs), 1176 (vs), 1160 (s), 1074 (vs), 1017 (s), 1000 (w), 924 (m), 876 (w), and 847 cm^{-1} (m); nmr ($CDCl_3$) δ 8.16 (d, 4, J = 8 Hz), 7.25 (m, 19), and 5.70 (s, 1).

Band 1′ (0.01 g) was too small to obtain any positive information. Bands 2′ (0.24 g), 4′ (0.28 g), and 5′ (0.11 g) yielded crystalline products upon recrystallization from hexane–dichloro-

(27) J. F. Norris and A. Cresswell, *J. Amer. Chem. Soc.*, **56**, 423 (1934).

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(29) P. D. Bartlett, E. P. Benzing, and R. E. Pincock, *ibid.*, **82**, 1762 (1960).

(30) J. Schmidlin and H. H. Hodgson, *Chem. Ber.*, **41**, 444 (1908).

methane, but complete structural assignments could not be made for these compounds.

Registry No.—**1a**, 34839-56-0; **1b**, 34839-57-1; **4**, 519-73-3; **5a**, 5467-21-0; **5b**, 34823-77-3; **6a**, 34823-78-4; **6b**, 34823-79-5; **7a**, 34823-80-8; **8b**, 34823-81-9; methyl carbazate, 6294-89-9; methyl 3-tritylcarbazate, 34823-82-0; phenyl carbazate, 20605-43-0; phenyl 3-tritylcarbazate, 34823-83-1.

Acknowledgment.—We thank Professor Glen A. Russell for helpful discussions of this work.

Strained Ring Systems. XII.[1a] The Synthesis of Several Dimethyl Δ^1-Cycloalkene-1,2-dicarboxylates and Certain 4-Substituted Bicyclo[2.1.0]pentane-1-carboxylic Acids

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Received December 7, 1971

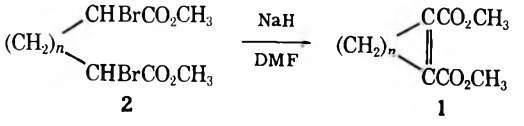
A one-step synthesis of dimethyl Δ^1-cycloalkene-1,2-dicarboxylates (**1**) (cyclobutene to cycloheptene) from the corresponding dimethyl α,α'-dibromoalkanedicarboxylates is given. While dimethyl Δ^1-cyclopropene-1,2-dicarboxylate (**1a**) is believed produced from the reaction of dimethyl α,α'-dibromoglutarate (**2a**) and potassium *tert*-butoxide, cis addition of an alcohol to **1a** proceeds to yield the dimethyl 1-alkoxycyclopropane-*cis*-1,2-dicarboxylates **4** and **5**. Reaction of dimethyl Δ^1-cyclobutene-1,2-dicarboxylate (**1b**) with diazomethane followed by photolysis of the product pyrazoline yields dimethyl bicyclo[2.1.0]pentane-1,4-dicarboxylate (**6**). Through standard reaction sequences **6** is converted to bicyclo[2.1.0]pentane-1,4-dicarboxylic acid, 4-carbomethoxy-, 4-carbamyl-, and 4-cyanobicyclo[2.1.0]pentane-1-carboxylic acids. Bicyclo[2.1.0]pentane-1-carboxylic acid was prepared by hydrolysis of its methyl ester.

We recently reported the preparation of several 5-substituted bicyclo[3.1.0]hexane-1-carboxylic acids[2] using standard reaction sequences for modifying the carboxylic acid group[3-6] of 5-carbomethoxybicyclo-[3.1.0]hexane-1-carboxylic acid. We wish to report in this paper the synthesis of certain 4-substituted bicyclo[2.1.0]pentane-1-carboxylic acids which were required to determine the effect of bridgehead substituent groups on the acidity of bicyclo[*n*.1.0]alkane-1-carboxylic acids.

The synthetic approach to dimethyl bicyclo[2.1.0]-pentane-1,4-dicarboxylate (**6**) which appeared most promising was the addition of diazomethane to dimethyl Δ^1-cyclobutene-1,2-dicarboxylate (**1b**) followed by photolytic decomposition of the resulting pyrazoline, similar to the reported method used for preparing methyl bicyclo[2.1.0]pentane-1-carboxylate.[7,8]

Synthesis of Dimethyl Δ^1-Cycloalkene-1,2-dicarboxylates.—The reported procedures for the preparation of diester **1b** or its diacid are quite lengthy[9,10] and involve cyclobutane-1,2-dicarboxylic acid as an intermediate. By analogy to the four-membered ring formation in the reaction of dimethyl α,α'-dibromoadipate (**2b**) with cyanide ion, which is part of the sequence leading to cyclobutane-1,2-dicarboxylic acid,[11] it appeared that reaction of **2b** with 2 equiv of base should accomplish both cyclization and vicinal elimination of hydrogen bromide to yield **1b** directly.

Our first attempt at such a reaction proved fruitful. When **2b** was allowed to react with 2 equiv of sodium hydride in dimethylformamide, **1b** was isolated in 68% yield. Since this procedure offered a simple, reasonably direct synthesis of **1b**, we decided to examine its possible generality for the synthesis of dimethyl Δ^1-cycloalkene-1,2-dicarboxylates. A series of dimethyl α,α'-dibromoalkanedicarboxylates (**2**) derived from glutaric acid through sebacic acid[12a] were prepared and allowed to react with sodium hydride in dimethylformamide; the conditions and results are given in Table I.[12b,13,14]



2 **1**

a, $n = 1$ **d**, $n = 4$
b, $n = 2$ **e**, $n = 5$
c, $n = 3$ **f**, $n = 6$

The reactions of **2a–d** proceeded smoothly at ice-bath or room temperature. However, the reactions with **2e** and **2f** were quite slow even at room temperature. While this procedure gives good yields of **1b–d** and an acceptable yield of **1e**, none of the desired products **1a** or **1f** were obtained from **2a** and **2f**, respectively.

(1) (a) For paper XI in this series, see R. N. McDonald, D. G. Frickey, and G. M. Muschik, *J. Org. Chem.*, **37**, 1304 (1972). (b) NDEA Fellow, 1968–1970; NSF Trainee, 1970–1971.

(2) R. N. McDonald and R. R. Reitz, *J. Org. Chem.*, **35**, 2666 (1970).

(3) F. W. Baker and L. M. Stock, *ibid.*, **32**, 3344 (1967).

(4) J. D. Roberts and W. T. Moreland, *J. Amer. Chem. Soc.*, **75**, 2167 (1953).

(5) C. F. Wilcox and C. Leung, *J. Org. Chem.*, **33**, 877 (1968).

(6) C. F. Wilcox and J. S. McIntyre, *ibid.*, **30**, 777 (1965).

(7) W. G. Dauben and J. R. Wiseman, *J. Amer. Chem. Soc.*, **89**, 3545 (1967).

(8) P. G. Gassman and K. T. Mansfield, *J. Org. Chem.*, **32**, 915 (1967).

(9) F. B. Kipping and J. J. Wren, *J. Chem. Soc.*, **51**, 1537 (1929).

(10) W. H. Perkins, *ibid.*, **65**, 950 (1894).

(11) R. C. Fuson and T. Y. Kao, *J. Amer. Chem. Soc.*, **51**, 1537 (1929).

(12) (a) The procedure used in the synthesis of esters **2** followed that reported for the preparation of **1b**: E. Buchman, A. Reims, T. Skei, and M. Schlatter, *ibid.*, **64**, 2697 (1942); P. C. Guha and D. K. Sankaran, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 623. (b) A similar procedure for the synthesis of **1c** has been reported by D. C. Owsley and J. J. Bloomfield, *Org. Prep. Proced. Int.*, **3**, 61 (1971).

(13) (a) Small amounts of the diacids of **1b**, **1c**, and **1d** have been obtained from base hydrolyses of the corresponding esters of **2**; see A. Hassell and C. K. Ingold, *J. Chem. Soc.*, 1465 (1926), and F. R. Goss and C. K. Ingold, *ibid.*, 1471 (1926). (b) **1b** has been obtained in low yield from the dehalogenation of dimethyl *cis*-1,2-dihalocyclobutane-1,2-dicarboxylate (X = Cl, Br) with $Ni(CO)_4$; see H.-D. Scharf and F. Korte, *Chem. Ber.*, **98**, 764 (1965).

(14) A reported attempt at formation of Δ^1-cyclobutene-1,2-dicarboxylic acid by a Ramberg–Bachlund reaction was unsuccessful; see T. Bacchetti and A. Arnaboldi, *Atti Accad. Naz. Lincei, Rend., Cl. Sci. Fis., Mat. Natur.*, **15**, 75 (1953); *Chem. Abstr.*, **49**, 2301*b* (1955).

TABLE I

RESULTS OF CYCLIZATION–ELIMINATION REACTION

Dibromo diester 2	Reaction time, hr	Temp, °C	Yield of 1,[a] %
a (glutarate)	1.5	0	0[b]
b (adipate)	4.0	25	68
c (pimeltate)	1.5	0	69
d (suberate)	3.0	0	71
e (azelate)	36	25	21
f (sebacate)	36	25	0

[a] None of the isomeric dimethyl cycloalkene-1,2-dicarboxylates were found. [b] Longer reaction times and increased temperatures gave only increased amounts of polymeric material.

Although little reaction was observed between **2f** and sodium hydride in dimethylformamide, the results obtained from reactions of **2a** with this and another basic system deserve special comment. Reaction of **2a** with 2 equiv of sodium hydride in dimethylformamide at 0°, after the steady evolution of hydrogen had ceased, gave a 77% yield of dimethyl 1-bromocyclopropane-*cis*- and -*trans*-1,2-dicarboxylate (**3**) in a ratio of 1:3, respectively. The structural assignments of the two isomers of **3** were based on analysis of their nmr spectra when compared to those of **4** and **5**.

Reaction of **2a** with 2 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol gave two products, dimethyl 1-*tert*-butoxy- (**4**, 46%) and dimethyl 1-methoxycyclopropane-*cis*-1,2-dicarboxylate (**5**, 9%). Both **4** and **5** exhibited almost superimposable ABC multiplets for the ring protons in their nmr spectra, which established their structures as having the same geometric relationship of the carbomethoxy groups (probably cis). This ABC multiplet portion of the nmr spectra was used to assign structures to the cis and trans isomers of **3**.

The cis relationship of the carbomethoxy groups in **4** and **5** was verified by hydrolysis of a mixture of **4** and **5** to their respective dicarboxylic acids, formation of the two anhydrides (ir absorptions at 1850 and 1780 cm^{-1}) with acetic anhydride, and hydrolysis with warm water to regenerate the diacids. Reaction of these two diacids with diazomethane reformed **4** and **5**.

Reaction of **2a** with 1 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol produced a mixture containing *cis*- and *trans*-**3** along with some **4** and **5**. Similar reaction with a mixture of *cis*- and *trans*-**3** produced a mixture of **4** and **5**.

The observation of **3** as the primary product from the reaction of **2a** with potassium *tert*-butoxide rules out nucleophilic displacement of bromide by the alkoxide followed by cyclization as the mechanism involved in the formation of **4** and **5**. A more reasonable mechanism for producing **4** and **5** would be a stepwise 1,3 elimination from **2a** to **3**, vicinal elimination in **3** to yield the highly reactive intermediate dimethyl Δ^1-cyclopropene-1,2-dicarboxylate (**1a**), followed by cis addition of the alcohol to the strained double bond.[15] The presence of methanol in these reactions is probably due to transesterification of the methyl ester groups.

Synthesis of Certain 4-Substituted Bicyclo[2.1.0]-pentane-1-carboxylic Acids.—Utilizing the synthetic approach already outlined for the synthesis of dimethyl bicyclo[2.1.0]pentane-1,4-dicarboxylate (**6**), **1b** was allowed to react with diazomethane to give pyrazoline **7** in 92% yield.[16] Photolysis of **7** in ether using a Hanovia 450-W (type L) lamp and a Corex filter in a quartz immersion well gave **6** in 51% yield. With no filter the photolysis proceeded much faster but more polymeric material was obtained along with a reduced yield of **6**. Use of a Pyrex filter slowed the reaction considerably.

From **6** several 4-substituted bicyclo[2.1.0]pentane-1-carboxylic acids were prepared by standard routes,[2-6] as shown in Scheme I. Diester **6** was saponified completely to diacid **8** and partially to half-ester **9**. Half-ester **9** was converted to carbamyl ester **10**, which was dehydrated to cyano ester **11**. Esters **10** and **11** were

SCHEME I

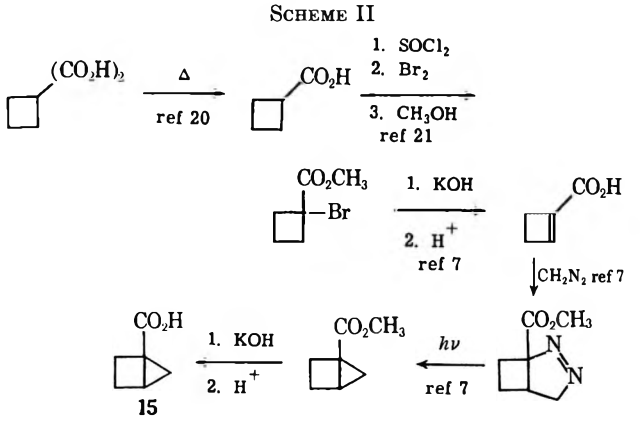
(15) K. B. Wiberg, R. K. Barnes, and J. Albin [*J. Amer. Chem. Soc.*, **79**, 4994 (1957)] suggested a similar addition of *tert*-butyl alcohol to ethyl Δ^1-cyclopropenecarboxylate to account for the formation of ethyl *trans*-2-*tert*-butoxycyclopropanecarboxylate from ethyl *trans*-2-bromocyclopropanecarboxylate.

(16) Addition of diazomethene to **1c** was slow at 0° and required only 24 hr at room temperature to give a 90% yield of the pyrazoline, which was photolyzed to dimethyl bicyclo[3.1.0]hexane-1,5-dicarboxylate (see Experimental Section). However, no pyrazoline formation was observed with **1d** even after several days at room temperature with excess diazomethane.

hydrolyzed to their respective acids, **12** and **13**. A Hunsdiecker reaction[17] using mercuric oxide and bromine on half-ester **9** did not produce the desired compound, methyl 4-bromobicyclo[2.1.0]pentane-1-carboxylate, the bicyclo[2.1.0]pentane nucleus being apparently unstable to these reaction conditions.[18,19]

Preparation of methyl bicyclo[2.1.0]pentane-1-carboxylate (**14**) was accomplished according to the procedures of Dauben[7] and Gassman,[8] and is outlined in Scheme II[20,21] starting from commercially available

Scheme II



cyclobutane-1,1-dicarboxylic acid. Ester **14** was hydrolyzed to bicyclo[2.1.0]pentane-1-carboxylic acid (**15**).

Experimental Section[22]

General Procedure for Synthesis of Dimethyl α,α′-Dibromoalkanedicarboxylates (2).—The method applied to the conversion of adipic acid to dimethyl α,α′-dibromoadipate[12] of stepwise reactions of the diacid with thionyl chloride, bromine, and methanol was employed.

Dimethyl α,α′-Dibromoglutarate (2a).—Glutaric acid (50 g) produced after distillation [120° (0.01 mm)] 126 g (90%) of **2a** as a viscous liquid: ir (thin film) 1740 cm^{-1} (C=O); nmr (CCl_4) τ 5.33–5.75 (m, $C_\alpha H$'s, 2), 6.15 (s, OCH_3, 6), 7.05–7.45 (m, $C_\beta H_2$'s, 2).

Dimethyl α,α′-Dibromoadipate (2b).—Adipic acid (220 g) produced after distillation [175–180° (0.2 mm)] 450 g (90%) of **2b**: ir (thin film) 1730 cm^{-1} (C=O); nmr (CCl_4) τ 5.5–5.9 (m, $C_\alpha H$'s, 2), 6.20 (s, OCH_3, 6), and 7.5–8.0 (m, $C_\beta H_2$'s, 4).

Dimethyl α,α′-Dibromopimelate (2c).—Pimelic acid (25 g) produced after distillation [130–140° (0.01 mm)] 52.5 g (96%) of viscous, liquid **2c**: ir (thin film) 1740 cm^{-1} (C=O); nmr (CCl_4) τ 5.33–5.74 (m, $C_\alpha H$'s, 2), 6.15 (s, OCH_3, 6), 7.6–8.15 [m (shape of triplet centered at τ 7.95, J = 6.5 Hz), $C_\beta H_2$'s, 4], and 8.15–8.70 (m, $C_\gamma H_2$, 2).

Dimethyl α,α′-Dibromosuberate (2d).—Suberic acid (25 g) gave after distillation [110–120° (0.01 mm)] 48.0 g (93%) of yellowish, viscous **2d**: ir (thin film) 1740 cm^{-1} (C=O); nmr (CCl_4) τ 5.73 [t center (J = 7.0 Hz), $C_\alpha H$'s, 2], 6.18 (s, OCH_3, 6), 7.6–8.2 (m, $C_\beta H_2$'s, 4), and 8.2–8.7 (m, $C_\gamma H_2$'s, 4).

Dimethyl α,α′-Dibromoazelate (2e).—Azelaic acid (50 g) produced after distillation [120–130° (0.01 mm)] 92.1 g (92%) of viscous **2e**: ir (thin film) 1740 cm^{-1} (C=O); nmr (CCl_4) τ 5.87 [t center (J = 7.4 Hz), $C_\alpha H$'s, 2], 6.21 (s, OCH_3, 6), 7.6–8.3 (m, $C_\beta H_2$'s, 4), and 8.3–8.8 (m, $C_\gamma H_2$'s and $C_\delta H_2$'s, 6).

Dimethyl α,α′-Dibromosebacate (2f).—Sebacic acid (50 g) gave after distillation [120–130° (0.01 mm)] 89.0 g (91%) of viscous **2f**: ir (thin film) 1740 cm^{-1} (C=O); nmr (CCl_4) τ 5.87 [t center (J = 7.2 Hz), $C_\alpha H$'s, 2], 6.21 (s, OCH_3, 6), 7.6–8.3 (m, $C_\beta H_2$'s, 4), and 8.3–8.8 (m, $C_\gamma H_2$'s and $C_\delta H_2$'s, 8).

Dimethyl Δ¹-Cyclobutene-1,2-dicarboxylate (1b). General Procedure.[23,24]—To 50.0 g (150 mmol) of dimethyl α,α′-dibromoadipate in 350 ml of dry dimethylformamide, cooled to ice-bath temperature, was added 13.2 g (310 mequiv) of sodium hydride (57% in mineral oil). After a few minutes of vigorous stirring, the ice bath was removed and the stirring was continued until the evolution of hydrogen had ceased (about 4 hr) and the mixture had taken on a slight yellow color. If the evolution of hydrogen became too rapid, since the reaction was exothermic, a steady evolution of hydrogen could be reestablished by control with the ice bath. To the reaction mixture was added 600 ml of ether. The precipitate of sodium bromide and unreacted sodium hydride could be removed by filtration. The filtrate was then extracted with four 150-ml portions of brine to remove the DMF. The aqueous layers obtained were washed several times with additional ether. The ether solutions were combined and dried ($MgSO_4$). The ether was then removed at reduced pressure leaving a reddish-brown liquid residue.

This liquid was trap to trap distilled [65–100° (0.1 mm)], giving a product composed mainly of white solid. This crude distillate was fractionated using an 8-in. Vigreux column with collection of the lower boiling fraction [60–80° (1 mm)] giving 17.5 g of product. Analysis of glpc on a 6 ft × 0.25 in. 10% QF-1 on Anachrom ABS column showed one main component and about 15% impurity. Correction for impurities gave a yield of 68%. The ir[13b] and nmr spectra[25] agreed with those reported. The product could be further purified by recrystallization from ether–hexane, mp 44–45° (lit.[13b] mp 45°).

Dimethyl Δ¹-Cyclopentene-1,2-dicarboxylate (1c).—Dimethyl α,α′-dibromopimelate (20.0 g, 60.5 mmol) and 5.5 g (131 mequiv) of sodium hydride (57% in oil) in 250 ml of dry DMF were stirred at ice-bath temperature for 1.5 hr until hydrogen evolution had ceased and the mixture had become yellowish. After work-up and trap-to-trap distillation [100° (0.01 mm)], 7.73 g of product was obtained. Glpc analysis showed the presence of 9% impurities, giving a corrected yield of 69% of **1c**: ir (thin film) 1725 (C=O) and 1650 cm^{-1} (C=C); nmr (CCl_4) τ 6.30 (s, OCH_3, 6), 7.29 [t (complex) (J = 7.0 Hz), allylic methylene protons, 4], and 7.95 [q (complex) (J = 7.0 Hz), central methylene protons, 2]. An analytical sample was collected by glpc and trap to trap distilled.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.30; H, 6.95.

Dimethyl Δ¹-Cyclohexene-1,2-dicarboxylate (1d).—Dimethyl α,α′-dibromosuberate (48 g, 133 mmol) and 15 g (313 mequiv) of sodium hydride (57% in oil) in 300 ml of dry DMF were stirred at ice-bath temperature for 3 hr (hydrogen evolution slowed considerably after 2.5 hr). After work-up and trap-to-trap distillation [100° (0.01 mm)], 18.73 g (71%) of **1d** was obtained which was "pure" as judged from its nmr spectrum: ir (thin film) 1740 (C=O) and 1650 cm^{-1} (C=C); nmr (CCl_4) τ 6.33 (s, OCH_3, 6), 7.5–8.0 [m (A_2B_2 pattern with a characteristic peak at τ 7.71), allylic methylene protons, 4], 8.0–8.5 [m (A_2B_2 pattern with a characteristic peak at τ 8.33), central methylene protons, 4]. An analytical sample was collected by glpc and trap to trap distilled.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.73; H, 7 28.

Dimethyl Δ¹-Cycloheptene-1,2-dicarboxylate (1e).—Dimethyl α,α′-dibromoazelate (20.0 g, 53.5 mmol) and 4.52 g (107 mequiv) of sodium hydride (57% in oil) in 200 ml of dry DMF were stirred

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(18) R. Criegee and R. Rimmelin, *Chem. Ber.*, **90**, 414 (1957).
(19) R. T. LaLonde, *J. Amer. Chem. Soc.*, **87**, 4217 (1965).
(20) J. Cason and F. Allen, *J. Org. Chem.*, **14**, 1036 (1949).
(21) A. Cambell and H. N. Rydon, *J. Chem. Soc.*, 3002 (1953).
(22) All melting points were determined on a Kofler hot stage. Boiling points are uncorrected. "Boiling points" for trap-to-trap distillations are pot temperatures. Infrared and nmr spectra were obtained on a P-E 137 spectrophotometer and on Varian A-60 and T-60 spectrometers. Gas chromatographic analyses were performed using a F & M Model 500 temperature-programmed gas chromatograph. Near infrared spectra were obtained on a Cary 14 spectrophotometer. Microanalyses were done by Atlantic Microlabs, Inc., Atlanta, Ga. Mass spectra were determined on a MS-9 spectrometer.

(23) The authors wish to thank Mr. David Cole for repetition of this experiment and consistently obtaining the higher yield reported here. R. N. McDonald and R. R. Reitz [*Chem. Commun.*, 90 (1971)] previously reported the yield of **1b** to be 48%.
(24) Dr. J. Bloomfield has informed us that when this reaction is run on a 1-mol scale a large exotherm is observed. A large flask and cooling should be employed.
(25) D. Seebach, *Chem. Ber.*, **97**, 2953 (1964).

for 24 hr at room temperature. After work-up and trap-to-trap distillation [110° (0.01 mm)], 2.42 g (21%) of **1e** was obtained pure by nmr and glpc: ir (thin film) 1725 (C=O) and 1640 cm^{-1} (C=C); nmr (CCl_4) τ 6.33 (s, OCH_3, 6), 7.4–7.6 (m, allylic methylene protons, 4), and 8.2–8.6 (m, central methylene protons, 6). An analytical sample was collected by glpc and trap to trap distilled.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.55; H, 7.78.

Reactions of Dimethyl α,α'-Dibromoglutarate (2a) with Strong Bases. A. With Sodium Hydride.—**2a** (10.0 g, 31.4 mmol) and 2.5 g (58 mequiv) of sodium hydride (57% in oil) in 125 ml of dry DMF were stirred at ice-bath temperature for 1.5 hr (hydrogen evolution had ceased). After work-up and trap-to-trap distillation [90° (0.01 mm)], 5.80 g (77%) of a colorless liquid product was obtained. Nmr spectral and glpc analysis showed this to be a 1:3 mixture of the dimethyl esters of 1-bromo-*cis*- and -*trans*-cyclopropane-1,2-dicarboxylic acid (**3**). Glpc collection gave pure samples of each diester.

The data on *cis*-**3** are as follows: ir (thin film) 1740 (C=O) and 1025 cm^{-1} (cyclopropyl CH_2); nmr (CCl_4) τ 6.27 (s, OCH_3, 3), 6.32 (s, OCH_3, 3), 7.62 [m (four lines), methine proton, 1], 7.93 [m (four lines), ring proton cis to CO_2CH_3's, 1], 8.39 [m (four lines), ring proton trans to CO_2CH_3's, 1], and coupling constants for the ABC pattern J (trans) = 7.0, J (cis) = 9.2, and J (geminal) = −6.0 Hz.

Anal. Calcd for $C_7H_9O_4Br$: C, 35.47; H, 3.83. Found: C, 35.72; H, 3.98.

The data on *trans*-**3** are as follows: ir (thin film) 1730 (C=O) and 1030 cm^{-1} (cyclopropyl CH_2); nmr (CCl_4) τ 6.23 (s, OCH_3, 3), 6.26 (s, OCH_3, 3), 7.48 [m (four lines), methine proton, 1], 7.9–8.3 [m (characteristic peaks at τ 7.96, 8.05, 8.20, and 8.22), methylene protons, 2], and coupling constants for the ABC pattern J (trans) = 7.8, J (cis) = 8.8, and J (geminal) = −6.0 Hz.

Anal. Calcd for $C_7H_9O_4Br$: C, 35.47; H, 3.83. Found: C, 35.80; H, 3.85.

B. With 2 Equiv of Potassium *tert*-Butoxide.—A solution of potassium *tert*-butoxide in *tert*-butyl alcohol [prepared from 5.0 g (0.128 g-atom) of potassium and 100 ml of *tert*-butyl alcohol] was added dropwise over a 1-hr period to 20.0 g (62.9 mmol) of **2a** in 60 ml of *tert*-butyl alcohol. A precipitate of potassium bromide formed immediately. After addition of the base was complete, the reaction was stirred for an additional 0.5 hr at room temperature. Ether (300 ml) was added and the ether solution was washed with three 200-ml portions of water, dried ($MgSO_4$), and concentrated. The residue was trap to trap distilled [100° (0.01 mm)] giving 7.73 g of colorless liquid. Glpc analysis on a 10 ft × 0.25 in. 10% Carbowax on Chromosorb W column showed the presence of two components in a ratio of 13:87. These components were preparatively collected and identified.

The first component (8.6%) was assigned the structure of dimethyl 1-methoxy-*cis*-cyclopropane-1,2-dicarboxylate: ir (thin film) 1730 (C=O) and 1030 cm^{-1} (cyclopropyl CH_2); nmr (CCl_4) τ 6.30 (s, OCH_3, 3), 6.33 (s, OCH_3, 3), 6.59 (s, OCH_3, 3), 7.89 [m (four lines), methine proton, 1], 8.23 [m (four lines), CH_2 ring proton cis to CO_2CH_3's, 1], 8.62 [m (four lines), CH_2 ring proton trans to CO_2CH_3's, 1]. The coupling constants for the ABC pattern were J (trans) = 7.5, J (cis) = 10.0, and J (geminal) = −5.4 Hz.

Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.42. Found: C, 51.46; H, 6.72.

The second component (46.3%) was assigned the structure of dimethyl 1-*tert*-butoxy-*cis*-cyclopropane-1,2-dicarboxylate: ir (thin film) 1730 cm^{-1} (C=O); nmr (CCl_4) τ 6.35 (s, OCH_3, 3), 6.38 (s, OCH_3, 3), 7.92 [m (four lines), methine proton, 1], 8.25 [m (four lines), CH_2 ring proton cis to CO_2CH_3's, 1], 8.62 [m (four lines), CH_2 ring proton trans to CO_2CH_3's, 1], and 8.76 [s, $OC(CH_3)_3$, 9]. The coupling constants for the ABC pattern were J (trans) = 7.5, J (cis) = 9.5, and J (geminal) = −5.0 Hz.

Anal. Calcd for $C_{11}H_{18}O_6$: C, 57.38; H, 7.88. Found: C, 57.46; H, 7.97.

C. With 1 Equiv of Potassium *tert*-Butoxide.—A solution of potassium *tert*-butoxide in *tert*-butyl alcohol [prepared from 3.9 g (0.095 g-atom) of potassium and 50 ml of *tert*-butyl alcohol] was added dropwise to 30 g (95 mmol) of **2a** in 30 ml of *tert*-butyl alcohol. The reaction was worked up in the same manner as was the reaction with 2 equiv of base. Trap-to-trap distillation [100° (0.01 mm)] gave 16.9 g of colorless liquid. An nmr spectrum of this crude product showed starting material and several other ester products. These other ester products were identified by glpc analysis by comparison of retention times with those of authentic samples. Glpc analysis using a 6 ft × 0.25 in. 10% DEGS on Anakrom ABS column showed the presence of four peaks with the following retention times and relative percentages: 10.3 (18%), 11.0 (22%), 11.6 (14%), and 13.8 min (46%). These compounds were assigned the structures of the dimethyl esters of 1-methoxy-*cis*-, 1-*tert*-butoxy-*cis*-, 1-bromo-*cis*-, and 1-bromo-*trans*-cyclopropane-1,2-dicarboxylic acids, respectively, from their glpc retention times compared with those of authentic samples.

Reaction of Dimethyl 1-Bromo-*cis*- and -*trans*-cyclopropane-1,2-dicarboxylate with 1 Equiv of Potassium *tert*-Butoxide.—To 1.673 g (7.06 mmol) of dimethyl 1-bromo-*cis*- and -*trans*-cyclopropane-1,2-dicarboxylate (**3**) in 20 ml of *tert*-butyl alcohol was added 0.80 g (7.15 mequiv) of potassium *tert*-butoxide (MSA Research Corp.). A precipitate formed immediately. The reaction was worked up in the same manner as described above, giving 0.7 g of liquid. Glpc analysis showed three main products which were identified, by retention time comparison with authentic samples, as the dimethyl esters of 1-methoxy-*cis*- (38%), 1-*tert*-butoxy-*cis*- (31%), and 1-bromo-*trans*-cyclopropane-1,2-dicarboxylic acids (31%).

1-*tert*-Butoxy-*cis*- and 1-Methoxy-*cis*-cyclopropane-1,2-dicarboxylic Anhydride.—A 1.0-g sample of an 87:13 mixture of the dimethyl esters of 1-*tert*-butoxy-*cis*- and 1-methoxy-*cis*-cyclopropane-1,2-dicarboxylic acids was treated with excess potassium hydroxide in 80% methanol under reflux for 1 hr. Work-up was in the usual manner, giving about 0.2 g of crude diacids, ir (Fluorolube mull) 2400–3400 (acid OH) and 1700 cm^{-1} (C=O). This crude mixture of diacids was allowed to stir at 50° in 15 ml of acetic anhydride for 30 min. The resulting mixture of anhydrides was trap to trap distilled [70–80° (0.01 mm)] giving a small amount of colorless liquid which solidified upon standing: ir (thin film) 1850 and 1780 cm^{-1} (C=O); nmr (CCl_4) τ 6.40 (s, OCH_3), 7.08–7.32 [m (four lines)], 7.7–8.3 (m), and 8.68 [s, $OC(CH_3)_3$]. This mixture of anhydrides was hydrolyzed in warm water and extracted into ether. The ether solution was treated with excess diazomethane in ether, which after concentration, gave the starting methyl esters as shown from nmr spectral comparison.

Dimethyl 2,3-Diazabicyclo[3.2.0]hept-2-ene-1,5-dicarboxylate (7).—An ether solution (800 ml) of diazomethane (prepared from 26 g of *N*-nitroso-*N*-methylurea) and 21.40 g (0.125 mol) of dimethyl Δ^1-cyclobutene-1,2-dicarboxylate was allowed to stand in the refrigerator (0–10°) for 20 hr, after which an nmr spectrum of an aliquot showed no starting material remaining. Excess diazomethane and ether were distilled off and the residue was recrystallized from ether–hexane and sublimed [50° (0.01 mm)], giving 24.87 g (92%) of crystalline **7**: mp 38–39°; ir (thin film) 1740 (C=O) and 1550 cm^{-1} (N=N); nmr (CCl_4) τ 5.18 [q (J = 18 Hz), CH_2N, 2], 6.29 (s, OCH_3 3), 6.34 (s, OCH_3, 3) 6.8–8.7 (complex m, cyclobutane ring protons, 4).

Anal. Calcd for $C_9H_{12}O_4N_2$: C, 50.94; H, 5.70. Found: C, 50.94; H, 5.81.

Dimethyl 2,3-Diazabicyclo[3.3.0]oct-2-ene-1,5-dicarboxylate.—Dimethyl Δ^1-cyclopentene-1,2-dicarboxylate (8.49 g, 46.1 mmol) was allowed to stand in a solution of excess diazomethane in ether in the refrigerator (0–10°) for 3 days, after which time the nmr spectrum showed that about 50% reaction had taken place. After the solution had stood for an additional day at 25°, no starting material remained. The mixture was concentrated and the liquid product was trap to trap distilled [100° (0.01 mm)] giving 9.45 g of colorless liquid that showed about 10% impurity by nmr spectral analysis (90% yield). A second distillation left only 5% impurity: ir (thin film) 1740 (C=O) and 1560 cm^{-1} (N=N); nmr (CCl_4) τ 5.20 [q (J = 18.2 Hz), CH_2N, 2], 6.35 (s, OCH_3, 3), 6.38 (s, OCH_3, 3), and 7.4–9.1 [m (characteristic peaks at τ 7.47, 7.54, 7.62, 7.70, and 8.30), cyclopentane ring protons, 6].

Dimethyl Bicyclo[2.1.0]pentane-1,4-dicarboxylate (6).—A solution of 10.0 g (47.1 mmol) of pyrazoline **7** in 600 ml of ether was irradiated for 6 hr with a Hanovia 450-W lamp (type L) using a quartz immersion well and a Corex filter. The temperature was kept near 25° by circulating tap water through the jacketed well. Evolution of nitrogen could be observed as the reaction proceeded. Progress of the reaction was followed *via* the nmr spectra of small aliquots. The ether solution was concentrated to a yellow liquid, which was chromatographed on 150 g of neutral, activity 3 alumina with benzene to remove polymer. Trap-to-trap distillation [60–70° (0.001 mm)] of the benzene eluted product from

two 10-g runs gave 9.45 g of liquid. Glpc analysis on a 6 ft × 0.25 in. 10% Carbowax on Chromosorb P column showed the presence of four components. Their retention times and percent compositions were 2.7 (1.7%), 4.0 (5.5%), 5.4 (4.2%), and 6.6 min (88.5%). The first peak was identified as diester **1b** by retention time comparison with that of an authentic sample. The second and third components were collected and their ir and nmr spectra indicated then to be olefinic products of unknown structure. The major component, peak four, was the desired product; however, thermal rearrangement occurred on the glpc column as a collected sample indicated the rearranged product to probably be dimethyl Δ^1- or Δ^5-cyclopentene-1,3-dicarboxylate: ir (thin film) 1720 (C=O) and 1640 cm^{-1} (C=C); nmr (CCl_4) τ 3.40 [m (crude triplet) (J = 3 Hz), vinyl proton, 1], 6.30 (s, OCH_3, 3), 6.32 (s, OCH_3, 3), and 7.2–7.9 (m, 5).

Dimethyl bicyclo[2.1.0]pentane-1,4-dicarboxylate (**6**) was purified by recrystallization from hexane at Dry Ice–acetone bath temperature. Assuming the distilled product to be 88.5% pure, the corrected yield was 51%. Pure material had a melting point between 10 and 20°; ir (thin film) 1730 cm^{-1} (C=O); nmr (CCl_4) τ 6.36 (s, OCH_3, 6), 7.25–7.83 [m (characteristic peaks at τ 7.41, 7.53, and 7.65), exo ring protons, 3], 8.10–8.68 [m (characteristic peaks at τ 8.40, 8.43, and 8.51), endo ring protons, 3]; near-ir (CCl_4) 1.636 μ (ϵ 0.33).

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 58.84; H, 6.66.

Photolysis of Dimethyl 2,3-Diazabicyclo[3.3.0]oct-2-ene-1,5-dicarboxylate to Produce Dimethyl Bicyclo[3.1.0]hexane-1,5-dicarboxylate.—Dimethyl 2,3-diazabicyclo[3.3.0]oct-2-ene-1,5-dicarboxylate (8.25 g, 36.4 mmol) (corrected for 5% impurity) was photolyzed using the same conditions as employed above for dimethyl 2,3-diazabicyclo[3.2.0]hept-2-ene-1,5-dicarboxylate. After 1.25 hr the nmr spectrum of an aliquot showed no starting material remaining. The product was trap to trap distilled [100° (0.01 mm)], giving 7.29 g of colorless liquid. The product was identified as dimethyl bicyclo[3.1.0]hexane-1,5-dicarboxylate by comparison of its nmr spectrum and of glpc retention times with those of an authentic sample.[2] The distilled product was shown to be 88% pure by glpc analysis, which gave a corrected yield of 84%.

Bicyclo[2.1.0]pentane-1,4-dicarboxylic Acid (8).—To 2.395 g (13 mmol) of **6** dissolved in 20 ml of 80% methanol was added 3.0 g (55 mequiv) of potassium hydroxide in 10 ml of 80% methanol. The mixture was allowed to stand at room temperature for 2 days, concentrated by flash evaporation, diluted to 35 ml with water, acidified to pH 2, and continuously extracted with ether for 10 hr. The ether extract was dried ($MgSO_4$) and concentrated, giving a white solid that produced 1.675 g (82.5%) of product upon recrystallization from ethyl acetate–hexane: mp 169–170° (some decomposition); ir (Fluorolube mull) 2200–3300 (acid OH) and 1700 cm^{-1} (C=O). Reaction of a small portion of this diacid with diazomethane in ether gave the starting diester.

Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 54.10; H, 5.34.

4-Carbomethoxybicyclo[2.1.0]pentane-1-carboxylic Acid (9).—A solution of 8.31 g (0.126 equiv) of potassium hydroxide and 50 ml of methanol was added dropwise over a 4-hr period to 23.25 g (0.126 mol) of **6** dissolved in 50 ml of methanol at room temperature. The mixture was stirred for 12 hr, concentrated, and diluted with 50 ml of water. The remaining diester was extracted with ether before saturating the solution with sodium chloride and acidifying to pH 2. The acidified solution was continuously extracted with ether for 10 hr, and the extracts were dried ($MgSO_4$) and concentrated, giving a viscous liquid that crystallized. This material was recrystallized from ether–cyclohexane and sublimed twice [90° (0.01 mm)], giving 15.10 g (67%) of the desired half-ester: mp 71–72°; ir (Fluorolube mull) 2400–3300 (acid OH), 1720 (ester C=O), and 1690 cm^{-1} (acid C=O); nmr (CCl_4) τ −1.3 (s, CO_2H, 1), 6.32 (s, OCH_3, 3), 7.3–8.8 [m (characteristic peaks at τ 7.39 and 7.49), exo ring protons, 3], and 8.0–8.7 [m (characteristic peaks at τ 8.35, 8.39, 8.44, and 8.50), endo ring protons, 3]; mass spectrum (70 eV, direct insert) $M\cdot^+$ at m/e 170.

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.71; H, 6.00.

Methyl 4-Carbamylbicyclo[2.1.0]pentane-1-carboxylate (10).—A solution of 3.00 g (17.6 mmol) of **9** and 2.6 ml (18.61 mmol) of triethylamine in 40 ml of chloroform was cooled in an ice bath and 1.6 ml (20 mmol) of ethyl chloroformate was added rapidly with stirring. After 15 min anhydrous ammonia was bubbled through the solution (immediate formation of a precipitate) for 1 hr. After standing at room temperature for 3 hr, the mixture was filtered and concentrated, giving a viscous liquid which was crystallized from ether–hexane giving 2.05 g (69%) of the product: mp 81.5–82.5°; ir (Fluorolube mull) 3300 and 3120 (NH), 1725 (ester C=O), 1665 (carbamyl C=O), and 1625 cm^{-1} (carbamyl); nmr ($DCCl_3$) τ 3.5–4.8 (broad m, NH_2, 2), 6.24 (s, OCH_3, 3), 7.4–7.7 (m, 2), 7.7–8.0 (m, 1), and 8.0–8.6 [m (characteristic peaks at τ 8.21, 8.28, 8.31, and 8.43), 3]; mass spectrum (70 eV, direct insert) $M\cdot^+$ at m/e 169.

Anal. Calcd for $C_8H_{11}O_3N$: C, 56.80; H, 6.55. Found: C, 56.98; H, 6.69.

4-Carbamylbicyclo[2.1.0]pentane-1-carboxylic Acid (12).—Ester **10** (0.88 g, 5.2 mmol) was stirred with 1.2 g (21 mequiv) of potassium hydroxide in 50 ml of 80% methanol for 4 hr. The mixture was concentrated and diluted with 25 ml of water. The solution was then washed with ether, acidified, saturated with sodium chloride, and continuously extracted with ether for 2.5 days. The final ether extract was concentrated and the product was recrystallized from ethyl acetate–hexane, giving 0.60g (75%) of the product: mp 179–182° dec; ir (Fluorolube mull) 3450 and 3290 (NH), 2200–2600 (acid OH), 1900 (broad hydrogen-bonded peak), and 1675 cm^{-1} (C=O).

Anal. Calcd for $C_7H_9O_3N$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.38; H, 5.96; N, 9.15.

Methyl 4-Cyanobicyclo[2.1.0]pentane-1-carboxylate (11).—A solution of 2.00 g (11.8 mmol) of **10** and 5.0 g (33 mmol) of phosphorus oxychloride in 40 ml of ethylene dichloride was stirred at 75–80° for 30 min, after which the evolution of hydrogen chloride could not be observed. The reaction mixture was diluted with chloroform and eluted rapidly over 70 g of neutral, activity 3 alumina with chloroform. Heat was given off as the solution passed down the column. The eluent was trap to trap distilled [80° (0.001 mm)], giving 1.335 g of colorless liquid which was shown by nmr spectroscopy to contain three major methyl ester components. This mixture was chromatographed over 100 g of neutral, activity 2–3 alumina. The desired product began eluting from the column using 85:15 benzene–CCl_4 and trailed in small amounts until methylene chloride eluted the remaining product in fairly pure form. The impurities were not isolated or characterized. The fractions containing the product were combined and distilled using a Hickman still, giving 190 mg of colorless liquid (pure by nmr): ir (thin film) 2225 (C=N) and 1730 cm^{-1} (C=O); nmr (CCl_4) τ 6.27 (s, OCH_3, 3), 7.3–7.7 (m, 2), 7.7–8.0 (m, 1), and 8.1–8.5 [m (characteristic peaks at τ 8.30 and 8.39), 3].

4-Cyanobicyclo[2.1.0]pentane-1-carboxylic Acid (13).—Ester **11** (190 mg, 1.26 mmol) was hydrolyzed with 0.3 g (5 mequiv) of potassium hydroxide in 15 ml of 80% methanol for 2 hr. The mixture was concentrated, diluted with 20 ml of water, saturated with sodium chloride, acidified to pH 2, and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated. The residue was recrystallized from ether–hexane, giving 130 mg (75%) of long needles which were further purified by sublimation [80° (0.01 mm)]: mp 112.5–113.5°; ir (Fluorolube mull) 2400–3300 (acid OH), 2220 (C=N), and 1675 cm^{-1} (C=O).

Anal. Calcd for $C_7H_7O_2N$: C, 61.31; H, 5.14. Found: C, 61.43; H, 5.22.

Bicyclo[2.1.0]pentane-1-carboxylic Acid (15).—Ester **14**[7] (0.870 g, 6.9 mmol) was treated with 1.2 g (21 mequiv) of potassium hydroxide in 20 ml of 80% methanol for 24 hr. The solution was concentrated, diluted with water, acidified, and extracted with ether. The ether extract was dried ($MgSO_4$), and the small amount of product (loss of a good portion due to a laboratory accident on evaporation of the solvent) was distilled [50° (0.001 mm)] using a Hickman still, giving 211 mg (27%) of colorless liquid: ir (thin film) 2400–3300 (acid OH) and 1700 cm^{-1} (C=O); nmr (CCl_4) τ −1.3 (s, CO_2H, 1), 7.2–8.1 (m, 3), and 8.1–8.9 (m, 4).

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 63.90; H, 7.24.

Registry No.—**1c**, 13368-79-1; **1d**, 4336-19-0; **1e**, 31150-45-5; **2a**, 869-09-0; **2b**, 868-72-4; **2c**, 868-73-5; **2d**, 868-74-6; **2e**, 18281-62-4; **2f**, 34731-71-0; *cis*-**3**, 30630-38-7; *trans*-**3**, 30630-39-8; **6**, 22248-45-9; **7**, 22248-46-0; **8**, 34731-76-5; **9**, 34731-77-6; **10**, 34731-

78-7; **11**, 34731-79-8; **12**, 34731-80-1; **13**, 34731-81-2; **15**, 32811-83-9; dimethyl 1-methoxy-*cis*-cyclopropane-1,2-dicarboxylate, 30630-35-4; dimethyl 1-*tert*-butoxy-*cis*-cyclopropane-1,2-dicarboxylate, 30630-40-1.

Acknowledgment.—The authors wish to thank the National Science Foundation (GP-7818, GP-10691) for support of this research and for matching funds to purchase the T-60 and MS-9 spectrometers.

Conformational Analysis. LXXXV. The *cis,cis*-1,6-Cyclodecadiene System[1,2a]

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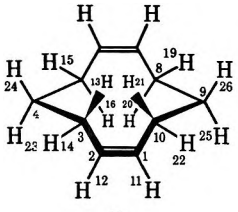
Received December 21, 1971

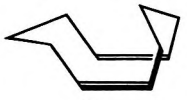
Molecular force field calculations were carried out on *cis,cis*-1,6-cyclodecadiene and on *cis,cis*-cyclodeca-3,8-diene-1,6-dione. The former is calculated to be a 65:35 mixture of chair and boat forms. The bond lengths and angles are in good agreement with the electron diffraction values. The dione is calculated to be a mixture of chair, boat, half-boat in the ratio of 0.59, 0.32, 0.09. Bond lengths and angles are predicted. The dipole moment of the mixture is calculated to be 1.5 D and measured experimentally as 1.4 D. The heats of formation were also calculated.

A great many studies have been reported on the conformational analysis of the 1,6-cyclodecadiene ring system (I) during the past several years.[3-14] These have included a variety of nmr studies of the hydrocarbon itself and a number of derivatives, an electron diffraction study of the hydrocarbon (I) in the gas phase, and an X-ray study of the crystalline dione derivative (II), among others. In each case it was concluded that the chair conformation (Ia, IIa) was the predominant or exclusive structure present.



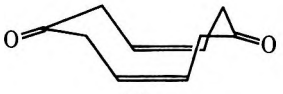
Ia

Ib

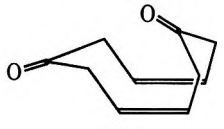


Ic

IIa



IIb



IIc

Earlier papers have described force field calculations which permit us to determine with reasonable accuracy the molecular geometries and conformational energies of various kinds of molecules, including alkanes,[15] alkenes,[1] and ketones.[16] The calculations deal with all of the usual steric effects, torsion, etc., and a classical electrostatic calculation between dipoles is used to allow for interaction between polar groups (double bonds and carbonyl groups).[17]

We have studied the three conformations which models indicate most probable: The chair conformation of symmetry C_{2h} (a), the boat conformation of C_{2v} (b), and a conformation of symmetry C_s (c). We have examined separately the parent hydrocarbons I, and also the diketo derivatives II.

Our calculations give relative energies for Ia, Ib, and Ic of 0.0, 0.34, and 5.01 kcal/mol, respectively. These calculations suggest that the chair conformation (Ia) will predominate over the boat (Ib) by about 65:35 at room temperature, and the amount of the C_s conformation will be negligible. Since the two former structures each have a symmetry number of 2, the predominance of the chair form will increase with a lowering of temperature, and this seems to be consistent with the electron diffraction work. The available experimental nmr work has been interpreted in terms of a single stable conformation (Ia) at low temperatures, which rapidly inverts at higher (room) temperature.

The calculated structure for the chair form is compared with the electron diffraction structure in Table I.

Dale[5,6] has suggested from double bond isomerization studies in some C_6–C_{24} cyclic dienes that in the C_6, C_{10}, and C_{14} ring series the conformation with the cis double bonds diametrically opposed is a "strain-free" one, due to the lack of intramolecular van der Waals contact between ring hydrogens and the double bond

(1) Paper LXXXIV: N. L. Allinger and J. T. Sprague, *J. Amer. Chem. Soc.*, in press.

(2) (a) Supported by Grant No. GP-15263 from the National Science Foundation; (b) inquiries concering this paper should be addressed to this author at the University of Georgia; (c) National Institutes of Health Postdoctoral Fellow, 1968–1970; (d) National Defense Education Act Predoctoral Fellow, 1966–1969.

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

(4) C. A. Grob and P. W. Schiess, *ibid.*, **47**, 558 (1964).

(5) J. Dale and C. Moussebois, *J. Chem. Soc. C*, 264 (1966).

(6) J. Dale, *Angew. Chem., Int. Ed. Engl.*, **5**, 1000 (1966).

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(12) A. Almenningen, G. G. Jacobsen, and H. M. Seip, *Acta Chem. Scand.*, **23**, 1495 (1969).

(13) J. R. Scheffer and M. L. Lungle, *Tetrahedron Lett.*, 845 (1969).

(14) A. Feigenbaum and J. Lehn, *Bull. Soc. Chim. Fr.*, 3724 (1969).

(15) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, **93**, 1637 (1971).

(16) N. L. Allinger, M. T. Tribble, and M. A. Miller, *Tetrahdron*, **28**, 1173 (1972).

(17) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *J. Amer. Chem. Soc.*, **91**, 337 (1969).

TABLE I
CALCULATED AND EXPERIMENTAL STRUCTURES OF Ia AND IIa (CHAIR FORMS)

	cis,cis-1,6-Cyclodecadiene		cis,cis-Cyclodeca-3,8-diene-1,6-dione, calcd
	Calcd	Obsd[a]	
$C_1=C_2$	1.342	1.326 ± 0.006 Å	1.341
C_2-C_3	1.508	1.506 ± 0.006 Å	1.505
C_3-C_4	1.535	1.534 ± 0.006 Å	1.515
C_1-H_{11}	1.096	1.102 ± 0.012 Å	1.096
C_4-H_{23}	1.101	1.112 ± 0.004 Å	1.223 ($C_4=O_{23}$)
$C_1C_2C_3$	128.7	128.2 ± 0.3°	128.0
$C_2C_3C_4$	112.4	112.8 ± 0.3°	111.4
$C_3C_4C_5$	112.9	114.1 ± 0.6°	117.6
$C_1C_2H_{12}$	118.0	116.6 ± 1.0°	118.2
$H_{23}C_4H_{24}$	105.5	105.6 ± 1.0°	121.2 ($C_3C_4O_{23}$)
Heat of formation gas phase, 25°, kcal/mol	+8.88		−42.02

[a] Reference 12.

π cloud. Our calculations indicate that Ia possesses a strain energy of 6.01 kcal/mol, much of which involves the two cis double bonds. The repulsion between carbons 1 and 7 in Ib amounts to 0.3 kcal/mol. This repulsion is therefore small, but not negligible.

The ketone derivatives II were also studied. As far as their relative energies, IIa and IIb do not differ much from the hydrocarbons. The chair form is again the more stable, by 0.35 kcal/mol. Approximately 0.1 kcal/mol of this energy difference is due to each of the following: torsion, van der Waals, dipole–dipole. In this case, the C_s conformation is calculated to be only 1.56 kcal/mol higher in energy than the chair conformation. It is in addition favored by entropy, since its symmetry number is only 1. Thus we calculate that IIa, IIb, and IIc will constitute mole fractions of 0.59, 0.32, and 0.09 in the molecular mixture in benzene solution (dielectric constant equals 2) at room temperature.

The relatively higher stability of the C_s conformation with the diketone, as opposed to the hydrocarbon, results from the absence of the hydrogen on the methylene group which is pointed back over the molecule. The dipole–dipole interaction energy in this conformation is actually favorable, by 0.2 kcal/mol, compared to the chair. The favorable energy can be ascribed to an attraction between the oxygen on the right in IIc and the carbonyl carbon on the left.

X-Ray crystallography has indicated that the dione exists as the chair form (IIa) in the crystal. The bond angles and bond lengths have not yet been reported. Our calculated bond angles and bond lengths are given in Table I.

To show that the molecule existed as a mixture of conformations in solution, we studied the dipole moment experimentally. The dipole moments calculated for IIa, IIb, and IIc are respectively 0, 1.63, and 3.67 D. However, because of vibrational motion (atomic polarization) we anticipate that IIa will actually show a dipole moment of about 0.7 D (as is shown by the analogous *p*-benzoquinone,[18] for the same reason). From our calculated mole fractions and these moments for the individual conformations, the calculated dipole moment[19] for the mixture is 1.53 D. If the 0.7 D moment for conformation IIa was instead taken to be 0, the calculated apparent moment for the mixture was 1.43 D. The observed moment, in benzene solution, was 1.40 ± 0.02 D. The calculated and experimental values are thus in good agreement. It may be noted that the size of the observed moment depends quite strongly on the 9% of the C_s conformation. If this conformation were not present, then conformations IIa and IIb would be present in mole fractions of 0.64 and 0.36, respectively. This mixture would give a calculated dipole moment of 0.98–1.13 D, depending on whether the 0.7 D moment for conformation IIa was or was not used.

Thus we conclude that for both the hydrocarbon and diketone, the major conformation in solution is, as previously suggested by others, the chair. The other conformations are, however, present in substantial amounts, and significantly affect the properties of the compound.

Experimental Section

A sample of *cis,cis*-cyclodeca-3,8-diene-1,6-dione (II) was kindly provided by Dr. J. J. Vollmer,[20] and was used as obtained.

The dipole moment measurements were carried out on benzene solutions at 25° using previously described procedures, apparatus, and calculations.[21]

Registry No.—Ia, 1124-79-4; IIa, 20771-23-7.

(18) A. L. McClellan, "Tables of Experimental Dipole Moments," W. H. Freeman, San Francisco, Calif., 1963, p 172.

(19) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley-Interscience, New York, N. Y., 1965, p 159.

(20) The authors are indebted to Dr. Vollmer for this sample.

(21) N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959); N. L. Allinger, H. M. Blatter, M. A. DaRooge, and L. A. Freiberg, *ibid.*, **26**, 2550 (1961).

Nuclear Magnetic Resonance Studies of *cis*- and *trans*-2,3-Dimethylcycloalkanones

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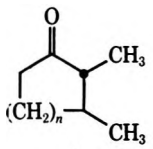
Received January 24, 1972

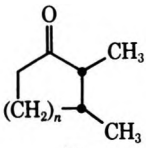
The nmr methyl shifts of six *cis*- and *trans*-2,3-dimethylcycloalkanones were identified by deuteration and pseudocontact shift techniques. The chemical shift assignments in 2,3-dimethyl-substituted C_5, C_6, and C_7 ketones indicate a preferential axial orientation of the 3-methyl protons in the respective cis isomers, while the 2-methyl protons maintain a predominant equatorial position. Conformational considerations are proposed to support this hypothesis.

Nmr investigations concerned with the configuration and conformation of 1,2-dimethylcycloalkanes have been reported.[2] The purpose of these studies was to assign the ring proton resonances of both equatorial and axial protons and to correlate these chemical shift positions with the environments of the ring.

Surprisingly, the nmr spectra of cycloalkanones of structures I and II have received little attention. In



I



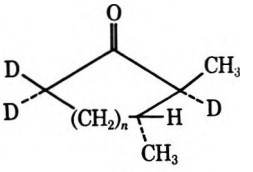
II

fact, no rigorous assignment for the 2- or 3-methyl groups in either of these isomers has been made.[3]

In the present study we describe some of the nmr studies we have made to elucidate the chemical shifts of the methyl groups in 2,3-dimethylcycloalkanones (I and II, n = 1, 2, 3) and the conformational preferences inherent in these assignments.

Results

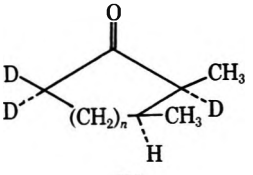
Nmr Assignments.—By use of Eu(fod)$_3$ shift reagent,[4] chemical shift assignments were made for the 2- and 3-CH_3 group protons in all of the *trans*-2,3-dimethylcycloalkanones (I). Upon complexation, the high-field methyl doublet underwent a preferential downfield displacement. This displacement was found to be twice the magnitude of the one exhibited by the low-field doublet. On the basis of this evidence, the upfield doublet was assigned to the 2-CH_3 protons and the lowfield doublet to the 3-CH_3 protons.[5] Incorporation of three deuterium atoms α to the carbonyl group through equilibration with $NaOCH_3$ in CH_3OD also supports this conclusion. The nmr spectra of the uncomplexed deuterated isomers (III) exhibited singlets in place of the high-field doublets observed in the corresponding proteo compounds (I).



III

n = 1, 2, 3

Methyl group chemical shift assignments of the cis isomers II, unlike those of the *trans* isomers I, could not be readily made using the Eu(fod)$_3$ complexation technique because of the indistinguishability of the 2- and 3-CH_3 group resonances (both doublets have the same coupling constants). However, the methyl proton chemical shift assignments for the cis isomers II were made, using the corresponding deuterated compounds IV. The nmr spectra of the uncomplexed IV,



IV

n = 1, 2, 3

unlike those of III, showed collapse of the low-field doublets to singlets. Thus, in the cis isomers II, the 2-CH_3 protons were assigned to the low-field resonance while the 3-CH_3 protons were assigned the high-field resonance position.

Further confirmation of the methyl group assignments in all six deuterated ketones have been made using Eu(fod)$_3$. In all cases the singlet methyl group resonances underwent proportionally larger downfield displacements than did the methyl group doublets [at a ratio of Eu(fod)$_3$/ketone of 0.5]. These findings further substantiate our assignments and establish unambiguously that the 2-CH_3 group resonances undergo greater displacements than the 3-CH_3.

In Table I chemical shift data are tabulated for the *cis*- aud *trans*-2,3-dimethylcycloalkanones (I and II). Two representative examples of deuterated and nondeuterated *cis*- and *trans*-2,3-dimethylcycloalkanones examined are shown in Figure 1.

Structural Assignments.—In both the cyclopentanone and cyclohexanone series, isomeric structure assignments were readily made through equilibration to the known thermodynamic mixtures respectively. In each case the trans isomer was predominant (see Experimental Section). For the cycloheptanone series, equilibration techniques were of no value, since equilibration yielded an equimolar mixture of cis and trans

(1) Eastern Marketing and Nutrition Research Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) (a) N. Muller and W. C. Tosch, *J. Chem. Phys.*, **37**, 1167 (1962); (b) J. I. Musher, *Spectrochim. Acta*, **16**, 835 (1960).

(3) One report of *trans*-2,3-dimethylcyclobutanone has made assignments for the methyl resonances. (a) J. L. Ripoll and J. M. Conia, *Bull. Soc. Chim. Fr.*, 2755 (1965). Another study has reported the nmr spectra both of *cis*- and *trans*-2,3-dimethylcyclobutanone without reference to the methyl proton assignments. (b) N. J. Turro and R. B. Gagosian, *J. Amer. Chem. Soc.*, **92**, 2036 (1970).

(4) R. E. Rondeau and R. E. Sievers, *ibid.*, **93**, 1522 (1971).

(5) This assignment is not unexpected since one might expect the α-carbonyl to exert a shielding effect on the 2 position. See L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1959, p 122. Note also that in 2- and 3-methylcyclohexanones and pentanones the 2-methyl groups resonate at higher fields due to the shielding effects of the carbonyl group.

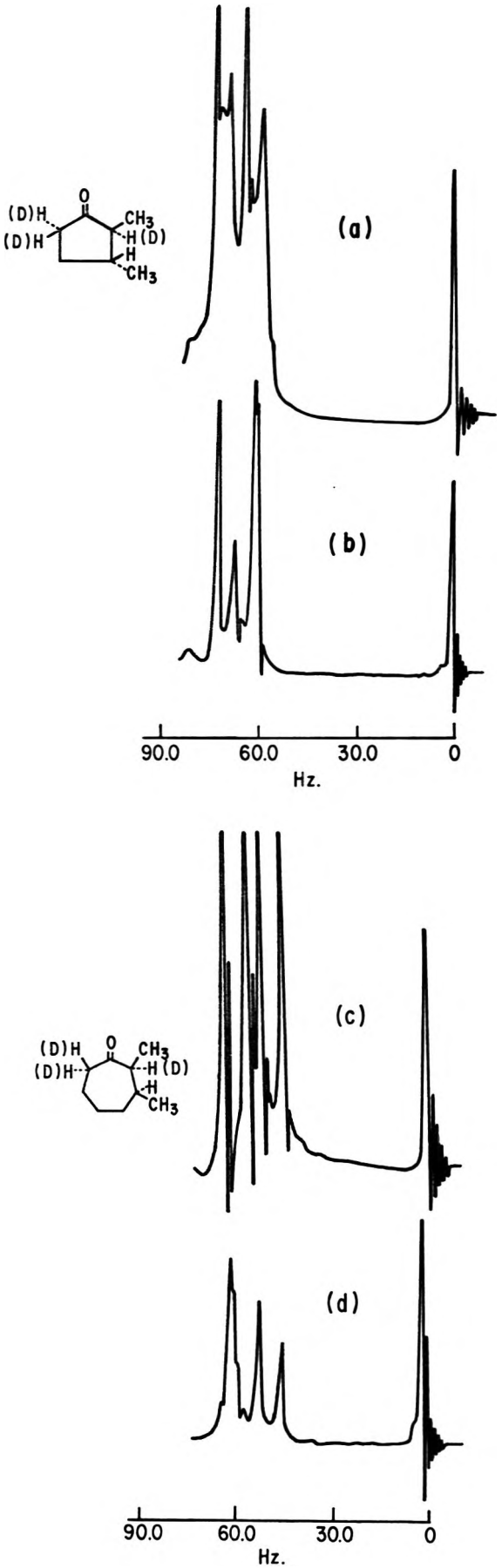
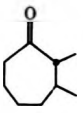
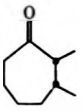


Figure 1.—Nmr spectra of the methyl protons in α-deuterated and nondeuterated *cis*- and *trans*-2,3-dimethylcycloalkanones: (a) *trans*-2,3-dimethylcyclopentanone; (b) *trans*-2,3-dimethylcyclopentanone-*2,5,5-d*$_3$; (c) *cis*-2,3-dimethylcycloheptanone; (d) *cis*-2,3-dimethylcycloheptanone-*2,7,7-d*$_3$.

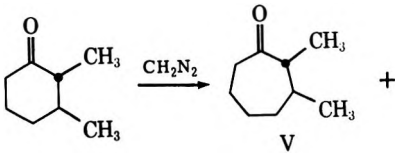
TABLE I

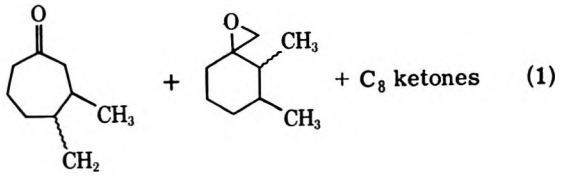
CHEMICAL SHIFTS[a] AND METHINE COUPLING CONSTANTS[b] FOR 2- AND 3-METHYL GROUP PROTONS IN 2,3-DIMETHYLCYCLOALKANONES

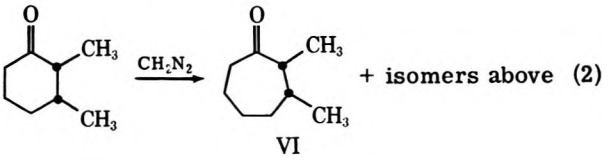
Registry no.	Ketone	δ_{2CH_3} (*J*, Hz)	δ_{3CH_3} (*J*, Hz)	Δδ (upfield) CH_3 shift in cis isomer relative to trans isomer 2-CH_3	3-CH_3
2867-24-5		60.0 (6.2)	69.0 (5.2)	4.1	14.9
2865-86-3		55.9 (7.1)	54.1 (6.9)		
1551-89-9		58.2 (6.5)	63.0 (5.6)	2.4	13.2
766-42-7		55.8 (6.9)	49.8 (7.0)		
34759-52-9		59.2 (5.9)	63.0 (6.9)	0	15.3
34759-53-0		59.1 (6.9)	47.7 (6.9)		

[a] In hertz at 60 MHz downfield from TMS as an internal standard. [b] In hertz.

isomers. However, assignments for the latter compounds could be made through an unequivocal synthesis from its next lower homolog. The isomeric cycloheptanones were each prepared by a homologization reaction of diazomethane with the corresponding cyclohexanone derivative.[6] A mixture of products was obtained.







The basic structural assignment of the 2,3-dimethylcycloheptanones V and VI was confirmed by mass spectral fragmentation of the deuterated compounds. The 2,3-dimethylcycloheptanones-*2,7,7-d*$_3$ (143) were readily distinguishable from the 3,4-dimethylcyclo-

(6) J. A. Marshall and J. J. Partridge, *J. Org. Chem.*, **33**, 4090 (1968).

heptanones-*2,7,7-d*$_3$ (144) as well as the 2,3-dimethylcyclooctanones-*2,8,8-d*$_3$ (157) and the 3,4-dimethylcyclooctanones-*2,8,8-d*$_3$ (158) by the *m/e* values of the respective molecular ions. Acyclic olefinic isomers were also eliminated as possible structures for the designated products since acylic olefinic isomers incorporate two or four deuteriums. The stereochemistry of the 2,3 isomers V and VI (eq 1 and 2) was unequivocally the same as that of the respective starting materials, since formation of V and VI through the insertion of methylene into the unsubstituted side of the carbonyl group does not disturb the original methyl–methyl relationship.

Mass spectral data substantiate the configurational assignments made for all of the 2,3-dimethylcycloalkanones. Under mass spectrometer source conditions, a preionization process occurs, giving rise to the loss of two hydrogens.[7] Since this process occurs more readily with the cis isomer, structural assignments of the cis and trans isomers were readily confirmed. The greater relative intensity of the $[M - 2]\cdot^+$ ion for each cis isomer is clearly demonstrated in Table II.

TABLE II
INTENSITY OF $[M - 2]\cdot^+$ ION RELATIVE TO $[M]\cdot^+$ IN CIS AND TRANS CYCLOALKANONES

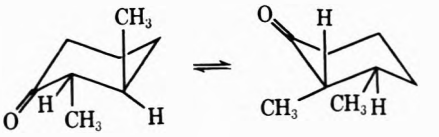
Cycloalkanone	$[M - 2]\cdot^+/[M]\cdot^+$ cis	trans
2,3-Dimethylcyclopentanone	0.25	0.1
2,3-Dimethylcyclohexanone	0.3	<0.01
2,3-Dimethylcycloheptanone	1	0.2

Discussion

All of the trans compounds exhibit higher field shifts associated with the 2-CH_3 protons, relative to the 3-CH_3, while the corresponding cis compounds show higher field shift positions for the 3-CH_3 protons (relative to the 2-CH_3). In both the trans and cis compounds of each respective ring size, the resonance positions of the 2-CH_3 protons remain constant within 4 Hz, whereas the 3-CH_3 proton resonances of the cis compounds appear at 13–15 Hz higher fields than the corresponding trans compounds. These results may be adequately explained in terms of conformational preferences.

Cyclohexanone differs very little in its geometry (chair conformation) from cyclohexane, if we disregard small deformations of the valence angles.[8] The energy differences between an axial and equatorial methyl group in 2-methyl-4-*tert*-butylcyclohexanone is 1.6 kcal/mol. The same energy is observed for the corresponding cyclohexanes. Thus, the value for the 1,3-diaxial CH_3–H interactions is given as 0.8 kcal/mol.[9] Furthermore, the 2,3-axial, equatorial, and diequatorial CH_3–CH_3 interactions of 2,3-dimethylcyclohexanones have an energy value of 0.8 kcal/mol each.[9] This value corresponds to the energy of interaction found for the CH_3–CH_3 interactions in 1,2-dimethylcyclohexane.

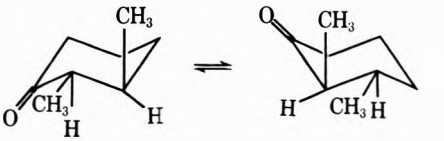
Examination of the interaction energies associated with the conformations of *trans*-2,3-dimethylcyclohexanone reveals that the diequatorial conformer VIII



diaxial interaction energy = 2.4 kcal/mol — VII

diequatorial interaction energy = 0.8 kcal/mol — VIII

predominates by about 1.6 kcal/mol. Introduction of a carbonyl group into an α position of the 1,2-dimethylcyclohexane ring has the effect of lowering the total energy of the system by removal of one 1,3-axial CH_3–H interaction.[10] Examination of *trans*-2,3-dimethylcyclohexanone reveals that one 1,3-axial CH_3–H interaction is absent in conformer VII relative to the respective cyclohexane conformer while conformer VIII has essentially the same energy content as its cyclohexane counterpart. In effect, the carbonyl group lowers the energy of the diaxial conformer VII by 0.8 kcal/mol. This is not a sufficient energy drop to change the conformer population significantly, since the diequatorial conformer VIII still predominates by 1.6 kcal/mol, a value that indicates that 93% of the molecules are in conformation VIII at room temperature. Comparison of the conformations of the *cis*-2,3-dimethylcyclohexanones shows that the carbonyl does assume a structurally important role in causing a conformational preference. This role is evident when we consider the energies associated with the corresponding *cis*-1,2-dimethylcyclohexane conformers. Since both cyclohexane conformers (equatorial, axial or axial, equatorial) have equal energy contents before introduction of the carbonyl group, preferential removal of any nonbonded interactions in one conformer should cause a shift in the equilibrium. With the introduction of the carbonyl group, the derived cyclohexanone conformer IX loses one axial CH_3–H interaction



equatorial, axial interaction energy = 1.6 kcal/mol — IX

axial, equatorial interaction energy = 2.4 kcal/mol — X

while conformer X remains essentially constant in energy content relative to the corresponding cyclohexane. Removal of the 1,3-axial CH_3–H interaction in conformer IX lowers its energy by 0.8 kcal/mol, making it more stable than X by 0.8 kcal/mol. This energy difference represents approximately a 3:1 preference for conformer IX at room temperature.

(7) (a) S. F. Osman, C. J. Dooley, and T. A. Foglia, 19th Annual Conference on Mass Spectrometry, Atlanta, Ga., May 7–14, 1971; (b) S. Osman, C. J. Dooley, T. A. Foglia, and L. M. Gregory, *Org. Mass Spectrom.*, **4**, 139 (1970).

(8) The inner angle of the carbonyl is 116° and the C–C bond of the trigonal carbon atom of the carbonyl is 1.5 Å compared to the normal C–C bonds of 1.54 Å. (a) C. C. Costain and B. P. Stoicheff, *J. Chem. Phys.*, **30**, 777 (1959). (b) R. D. Stolow, *J. Amer. Chem. Soc.*, **84**, 686 (1962).

(9) (a) N. L. Allinger, M. A. DaRooge, and R. B. Hermann, *J. Org. Chem.*, **26**, 3626 (1961). (b) M. Hanack, "Conformation Theory," Academic Press, New York, N. Y., 1965, p 109.

(10) N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **84**, 2201 (1962).

Since the 3-CH_3 protons of conformer IX are in the axial position, one might anticipate that the weighted average nmr chemical shift of the 3-CH_3 protons would be at higher fields.[11] This indeed is observed. Furthermore, since the 2-CH_3 protons still remain predominately in an equatorial environment, the chemical shift position of these protons remains relatively unchanged with respect to the trans isomer.[12]

The cycloheptanones exhibit the same chemical shift behavior as the cyclohexanones. This is not surprising, since the skewed butane 1,3-CH_3–H interactions and 1,2-CH_3–CH_3 interaction energies of cycloheptanones are the same order of magnitude as in the cyclohexanone series.[13] Again the nmr spectrum of the cis isomer shows a large upfield shift (15 Hz) for the 3-CH_3 protons, while the 2-CH_3 resonances remain relatively constant in position in both cis and trans isomers (see Table I). Although the shielding of the ring bonds on axial substituents in C_7 ring systems has not been reported, such an effect should not be considered unusual in light of the fact that the ring conformations for cycloheptanes are not very different from those of cyclohexanes.

The cyclopentanones, like the corresponding C_6 and C_7 homologs, show the same trend in the nmr shift data. However, the large number of ring conformations of the cyclopentanones (low energy barriers to interconversion) make it a difficult system to evaluate from a conformational point of view.[14] For this reason it is hard to interpret on conformational grounds why the same chemical shift phenomena are observed.

3,4-Dimethylcyclopentanone is a good model compound for demonstrating the shielding effects associated with the 3-axial CH_3 substituent. The chemical shift of the CH_3 groups in the trans isomer (equatorial, equatorial is 66.1 Hz. The CH_3 groups (equatorial, axial) in the cis isomer have an average chemical shift of 58.0 Hz. Since the *cis* isomer is a 50:50 mixture of equatorial and axial methyl groups, we can calculate that the chemical shift of the 3-axial CH_3 should be two times (66.1–58.0 Hz) or 16.2 Hz higher than the equatorial. Clearly, when the 3-CH_3 group occupies the axial position a large upfield shift is evident. This effect could be closely related to the interaction of the methyl and carbonyl group as well as the effects of the ring bonds. Again, the unusually high field resonance position exhibited by the 3-CH_3 of *cis*-2,3-dimethylcyclopentanone would lead us to believe that these protons are in an axial environment relative to the equatorial environment of the trans isomer. However, it is difficult to understand at this time why this is so, since the conformational preferences for this system are not well defined.

(11) In cyclohexane the axial proton resonances are found at 29 Hz higher field than for the equatorial protons. (a) F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, *J. Amer. Chem. Soc.*, **82**, 1256 (1960); **84**, 386 (1962). In acetone diperoxide the axial methyl proton resonances are at 26.5 Hz higher field than the equatorial. (b) R. W. Murray, P. R. Story, and M. L. Kaplan, *ibid.*, **88**, 526 (1966). In 1,2-dimethylcyclohexane there is only an 8-Hz difference between the axial and equatorial methyl chemical shifts (see ref 2a).

(12) This small upfield shift in position could be due to the small contribution of conformer X, whose 2-CH_3 protons maintain an axial position.

(13) Energy differences between the diequatorial *cis*-3,5-dimethylcycloheptanone and the equatorial, axial *trans*-3,5-dimethylcycloheptanone is 0.8–0.9 kcal/mol, about the same as between *cis*- and *trans*-3,5-dimethylcyclohexanone. N. L. Allinger, *J. Amer. Chem. Soc.*, **81**, 232 (1959).

(14) C. Ouannes and J. Jacques, *Bull. Soc. Chim. Fr.*, 3611 (1965).

Experimental Section

Nuclear magnetic resonance spectra were recorded on a Jeolco C-60H[15] high-resolution nmr spectrometer. All data were verified on a Varian HA-100 high-resolution nmr spectrometer. Mass spectra were obtained on a Dupont 492 or CEC 103 mass spectrometer and samples were introduced *via* the batch inlet system at ambient temperature. Analytical and preparative glpc analysis were performed on a Hewlett-Packard 800 gas chromatograph using 9 ft × 0.125 in. and 20 ft × 0.5 in. columns, respectively, packed with Carbowax 20M (10%) on Chromosorb W (40/60 mesh).

cis- and *trans*-2,3-Dimethylcyclopentanone.—*cis*- and *trans*-2,3-dimethylcyclopentanones were obtained as a commercial mixture. Equilibration of the two isomers was effected in 12 hr with a 100 molar excess of CH_3OH or CH_3OD and a catalytic amount of $NaOCH_3$. This procedure gave a mixture that was 93% trans and 7% cis.[16] The isomers were separated by preparative glpc. The mass spectrum of CH_3OD-exchanged samples showed that trideuteration was greater than 95%. Identification of each isomer was determined by mass spectral analysis (see results), and comparison with reported glpc retention data and equilibration values.[16]

cis- and *trans*-2,3-Dimethylcyclohexanone.—*cis*- and *trans*-2,3-dimethylcyclohexanones were prepared by chromic acid oxidation of commercially available isomeric 2,3-dimethylcyclohexanols. The stereochemical assignments were made on the basis of mass spectral data (see Results), and semicarbazone derivatization. The semicarbazone of the cis isomer had mp 176–177° (lit.[17] mp 179°). The semicarbazone of the trans isomer had mp 202° (lit.[17] mp 205°).

Equilibration as described above using CH_3OH or CH_3OD was performed on a mixture of *cis*- and *trans*-2,3-dimethylcyclohexanones (60:40, respectively). This mixture gave after equilibration 82% *trans*- and 18% *cis*-2,3-dimethylcyclohexanone. The isomers were separated by preparative glpc, and the deuterated isomers showed greater than 95% trideuteration by mass spectrometry.

cis- and *trans*-2,3-Dimethylcycloheptanones.—Each pure isomer (cis or trans) of 2,3-dimethylcyclohexanone was ring expanded to the corresponding cycloheptanone according to the method described by Marshall.[6] 2,3-Dimethylcyclohexanone (2 g, 0.016 mol) was added to an ether–methanol (1:1) solution (125 ml) of diazomethane (1.5 g, 0.035 mol). After 48 hr the solution was concentrated. The product mixture was determined by glpc–mass spectral analysis. It showed the presence of starting material, 2,3-dimethylcycloheptanone, 3,4-dimethylcycloheptanone, isomeric dimethylcyclooctanones, and cyclohexane epoxides. The structures of the 2,3-dimethylcycloheptanones were verified by mass spectrometry (see Results). The total product yield was *ca.* 50%, of which 50% was the desired 2,3-dimethylcycloheptanone.

Each isomer of *cis*- and *trans*-2,3-dimethylcycloheptanones was equilibrated as described above, to an equilibrium mixture of 53% trans and 47% cis. The isomers were separated by preparative glpc. Trideuteration in each isomer was greater than 95% as determined by mass spectrometry.

Acknowledgment.—The authors thank Dr. David Weisleder for the 100-MHz nmr spectra of our compounds.

(15) Reference to a particular manufactured product does not constitute a recommendation by the U. S. Department of Agriculture over similar products not mentioned.

(16) D. Varech, C. Ouannes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1662 (1965).

(17) W. Cocker, T. B. H. McMurray, and E. R. Simons, *J. Chem. Soc.*, 3022 (1965).

Relative Reactivities and Stereochemistry of Addition of Iodoperfluoroalkanes to Cyclic Olefins

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Received December 21, 1971

The relative reactivity of cyclic olefins toward the free-radical addition of 1-iodoperfluoropropane at 70° using azonitrile initiator was *cis*-cyclooctene (2.70) > cyclopentene (2.22) > cycloheptene (1.40) > cyclohexene (1.00). Under these conditions 1-heptene (a typical acyclic olefin) reacted 14 times faster than cyclohexene. *cis*-Cyclooctene gave four adducts: *cis*- and *trans*-1-iodo-2-perfluoropropylcyclooctane and, by 1,5 shift of the intermediate radical, *cis*- and *trans*-1-iodo-4-perfluoropropylcyclooctane. Zinc reduction of this mixture gave only perfluoropropylcyclooctane, and dehydrohalogenation formed two olefins in nearly equal amounts. By contrast, cyclopentene gave only a trans adduct, while cyclohexene and cycloheptene formed both cis and trans 1,2 adducts, probably as a result of ring flipping. These results are interpreted as the consequence, first, of preferred trans addition (with the bulky and electronegative R_F and iodine groups as far as possible from each other) and, secondly, a combination of steric strain and pseudorotation of the rings.

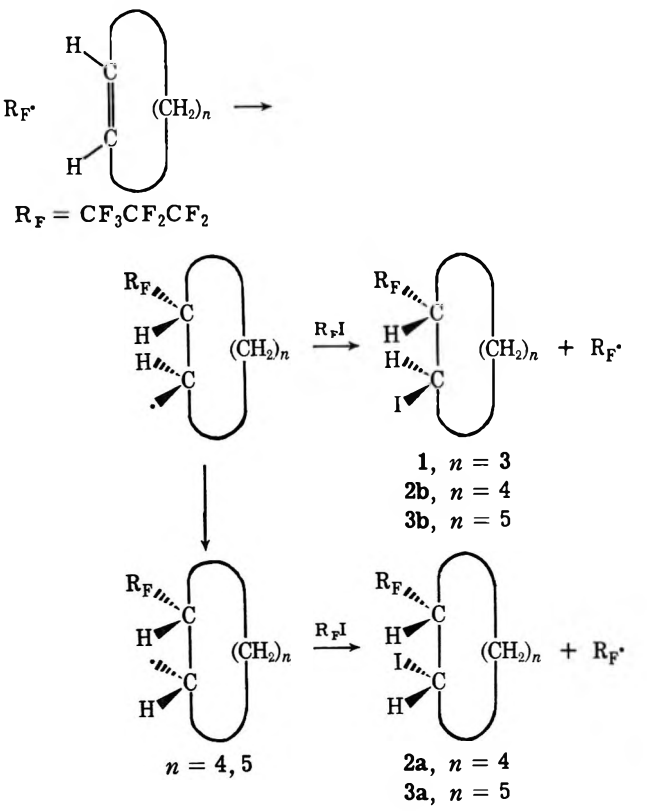
In a previous study[1] perfluoroalkyl iodides (R_FI) and cyclopentene or cyclohexene gave 1-iodo-2-perfluoroalkylcycloalkanes having marked differences in properties, depending on the size and shape of the perfluoroalkyl group. The nmr spectra,[2,3] rate of hydrogen iodide elimination, partial rate factors for Δ^1 and Δ^2 olefin formation, and equilibration between cis and trans isomers of 1-iodo-2-perfluoroalkylcyclohexanes[4] varied with the conformation of the ring. It was concluded that trans adducts having bulky R_F groups assume twist-boat conformations which are surprisingly stable at room temperature, while cis adducts appear to be locked into a stable chair form. The twist-boat conformation was subsequently observed by other workers in the analogous case of *trans*-1-bromo-2-trichloromethylcyclohexane.[5]

While reactions of cycloheptene and *cis*-cyclooctene with carbon tetrachloride or bromotrichloromethane have been reported,[5-7] addition of R_FI to these cyclic olefins has not been investigated. We were particularly interested in the influence that the greater mobility of these medium-size rings would have on the relative ease of addition, since cyclopentene and cyclohexene were unusually sluggish in their reactions with R_FI. Addition of R_FI to norbornene or norbornadiene occurred very readily,[8] probably as a result of relief of ring strain, and side reactions which were noted[1] in the case of cyclohexene were not important. It has been shown that bromotrichloromethane gave only 1,2 addition to *cis*-cyclooctene, while carbon tetrachloride gave 1,4 adduct by transannular rearrangement of the intermediate radical, and trichloromethanesulfonyl chloride gave both 1,2 and 1,4 adducts.[5,6] Study of the behavior of these cyclic olefins toward R_FI addition should contribute to our understanding of free radical reactions.

Results and Discussion

Synthesis of Adducts.—Azonitrile-initiated [2,2′-azobis(2-methylpropionitrile), ABN] reaction of 1-iodoperfluoropropane with the individual cyclic olefins at 70° gave adducts as shown in Chart I. (Charts II and III give more detailed structural data.) It was necessary to isolate and characterize the new compounds from cyclopentene, cycloheptene, and *cis*-cyclooctene. One reason was to quantify the gas–liquid phase chromatographic (glpc) analysis used to determine the amounts formed in competitive reactions. Cyclohexene adducts had been previously prepared; their unusual structures and properties provided further incentive to extend the synthesis to higher homologs.

CHART I



Cyclopentene gave a trans adduct (**1**) in 19% conversion (4 mol/mol of ABN). Its ir and nmr spectra resembled closely those of the *n*-perfluorobutyl analog which was characterized previously.[1]

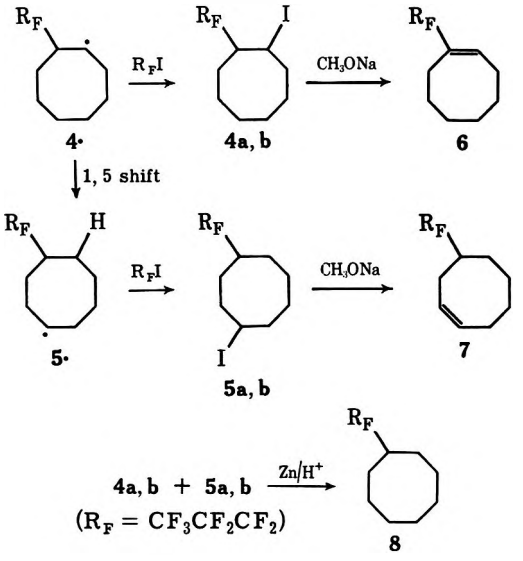
Cycloheptene adducts (**3a,b**) were formed in a 27:72 ratio (cis–trans), at 29% conversion (7.1 mol/mol of

(1) N. O. Brace, *J. Org. Chem.*, **28**, 3093 (1963).
(2) N. O. Brace, *J. Amer. Chem. Soc.*, **84**, 3020 (1962).
(3) N. O. Brace, *ibid.*, **86**, 665 (1964).
(4) N. O. Brace, *ibid.*, **86**, 2428 (1964).
(5) J. G. Traynham, A. G. Lane, and N S. Bhacca, *J. Org. Chem.*, **34**, 1302 (1969).
(6) J. G. Traynham and T. M. Couvillon, *J. Amer. Chem. Soc.*, **87**, 5806 (1965); **89**, 3205 (1967).
(7) L. H. Gale, *J. Org. Chem.*, **34**, 81 (1969).
(8) N. O. Brace, *ibid.*, **27**, 3077 (1962).

ABN). These isomers were separated by glpc and were thermally unstable. In the nmr spectrum of **3a,b** the resonance for CHI protons was at δ 4.95, comparable in chemical shift to trans-"twist" isomer 1-iodo-2-perfluoropropylcyclohexane (**2b**).[1] In glpc analyses this trans isomer **2b** always eluted from the column first, as did the principal isomer, **3b**. From these data it is concluded that **3b** has the trans configuration.

cis-Cyclooctene adducts proved to be particularly troublesome to isolate in pure condition, as they were very sensitive to heat, light, and air. By exercising necessary precautions, however, a 70–80% conversion (70–80 mol/mol of ABN) was obtained of the pure adducts **4a,b** and **5a,b** (glpc). Choice of conditions for reaction and for glpc analysis was critical. Samples of the isomer pairs were trapped by glpc for analysis and for study of their ir spectra. The entire mixture was converted to stable derivatives (Chart II).

CHART II



A mixture of isomers **4a,b** and **5a,b**, when treated with zinc and acid, gave a single substance, perfluoropropylcyclooctane (**8**). Hence, the differentiating features in **4a,b** and **5a,b** were the position of the iodine atom and the cis–trans arrangement of the two groups. By reaction with base, the isomer mixture **4a,b** and **5a,b** (41:57) gave a pair of olefins, 1-perfluoropropylcyclooctene (**6**) and 4- (or 5-) perfluoropropylcyclooctene (**7**), in about equal amount. The position of the double bond in **7** is not known, but only one of the two possible isomers (Δ^3 or Δ^4) was formed. A sample of **7** was trapped by glpc. The ir spectrum showed $\nu_{CH=CH}$ 3025, δ_{CH} 1460, 1440, 1340, and $\gamma_{CH=CH}$ 995, 920, 892, and 710 cm^{-1}. Bands at 3025, 895, and 710 cm^{-1} are also present in *cis*-cyclooctene, and bands at 990 and 920 cm^{-1} appear in 3-perfluoropropylcyclohexene.[4] The mixture of **6** and **7** showed (in addition to those in **7**) absorptions of $\nu_{CH=}$ 3035 and $\nu_{R_FC=C}$ 1660 and bands at 755, 722, and 690 cm^{-1}. Bands at 1667, 755, 717, and 683 cm^{-1} are also present in 1-perfluoropropylcyclohexene.[4] The bands at 3035 and 1667 cm^{-1} are in accord with a Δ^1 double bond position for **6**. The nmr spectrum of **6** and **7** (equal amounts) showed olefinic protons at δ 5.5–6.3 (1.5 protons) in a complex splitting pattern. These data conform to the anticipated behavior of **4a,b** and **5a,b** and for structures **6** and **7**.

Relative Rates of Reaction.—Mixtures of cyclopentene with each of the other cyclic olefins, competing for 1 mol of 1-iodoperfluoropropane and catalyzed by ABN at 70°, were run under standard conditions. Cyclopentene was chosen as reference olefin because it formed only one adduct, which facilitated comparison. A summary of results is given in Table I.

TABLE I
RELATIVE RATES OF REACTION OF CYCLIC OLEFINS

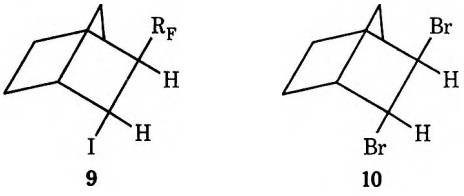
Olefin pair	Ret time[a] C_5	Ret time[a] C_x	Adducts, mmol[b] C_5	Adducts, mmol[b] C_x	Ratio of C_5/C_x
C_6/C_6	4.3	7.0, 10.4	7.99	3.57	1.00/0.450
C_6/C_7	4.3	12.5, 13.9	1.67	1.04	1.00/0.622
C_6/C_8	4.3	14.1, 15.6	1.52	1.87	1.00/1.23

[a] Retention time in minutes; the trans isomer eluted first in each case, except for cyclooctene adducts which were not resolved into four peaks on these conditions. [b] Average of three replicate determinations, ±0.02 mmol in most cases.

From these data the order of reactivity was found to be cyclo-$C_8 > C_5 > C_7 > C_6$, with proportions 2.70:2.22:1.40:1.00. Under identical reaction conditions 1-heptene reacted with 1-iodoperfluoropropane 14 times as fast as cyclohexene.[1] As shown by Gale,[7] this order corresponds to the irreversible addition of radicals and is comparable to the results obtained with acetaldehyde or $BrCCl_3$ with these cyclic olefins.

Significance of Results.—Free radical addition of R_FI in a trans mode to cyclopentene conforms to the pattern observed in reactions of this type.[8] Since the bulky and electronegative groups cannot bend away from each other in the cis arrangement, transfer occurs only in the trans manner (Chart I). Norbornene (a rigid cyclopentene model) reacted similarly, and the dipole moments of several related compounds support this conclusion (Table II).

For the norbornane derivatives **9** and **10**, using the proper dihedral angle and the correction for geometry



of the ring as applied by Krieger,[9] calculated dipole moments were obtained in excellent agreement with experimental values. These results clarify the confused picture obtained for bromotrichloromethane adducts of cyclopentene and norbornene.[5]

Group moment of D(C–I) = 2.06 D from iodocyclopentane[10] and group moment of D(ring–R_F) = 2.8 D were used.[4] Calculation was done using the equation

$$\mu \text{ (dipole moment)} = (m_1^2 + m_2^2 + 2m_1m_2 \cos\theta)^{1/2}$$

When applied to **1**, agreement between calculated and observed dipole moments again was satisfactory. Reported data[9] for *exo*-2-*endo*-3-dibromonorbornane (**10**), and two sets of isomers of **2a,b** are listed for comparison.

(9) H. Kreiger, *Suom. Kemistilehti B*, **31**, 348 (1958); *Chem. Abstr.*, **53**, 13195 (1959)
(10) M. T. Rogers and J. D. Roberts, *J. Amer. Chem. Soc.*, **68**, 843 (1946).

TABLE II

DIPOLE MOMENTS OF CYCLIC ADDUCTS

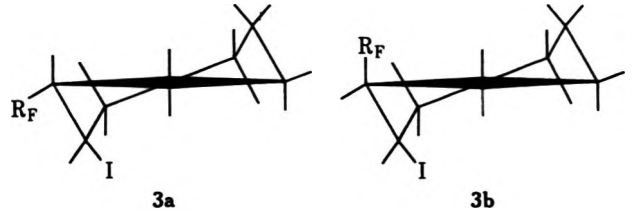
Compd	R_F	Dipole moment, D — Found[a] — Benzene solution	Neat	Calcd[b]	θ, Dihedral angle
9	$CF_3(CF_2)_2$	3.09	2.86	2.85	123°21′
9	$(CF_3)_2CF$	3.21	2.99	2.85	123°21′
1	$CF_3(CF_2)_3$	2.99[c]	2.58[c]	2.55	123°21′
2a (cis, e, a)	$CF_3(CF_2)_2$	3.45[b]	3.54[b]	4.00	70°32′
2b (trans twist a, a)	$CF_3(CF_2)_2$	2.28[b]	1.91[b]	1.55	147°
2a (cis, e, a)	$(CF_3)_2CF$	3.42[b]		4.00	70°32′
2b (trans twist e, e)	$(CF_3)_2CF$	3.35[b]	3.00[b]	3.59	86°54′
10		2.30[d]		2.33[d]	
Iodocyclopentane		2.06[e]			

[a] Unpublished work with M. R. Kegelmann. [b] See ref 4 for the method used. [c] Reference 1. [d] H. Kreiger, *Suom. Kemistilehti B*, **31**, 348 (1958); *Chem. Abstr.*, **53**, 13195 (1959). [e] M. T. Rogers and J. D. Roberts, *J. Amer. Chem. Soc.*, **68**, 843 (1946).

Correlation of dipole moments with structures of isomers **2a,b** and sources of error have been discussed previously.[4]

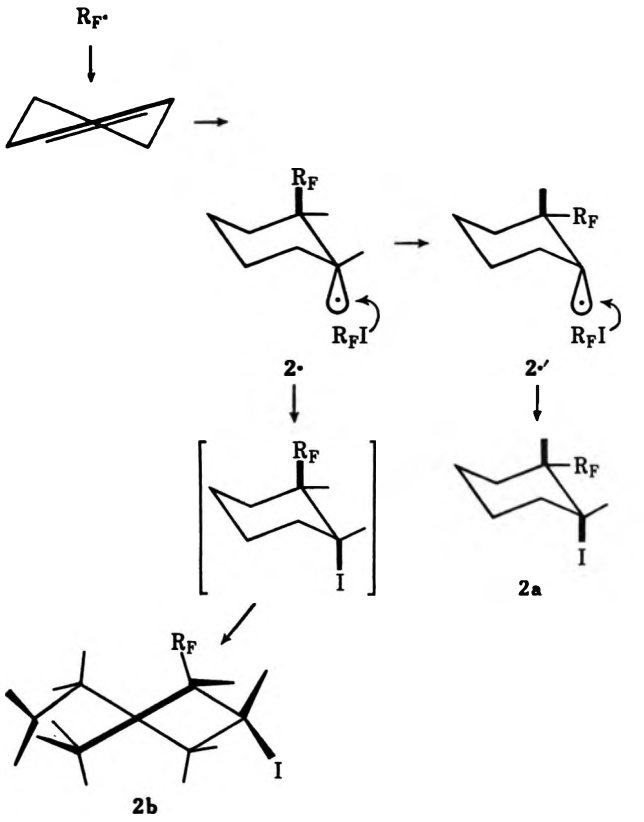
For cyclohexene, both cis and trans addition occurred, as previously shown.[1] Since flipping of the ring (**2**· → **2**·′) may occur before transfer of the intermediate radical with R_FI, a mixture of isomers somewhat dependent on the size and shape of the R_F group was obtained (Chart III). Twisting of the ring into twist-boat forms was observed, consistent with dipole moments and other data.[3,4] Again, the addition of $BrCCl_3$ conforms to this behavior.[5,11]

Cycloheptane has twist-chair and twist-boat conformations as its lowest energy forms.[12] The barrier to flipping from chair to boat family is 8.50 kcal/mol and the twist-boat is 2.49 kcal/mol less stable than the twist-chair. Due to pseudorotation, a substituent in one position may pass to every other, as detailed by Hendrickson.[12] In 1,2-disubstituted cycloheptanes it is possible to distinguish between two cis and two trans forms, but by pseudorotation these reduce to only one of each, separated by a high energy barrier. It thus becomes reasonable that cycloheptene adds R_FI more rapidly than does cyclohexene. The barrier to flipping is lower for cycloheptane than for cyclohexane (calcd, 12.7 kcal/mol),[12] and the trans-diequatorial arrangement of ordinary 1,2 substituents is preferred.[13] The intermediate radical may readily pseudorotate to relieve crowding and repulsion by R_F and I groups in the transfer step. Adducts **3a,b** having these bulky electronegative substituents may be tentatively represented in preferred conformations as shown.



3a **3b**

CHART III



$R_F = CF_3(CF_2)_2$

It is odd that $BrCCl_3$ has been reported[5] to give cis addition (only) to cycloheptene; orientation was based on coupling constants for vicinal protons in comparison to predicted values. Gale, however, gave nmr data which could be interpreted to mean that a trans adduct was obtained.[7] The chemical shifts for protons adjacent to Br and to CCl_3 in the cycloheptene adduct were closer to values found for the *trans*-1-bromo-2-trichloromethylcyclohexane than for the cis isomer.[5,7] In view of the discrepancy in these two sets of data, and the predicted lower energy for trans forms, it seems probable that trans addition had occurred.

cis-Cyclooctene was the most reactive of the four cyclic olefins studied toward R_FI addition. The same order of reactivity was found for CH_3CHO or $BrCCl_3$ addition. Gale[7] attributed this to the "medium-ring effect," in which two sp^2 carbons are converted to sp^3 carbons, and stated that the principal result is a great decrease in the rate of abstraction of the substituted cyclooctyl radical without affecting the rate constant for addition of the CCl_3· radical to *cis*-cyclooctene. It was suggested that the presence of one sp^2 carbon center imparts sufficient flexibility to minimize hydrogen-hydrogen nonbonded interactions. In radical addition of carbon tetrachloride to *cis*-cyclooctene, transannular rearrangement of the intermediate radical (analogous to **4**· → **5**·) was attributed by Traynham and Couvillon[6] to destabilization of the radical center by neighboring trichloromethyl substituent. This destabilization energy was estimated to be more than 3.5–4.0 kcal/mol. With a more active transfer agent ($BrCCl_3$) very little transannular addition occurred. In this re-

(11) The $BrCCl_3$–norbornene adduct is *endo*-2-bromo-*exo*-3-trichloromethylnorbornane, and its dipole moment is 2.60 D, in line with that of **9** and **10**.

(12) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **83**, 4537 (1961).

(13) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 208.

spect R_FI addition more closely resembled that of Cl_3CSO_2Cl, which also gave a mixture of both 1,2- and 1,4-addition products.[5,6] It is then somewhat surprising that relative rates of reaction of R_FI with *cis*-cyclooctene *vs.* the other cyclic olefins parallels so closely that found for CH_3CHO or $BrCCl_3$, which occurred without transannular rearrangement.

Rationalization of the order of reactivity found with R_FI may be summarized as follows. Because the cyclooctyl radical is flexible, having several conformations only about 2.0 kcal/mol higher in energy than the most stable boat–chair form,[14] trans addition to vicinal carbons can occur with only little energy expenditure. More important, however, is the fact that transannular reaction places the bulky and electronegative addends far apart. This minimizes the repulsions which tend to reduce rate of transfer with R_FI. Since torsional and nonbonded strain in cyclopentane is less than for cyclooctane or cycloheptane,[13] addition of R_F radicals to cyclopentene does not require as much energy. The transfer step with R_FI, however, is restricted to noneclipsing of these groups and therefore must go in a trans manner. Hence, cyclopentene is less reactive than cyclooctene. Cycloheptene is next most reactive because total strain energy in the adduct radical is higher than in cyclopentane, and transannular rearrangement cannot take place as with the cyclooctyl radical. Pseudorotation, while present, may be somewhat restricted by the bulky vicinal substituents; the preferred trans orientation of the cycloheptyl radical and R_FI may be more difficult to achieve as well. Cyclohexene is the least reactive for the following reasons: (1) trans addition requires both the R_F group and the approaching R_FI molecule to occupy crowded axial positions (Chart III); (2) formation of cis isomer **2a** necessitates ring flipping of **2**· to **2**·′ to place the bulky R_F group in an equatorial position before axial approach of R_FI occurs; (3) instead of obtaining a trans-diequatorial cyclohexane chair conformer, one actually obtains a twist-boat compound (**2b**) which must pass through a higher energy barrier before it can be formed.

A tentative conclusion from these results is that addition of the R_F radical and transfer with R_FI are coupled processes, which must both be considered in determining overall reaction rates of olefins with perfluoroalkyl iodides.

Experimental Section

Analyses, Sources, and Purification of Materials.—All experiments were carried out in an atmosphere of nitrogen. Cyclopentene was obtained from Columbia Organic Chemicals and redistilled in a 2-ft platinum spinning band column (column A), bp 44°, $n^{25}D$ 1.4198; cyclohexene (99%) was from Phillips Petroleum Co., $n^{25}D$ 1.4439; cycloheptene (99%) was from Chemical Samples Co., $n^{25}D$ 1.4562; *cis*-cyclooctene was from Cities Service Development Co. and redistilled in column A, bp 145°, $n^{25}D$ 1.4683, ir bands at 893 and 885 cm^{-1};[15] 1-iodoperfluoropropane (**11**) was from Pierce Chemical Co., redistilled, bp 41°; 2,2′-azobis(2-methylpropionitrile) (**12**) was from Eastman Kodak Co. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating spectrophotometer using KBr cells. Nmr spectra were obtained using a Varian A-60 spectrometer at ambient temperature.

trans-**1-Iodo-2-(perfluoropropyl)cyclopentane** (**1**).[16]—Cyclopentene (13.41 g, 17.5 ml, 0.200 mol), **11** (22.23 g, 11.84 ml, 0.0800 mol), and **12** (0.6568 g, 4.00 mmol) were charged to a Fischer-Porter aerosol tube, cooled to −78°, evacuated, filled with nitrogen three times, and sealed. The tube was heated at 70° for 24 hr in a stirred oil bath. The cloudy mixture was filtered through a sintered glass funnel and distilled in a variable take-off distilling head without a column. Cyclopentene and **11**, bp 35–40°, 24.1 g; adduct **1**, bp 58° (8 mm), $n^{25}D$ 1.4180, 5.4 g, bp 34° (2 mm), 0.3 g (19% conversion), 4 mol/mol of **12**; residue (0.9 g); and trap liquid (2.26 g, also cyclopentene and **11**) were recovered. The product **1** was 96% trans isomer (retention time 4.3 min) by glpc analysis; three other substances of about 2% each were also present, at 8.0, 9.6, and 10.2 min. Pure **1** was trapped from repetitive injections on a 6 ft × 0.25 in. column packed with 10% silicone oil (QF-1), operated at 120°. An ir spectrum showed ν_{CH} 2980, 2890, δ_{CH} 1450, 1350, ν_{CF} 1240, 1200, 1180, and bands at 1120, 1070, 790–760, and 730 cm^{-1}. An nmr spectrum showed δ 1.7–2.3 [6 protons, m, $(CH_2)_3$], 2.7–3.8 (1 proton, m, CHR_F), 4.58 (1 proton, q, J = 5 Hz, $CH_2CHICHR_F$).

Anal. Calcd for $C_8H_8F_7I$: C, 26.39; H, 2.21. Found: C, 26.53; H, 2.36.

cis- and *trans*-**1-Iodo-2-(perfluoropropyl)cycloheptane** (**3a,b**).[16]—Cycloheptene (48.0 g, 58.4 ml, 0.500 mol), **11** (29.6 g, 14.8 ml, 0.100 mol), and **12** (0.6568 g, 4.00 mmol) were processed as above and heated in the bath at 48–50° for 24.5 hr. The clear liquid product (75.8 g) was decanted from some solid precipitate and distilled in column A. Starting materials, bp 41–72°, 20 g, were removed; and, under reduced pressure, cycloheptene, bp 54–56° (100 mm), $n^{25}D$ 1.4561, 35.7 g; **3a,b**, bp 72–78° (3.5–4.2 mm), $n^{25}D$ 1.4405, 7.58 g, and bp 64–66° (2.0 mm), $n^{25}D$ 1.4421, 3.94 g (29% conversion). Reaction at 70° gave a 25% conversion to **3a,b**. A residue (0.70 g) and trap liquid (5.71 g of additional starting materials) were also obtained. **3a,b** was passed down alumina to remove color, rinsed with ligroin (bp 30–60°), and redistilled, bp 52–53° (0.55 mm), $n^{25}D$ 1.4394, 9.57 g. An ir spectrum gave ν_{CH} 2950, 2980, δ_{CH} 1460, 1450, 1350, ν_{CF} 1220, 1180, and bands at 1115, 1090, 980, 960, 950, 930, and 730 cm^{-1}. Glpc analysis gave at 12.5 min, 72.0%; 13.8 min, 27.3%; 15.2 min, 0.21%; and 18.8 min, 0.28% relative areas. An nmr spectrum of **3a,b** showed δ 1.4–2.4 [10 protons, m, $(CH_2)_5$], 2.5–3.7 (1.0 proton, m, $CHCF_2CF_2CF_3$), 4.95 [1.0 proton, partly resolved five-line pattern, J = 5 Hz, $(CH_2)_2CHI$].

Anal. Calcd for $C_{10}H_{12}F_7I$: C, 30.63; H, 3.09; F, 33.91; I, 32.36. Found: C, 30.70; H, 3.10; F, 33.72; I, 32.48.

cis- and *trans*-**1-Iodo-2-(perfluoropropyl)cyclooctane** (**4a,b**) and *cis*- and *trans*-**1-Iodo-4-(perfluoropropyl)cyclooctane** (**5a,b**).—*cis*-Cyclooctene (20.0 g, 23.6 ml, 0.180 mol), **11** (30.0 g, 15.0 ml, 0.100 mol), and **12** (0.164 g, 1.00 mmol) were processed as above. The tube was heated for 7 hr at 70.0° in the oil bath. The colorless product mixture (49.5 g) was distilled in column A, under reduced pressure; *cis*-cyclooctene, $n^{25}D$ 1.4679, 1.16 g; **4a,b** and **5a,b**, bp 56–66° (0.30 mm), $n^{25}D$ 1.4495, 28.5 g (70% conversion); and a solid residue (0.30 g) were obtained. Volatile compounds (21.75 g) collected in the −78° trap. The entire adduct mixture was analyzed by glpc using a 6 ft × $^3/_{16}$ in. stainless steel column, filled with Carbowax 400 on Porosil (100–200 mesh) at 105°. Peaks of 7.1, 34.1, 27.8, and 29.4% relative areas were obtained at 8.6, 9.4, 15.0, and 16.7 min, respectively: ir (entire mixture, KBr, liquid film) ν_{CH} 2920, 2850, δ_{CH} 1460, 1430, 1340, ν_{CF} 1230, 1195, 1180, 1150, 1110, bands at 1110, 990, 965, 950, 935, 908, 860, 845, 810, 750, 740, 710, 670, 650, 595, 565, and 535 cm^{-1}.

Reaction of 0.500 mol of *cis*-cyclooctene and 0.10 mol of **11** (3.00 mmol of **12**) at 76° for 22 hr gave an 84% conversion to **4a,b** and **5a,b**. Fractionation in column A gave four cuts, bp 67–72° (0.50 mm), containing three or four substances according to glpc analysis (6 ft × 0.25 in. column, Carbowax 20 M, 20% on Chromosorb W, 160° and 25-psi helium pressure). The adducts were sensitive to heat and light and tended to decompose. Individual peaks were trapped and infrared spectra were recorded: peak 1, **7**, retention time 1.3 min, 5.0%, ir $\nu_{CH=C-}$ 3025, ν_{CH_2} 2960, 2940, 2860 (overtone 1750), δ_{CH} 1460, 1440, 1340, ν_{CF} 1230 (vs), 1196, 1175, 1118, and bands at 1015, 995, 980, 962, 950, 920, 905, 892, 710, 668, and 642 cm^{-1}; peak 2, **4a,b**, 8.4 min, 40%, ir (KBr, CCl_4 solution), ν_{CH} of CH_2 2940, 2860; δ_{CH} 1460, 1440, 1340; ν_{CF} 1230, 1220 (vs), 1196, 1175, 1165, 1122, 1110, and

(14) J. E. Anderson, E. S. Glazer, D. L. Griffith, R. Know, and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 1386 (1969).

(15) A. C. Cope, R. A. Pike, and C. F. Spencer, *ibid.*, **75**, 3212 (1953).

(16) Assistance by D. R. Barnes in carrying out part of this experiment is gratefully acknowledged.

bands at 1010, 1000, 970, 945 (w), 925, 890 (w), 865, 745, 710, 670, and 665 cm^{-1}; peak 3, **5a,b**, 17 min, 55%, ir (KBr, CCl_4 solution) same as 2 from 4000 to 1000 cm^{-1}, bands at 990, 950, 940, 910, 860, 845, 750, 710, 670, 650, 595, 570, and 540 cm^{-1}. Nmr spectra of mixtures of **4a,b** and **5a,b** of varying isomer composition were recorded. All were similar: nmr (neat, A-60) δ 1.00–1.36 (13.0 protons, unresolved), 4.58 (1.0 proton, partially resolved multiplet of CHI).

Anal. Calcd for $C_{11}H_{14}F_7I$: C, 32.53; H, 3.47; F 32.75; I, 31.25. Found (mixture): C, 32.60; H, 3.37; F, 32.17; I, 30.98. Found (peak no. 2): C, 32.53; H, 3.47. Found (peak no. 3): C, 32.71; H, 3.60.

Dehydrohalogenation of Adduct Mixture 4a,b and 5a,b to 1-Perfluoropropylcyclooctene (6 and 7).[17]—**4a,b** and **5a,b** (7.00 g, 0.0172 mol), 25 ml of methanol, and 2.0 g (0.037 mol) of sodium methoxide were refluxed for 4 hr at 68°, and poured into 50 ml of water. The product was extracted with 10 ml of dichloromethane three times, dried over magnesium sulfate, and distilled to give **6** and **7**, bp 73° (18 mm), $n^{25}D$ 1.3856, 2.6 g (55% of theory). Glpc analysis (5 ft XE-60 silicone oil column, 15% on Chromosorb W, 115°, 25-psi helium) gave peaks at 5.8 (53.5%) and 6.2 min (46.5%). Similar results were obtained with a 10-ft SE-30 silicone oil column or a 4 ft "UCON Polar" LB550-X column, which gave peaks at 12.4 (2.15%), 14.0 (54.1%), and 15.3 min (43.8%); ir (KBr, liquid film) ν_{CH-C} 3040, ν_{CH} 2960, 2940, 2880, ν_{C-C} 1660 (w), δ_{CH} 1480, 1455, 1350, ν_{CF} 1220, 1180, 1120, bands at 1015, 982, 955, 940, 920, 908, 895, 845, 825, 775, 755, 745, 738, 722, and 710 cm^{-1}, weak bands appeared at 690, 670, 655, and 535 cm^{-1}. Comparison showed that **6** and **7** were present in small amount in the original adduct mixtures. Nmr (neat) showed proton resonances at δ 1.2–1.9 and 1.9–2.85 [11.4 protons, m, $(CH_2)_5$ or $(CH_2)_6$] and 5.3–6.4 (1.5 protons, –CH=CH– and R_FC=CH).

Anal. Calcd for $C_{11}H_{13}F_7$: C, 47.48; H, 4.71; F, 47.81. Found (isomer mixture): C, 47.52; H, 4.78; F, 47.60.

Zinc Reduction of 4a,b and 5a,b Adduct Mixture to Perfluoropropylcyclooctane (8).—**4a,b** and **5a,b** (10.8 g, 0.0266 mol), ethanol (25 ml), and zinc (30 mesh, 5.0 g, 0.077 g-atom) were heated to reflux with stirring, and 3 ml of 55% hydriodic acid was added; after 1.5 hr another 1 ml of acid was added. Later (0.5 hr) the mixture was poured into 100 ml of water, made acidic with hydrochloric acid, and extracted three times with 10 ml of dichloromethane. The organic layer was rinsed with dilute aqueous sodium bicarbonate, dried over magnesium sulfate, and distilled to give **8**, bp 93–94° (39 mm), $n^{25}D$ 1.3802, 3.4 g (45%).

Adduct mixture **4a,b** and **5a,b** (8.3 g, 0.020 mol), zinc dust (5.0 g, 0.076 mol), diethylene glycol (25 ml), and 36% aqueous HCl (5 ml) at 70–80° for 3 hr, followed by azeotropic distillation, gave **8** (4.0 g, 71%). Glpc analysis showed a single peak using a variety of columns and conditions; ir (liquid film on KBr plates) ν_{CH} 2960, 2940, 2880, δ_{CH} 1470, 1450, 1350, ν_{CF} 1220, 1180, 1120, 1110, and bands at 1020, 1010, 1000, 970, 950, 940, 915, 860, 845, 820, 808, 745, 738, and 705 cm^{-1}; nmr (neat) δ 1.6 [14 protons, s, $(CH_2)_7$] and 2.0–2.8 [1 proton, m, $CH(CF_2)_2CF_3$].

Anal. Calcd for $C_{11}H_{15}F_7$: C, 47.14; H, 5.40. Found: C, 47.14; H, 5.29.

Competition Reactions,[16] **1 and 2a,b.**—Cyclopentene (0.8364 g, 0.01228 mol), cyclohexene (1.0357 g, 0.0126 mol), **11** (3.0843 g, 0.0104 mol), and **12** (0.0823 g, 0.5 mmol) were placed in a heavy-walled glass ampoule, chilled to −78°, filled with nitrogen and evacuated three times, and sealed with a hand torch at 0.5 mm. The reaction tube was placed in an oil bath heated at 70° for 20 hr, and the liquid (4.45 g) was decanted from some flocculent precipitate and distilled in a small stillhead connected to a −78° trap. All the volatile material (3.37 g, $n^{25}D$ 1.4111) was pumped to the trap and the adduct mixture (**1** and **2a,b**) was distilled, bp 28–39° (1.5 mm), 0.51 g (9.7% conversion). The residue was 0.06 g. Reaction occurred with an efficiency of 2.76 mol of adducts/mol of **12**. Glpc analysis, using 0.1088 g (0.2933 mmol) of adduct mixture and 0.0186 g of chlorobenzene (internal reference), showed that there were 7.99 mmol of **1** and 3.57 mmol of **2a** and **2b**, in a ratio of 1.00:1.27, respectively. The ratio of **1** to **2a,b** was 1.000:0.4497. Glpc analyses were performed using a Perkin-Elmer Model 881 gas chromatograph with hydrogen flame detector, fitted with a 6-ft × 0.125 in. column packed with "UCON Polar" LB 550 (20%) on Chromosorb W (60–80 mesh), and temperature-programmed (4°/min to 150°) after 5 min at 105°. Nitrogen carrier gas at 28 ml/min and 0.2-μl samples were employed. These conditions were established after an extensive survey of columns and operating parameters to enable separation of all the components of mixtures.

1 and **3a,b.**—Cyclopentene (1.7028 g, 0.0246 mol), cycloheptene (2.4043 g, 0.0247 mol), **11** (6.0036 g, 0.02028 mol), and **12** (0.1640 g, 0.100 mmol) gave adducts **1** and **3a,b**, bp 35–49° (1.15–0.60 mm), 1.06 g (13.8% conversion); the −78° trap contained 5.47 g of recovered starting materials, and the residue was 0.24 g. The efficiency of reaction was 2.8 mol/mol of **12**. Glpc analysis using 0.0946 g (2.50 mmol) of adduct mixture and 0.0293 g of chlorobenzene showed that there were 1.68 mmol of **1** and 1.04 mmol of **3a** and **3b** in a ratio of 1.00:3.62, respectively. The ratio of **1** to **3a,b** was 1.000:0.6223.

1 and **4a,b**, **5a,b.**—Cyclopentene (0.8427 g, 0.01237 mol), cyclooctene (1.3854 g, 0.01257 mol), **11** (3.0527 g, 0.01035 mol), and **12** (0.0823 g, 0.500 mmol) gave adducts, bp 36–65° (0.95–0.075 mm) (bath 72–86°), 1.18 g (29.6% conversion). The −78° trap contained 1.90 g and the residue was 0.21 g. Glpc analysis, using 0.1040 g of adduct mixture and 0.0115 g of benzene, showed that there were 1.519 mmol of **1** and 1.805 mmol of **4a,b** and **5a,b** (1.00:1.10). The ratio of **1** to **4a,b** and **5a,b** was 1.000:1.227. Benzene was used as internal standard in this analysis.

Registry No.—**1**, 34541-93-0; **2a** [R_F = $CF_3(CF_2)_2$], 7589-43-7; **2a** [R_F = $(CF_3)_2CF$], 7589-45-9; **2b** [R_F = $CF_3(CF_2)_2$], 7589-44-8; **2b** [R_F = $(CF_3)_2CF$], 7589-46-0; **3a**, 34541-96-3; **3b**, 34541-97-4; **4a**, 34542-00-2; **4b**, 34542-01-3; **5a**, 34542-02-4; **5b**, 34542-03-5; **6**, 34542-04-6; **7**, 34542-05-7; **8**, 34542-06-8; **9** [R_F = $CF_3(CF_2)_2$] 34542-07-9; **9** [R_F = $(CF_3)_2CF$], 34542-08-0; **11**, 754-34-7; cyclopentene, 142-29-0; *cis*-cyclooctene, 931-87-3.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

(17) Assistance by H. H. Hoffman, Jr., in carrying out part of this experiment is gratefully acknowledged.

Predicting Selectivity in Thermal Cycloaddition Reactions

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Received February 4, 1972

In thermal cycloaddition reactions of large molecules where many products are allowed by orbital symmetry, the preferred reaction paths can be predicted by considering the formation and closure of a *hypothetical* intermediate diradical. The diradical should be formed by addition at the end of each conjugated polyene chain, and the preferred closures take place at the ends of the conjugated radicals thus produced. If all thermal cycloaddition reactions thus produced are not allowed by orbital symmetry, end-to-middle closures are next most favorable.

Until the advent of the Woodward–Hoffmann rules,[1] cycloaddition reactions of the larger conjugated polyenes were rarely explored, because of the large number of possible products that were expected from such reactions. The application of orbital symmetry principles to cycloaddition reactions simplified the problem by showing that the occurrence of many reactions that had earlier been thought possible was forbidden by the nature of the electronic structures of the molecules. There is still a problem remaining, however, since in large molecules there can be many allowed cycloadditions, and orbital symmetry arguments cannot help to predict which of the allowed reactions should be favored; many recent experiments have shown such reactions to be extremely selective.[2-10]

Several methods for calculation of reaction paths have been proposed,[11-13] that are in principle applicable to the present problem; such methods are either too complex for routine use by the chemist interested in synthesis, or not sufficiently reliable for such use.[14]

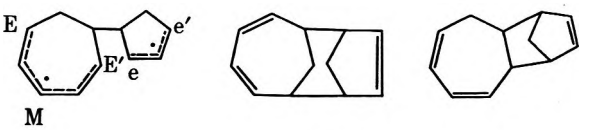
I report here a simple scheme that is in excellent agreement with reported experimental results, and can be used in conjunction with the Woodward–Hoffmann rules to make predictions for thermal cycloadditions.

The starting point for the scheme is the well-known formalism of approximating the Diels–Alder reaction as a two-step reaction with a diradical intermediate, which correctly predicts the products of reactions of unsymmetrically substituted dienes and dienophiles.[15] Applying the formalism of a hypothetical diradical intermediate to a thermal cycloaddition reaction between two larger conjugated polyenes leads, after consideration of the stabilities and reactivities of the hypothetical intermediate diradicals, to the following rules for predicting (I) the formation and (II) the closure of a diradical.

(I) In diradical formation, the most conjugated radical is formed by addition to a terminus of a polyene chain; so a diradical should be formed by *end-to-end addition.*

(II) In diradical closure, (A) each polyene radical thus formed reacts at its terminus to give *end-to-end closure*, if the overall cycloaddition is allowed by orbital symmetry; (B) if the cycloaddition arising from closure IIa is orbital-symmetry forbidden, *end-to-middle closure* is next most favored.

An example of applying this scheme would be instructive. For the thermal reaction of cycloheptatriene with cyclopentadiene, five reactions are allowed by orbital symmetry. Application of rule I gives di-



1 2 3

radical **1** to be considered. Closures E–e and E′–e are forbidden (for all-syn cycloadditions), since they are $_{\pi}6 + _{\pi}2$ and $_{\pi}2 + _{\pi}2$ cycloadditions, respectively. Closure M–e, although symmetry allowed, is predicted by the scheme to be disfavored since allowed end-to-end reactions are possible here. Closures E–e′ and E′–e′ give $_{\pi}6 + _{\pi}4$ adduct **2** and $_{\pi}4 + _{\pi}2$ adduct **3**, respectively, as the products predicted by the proposed method.[16] Although this reaction has not been reported, three very similar reactions have appeared in the recent literature: (A) reaction of a substituted cyclopentadienone with cycloheptatriene gives products of types **2** and **3**;[7] (B) reaction of tropone with cyclopentadiene gives a product of type **2**;[4] (C) reaction of tropone with a substituted cyclopentadienone gives a product of type **2**,[8] accompanied by a small quantity of an adduct whose formation is most easily rationalized by a dipolar mechanism.

(1) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969), and references cited therein.

(2) W. v. E. Doering and D. W. Wiley, *Tetrahedron*, **11**, 183 (1960).

(3) E. LeGoff, *J. Amer. Chem. Soc.*, **84**, 3975 (1962).

(4) R. C. Cookson, B. V. Drake, J. Hudec, and A. Morrison, *Chem. Commun.*, 15 (1966).

(5) G. Schröder and W. Martin, *Angew. Chem., Int. Ed. Engl.*, **5**, 130 (1966).

(6) S. Itô, Y. Fujise, and M. C. Woods, *Tetrahedron Lett.*, 1059 (1967).

(7) K. N. Houk and R. B. Woodward, *J. Amer. Chem. Soc.*, **92**, 4143 (1970).

(8) K. N. Houk and R. B. Woodward, *ibid.*, **92**, 4145 (1970).

(9) K. N. Houk, L. J. Luskus, and M. S. Bhacca, *ibid.*, **92**, 6392 (1970).

(10) G. C. Farrant and R. Feldmann, *Tetrahedron Lett.*, 4979 (1970).

(11) K. Fukui, *Accounts Chem. Res.*, **4**, 57 (1971), and references cited therein.

(12) (a) L. Salem, *J. Amer. Chem. Soc.*, **90**, 543, 553 (1968); (b) A. Devaquet and L. Salem, *ibid.*, **91**, 3793 (1969); (c) A. Devaquet, *Mol. Phys.*, **18**, 233 (1970).

(13) R. Sustmann and G. Binsch, *ibid.*, **20**, 1, 9 (1971).

(14) Calculations were performed according to the methods of Fukui (ref 11) and Salem (ref 12a) for all the reactions considered in the present work; the products which have been observed were only rarely predicted by the calculations.

(15) Y. A. Titov, *Russ. Chem. Rev.*, **31**, 267 (1962), and references cited therein. For discussion of the important question of the degree of concert in the Diels–Alder reaction, see M. Taagepera and E. R. Thornton, *J. Amer. Chem. Soc.*, **94**, 1168 (1972), and references cited therein, and W. v. E. Doering in "XXIIIrd International Congress of Pure and Applied Chemistry," Vol. 1, Butterworths, London, 1971, pp 237–250.

(16) The stereochemistry of these reactions has been predicted to be endo for the $_{\pi}4 + _{\pi}2$ and exo for the $_{\pi}6 + _{\pi}4$ reactions (ref 1, 17); the latter prediction has been experimentally confirmed in all known cases, and the former generalization is the well-known Alder endo rule. Houk (ref 18) has carried the prediction further, to generalize that $[_{\pi}4_{m} + _{\pi}2]$ cycloadditions should be endo when extending conjugation is present in the 2-π system, and $[(_{\pi}4_{m}) + (_{\pi}4_{n} + _{\pi}2)]$ $(n \neq 0)$ reactions should be exo.

(17) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 4388 (1965).

(18) K. N. Houk, *Tetrahedron Lett.*, 2621 (1970).

TABLE I

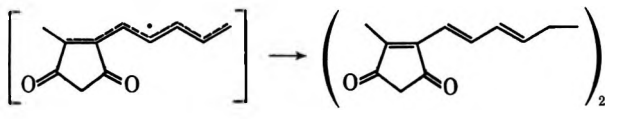
EVALUATION OF PREDICTION METHOD

Compounds	No. of allowed products[a]	No. found	No. predicted[b]	No. found bad fit to I	No. found bad fit to IIa	No. found bad fit to IIb[c]	No. found not predicted	No. predicted not found	Ref
Cyclo-C_7H_8 + cyclopentadienone (substituted)	5	2	2	0	0	0	0	0	7
Tropone + cyclo-C_6H_6	5	1	2	0	0		0	1	4
Tropone + cyclopentadienone (substituted)	5	2[d]	2	0	0		1[d]	1	8
Tropone + cyclo-C_7H_8	8	1	4	0	*e*	0	0	3	6
Tropone + dimethylfulvene[f,g]	9	2	4	0	*e*	0	0	2	9
Cyclooctatetraene dimer[g]	4	1	1	0	0		0	0	5
Heptafulvene + dimethyl acetylenedicarboxylate (DMA)	2	1	1	0	0		0	0	2
Ph_6-Pentalene + DMA	3	1	1	0	0		0	0	3
1,6-Dimethylene-2,4-cycloheptadiene + TCNE	2	1	1	0	0		0	0	10
Totals	43	12	18	0	0	0	1	7	

[a] Without considering stereochemistry (exo or endo), valence tautomers, or reaction products that violate Bredt's rule. [b] By I and IIa, or I and IIb if necessary. [c] If IIa is not allowed. [d] Including adduct through carbonyl group (see text). [e] Closure according to IIa forbidden. [f] Only 1:1 adducts considered. [g] Only initial products considered.

These results, together with the results of similar treatments of some other reported cycloaddition reactions, are collected in Table I, which clearly shows that this scheme is in good accord with the experimental facts. It will be noted that the proposed scheme occasionally predicts too many products for a reaction, but, except in the one case where there is a competing polar reaction, the prediction always includes all the known products.

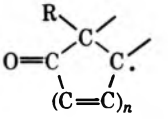
The assumption that a concerted cycloaddition reaction may be approximated by a two-step reaction with a diradical intermediate may be justified by the empirical successes of the proposed scheme[19] and of the diradical method for predicting Diels–Alder reactions. Beginning with this approximation, the success of the two end-to-end rules is not surprising, since all reactivity indices calculated for alternant hydrocarbon polyenes, including free valence and electron density in the highest occupied molecular orbital (for even alternant hydrocarbons) and self-polarizability (for even alternant hydrocarbons and odd alternant radicals), predict this kind of terminal reactivity. Such reactivity indices correctly predict, for instance, the observed coupling of radical **4** (a presumed intermediate



4

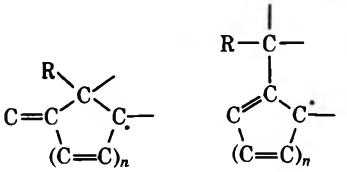
in the oxidation of pyrethrolone[20]). However, it is worthy of note that, in cases other than the open-chain alternant polyenes, use of such calculated parameters is *less* uniformly successful in predicting cycloaddition products than is the present set of qualitative rules (including the formalisms described below). Neither polarizabilities, localization energies, nor perturbation methods are consistently helpful when the qualitative scheme predicts too many products.

The cross-conjugated starting materials deserve additional comment. In reactions of cyclopentadienone or tropone, we should predict that addition will occur at the 2 position to give radical **5**, since the carbonyl



5

group does not stabilize a radical center on the adjacent carbon more than does a methylene group.[21] Thus the carbonyl group has little effect on the reaction path, and cycloadditions of cyclopentadienone resemble those of cyclopentadiene, reactions of tropone resemble those of cycloheptatriene (except for norcaradiene reactions), etc. In the analogous cases of fulvene and related compounds, not enough experimental data are available to justify a choice between a linearly conjugated cyclic radical such as **6** and the cyclic conjugated radical **7**.



6 **7**

The choice that the formation of **6** is preferable to that of **7** gives predictions that are consistent with the observed cycloadditions of fulvene[9] and heptafulvene;[2] this preference is consistent with the Hückel self-polarizabilities calculated for the starting materials, but *not* with the Hückel energies of the radicals.

It is apparent from the success of the method that

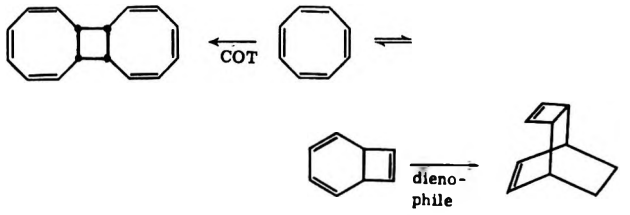
(19) The success of the diradical intermediate in predicting reactions may or may not be entirely relevant to the mechanisms of these reactions, since even a very small lack of synchronism in bond formation, associated with a small amount of diradical character in the transition state, may be product-determining. It should also be pointed out that, even in the cases where there is a symmetry plane relating the new bonds in the product, a plane of symmetry is not rigorously required in the transition state leading to that product [*cf.* Salem's discussion of "through the mirror" and "around the mirror" paths for narcissistic reactions: *Accounts Chem. Res.*, **4**, 322 (1971)].

(20) L. Crombie, J. A. Ellis, R. Gould, G. Pattenden, M. Elliot, N. F. Janes, and K. A. Keffs, *J. Chem. Soc. C*, 9 (1971).

(21) K. D. King D. M. Golden, and S. W. Benson, *J. Amer. Chem. Soc.*, **92**, 5541 (1970), and references cited therein.

alkyl and aryl substituents can be ignored, as a first approximation, although, in those cases where there is a selectivity among reactions predicted by the proposed method, that selectivity may arise in part from a combination of the effects of substituents on polarity, polarizability, and steric bulk. The effect of heteroatomic substituents (other than carbonyl) is not easily rationalized in the framework of the present scheme.[22]

Two problems remain; the first has to do with valence tautomerism in the starting materials. For instance, no way has been found within the present scheme to aid in explaining the difference between cyclooctatetraene reacting with itself ($_{\pi}8 + {}_{\pi}2$) in monocyclic form,[5] and reacting with most dienophiles ($_{\pi}4 + {}_{\pi}2$) as the bicyclic valence tautomer.[23]



The second problem is concerned with stereochemistry. Particularly in borderline cases, it is difficult to assess how much effect the spatial arrangements of the atoms will have on the course of a cycloaddition reaction. The reactants in Table I are for the most part geometrically constrained in such a way that the distinctions between stereochemically plausible and implausible reactions are relatively clear-cut; for instance, anti cycloadditions are unlikely in all these cases. Exceptions to this situation are likely to occur.

Applications of the proposed method to predict the products from several simplified model systems are shown in Table II. Neither the steric likelihood of each reaction nor the possibility of valence tautomerism has been considered in making the predictions in this table.

TABLE II
PREDICTIONS FOR MODEL COMPOUNDS[a]

Model reactants	Predicted products
Hexatriene + hexatriene	(6 + 4) + (4 + 2)
Octatetraene + ethylene	(8 + 2)
Octatetraene + butadiene	(4 + 2) + (8 + 2)
Octatetraene + hexatriene	(8 + 6) + (8 + 2)
Decapentaene + butadiene	(10 + 4) + (4 + 2)

[a] Only all-syn additions of open-chain valence tautomers are considered. No stereochemistry about double bonds is intended by the structural formulas.

Acknowledgment.—I wish to thank Professor G. Binsch for helpful discussion.

(22) Note, for instance, the differences between tropone and 2-chlorotropone on reaction with cyclopentadiene [S. Itô, K. Sakan, and Y. Fujise, *Tetrahedron Lett.*, 775 (1969)].

(23) G. Schröder, "Cyclooctatetraen," Verlag Chemie, Weinheim, 1965, pp 48–50.

Carbenoids with Neighboring Heteroatoms. III. Electrophilic Reactions of Two α-Halocyclopropyllithium Compounds[1a,b]

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Received July 26, 1971

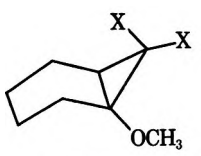
Solutions of carbenoids **4a** and **11a** were prepared by the reaction of alkyllithiums with dihalocyclopropanes **1**. Carbenoid **4a** had limited stability at −80° but could be trapped by carbonation which gave **2** in low yield and by protonation which gave **4b** in high yield. Bicyclobutane **5** was the major product of thermal decomposition of **4a**. Carbenoid **11a** was more stable at −80° as evidenced by reactions with H_2O, D_2O, and benzophenone. Thermal decomposition of **11a** at −20° gave diene **14**, presumably *via* dimerization of 1-methoxycyclohepta-1,2-diene (**16**).

We recently reported on the stereoselective preparation and nucleophilic reactivity of intramolecularly stabilized α-halocyclopropyllithium reagents.[1b] With the aim of preparing stereochemically known α-halolithium reagents which display the entire range of carbenoid reactivity, we have been investigating the structural requirements for the preparation of stabilized carbenoids. In this paper we wish to report on some nucleophilic and two electrophilic reactions (C–H insertion, allene formation) of the carbenoids derived from 1-methoxy-7,7-dihalobicyclo[4.1.0]heptane (**1**).

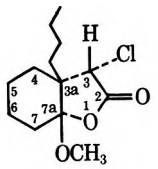
The Carbenoid from 1-Methoxy-7,7-dichlorobicyclo[4.1.0]heptane.—Treatment of the known[2] dichloronorcarane derivative **1a** with 1 equiv of ethereal butyllithium for 10 min at −80° followed by carbonation of the reaction mixture afforded a 7% yield of a neutral, crystalline product formulated as **2**. The structure of **2** rests on the following data and reasoning. We had previously encountered an α-chloro-γ-lactone, **3**, from the carbonation of 7-*exo*-chloro-2-oxabicyclo-

(1) (a) Supported in part by Grant 970-G1 from the Petroleum Research Fund, administered by the American Chemical Society, and in part by Grant GP-9543 from the National Science Foundation. (b) Part II: K. G. Taylor, W. E. Hobbs, and M. Saquet, *J. Org. Chem.*, **36**, 369 (1971). (c) NASA Trainee, 1966–1968.

(2) D. G. Lindsay and C. B. Reese, *Tetrahedron*, **21**, 1673 (1965).



1a, X = Cl
b, X = Br



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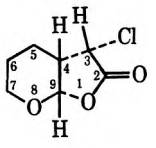

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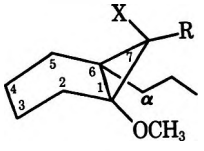
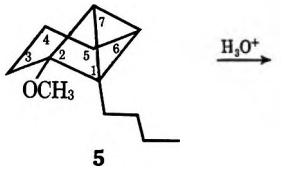
[4.1.0]heptyllithium,[1b] and the 1780-cm^{-1} C=O band of **2** indicated that it, likewise, was an α-chloro-γ-lactone. The nmr spectrum of **2** showed a singlet (1 H) at δ 4.82 assigned as the C-3 H by analogy with the C-3 H signal of **3**, δ 4.78 (1 H, d, J = 6.5 Hz). Elemental analysis (and nmr) indicated the presence of a butyl group in **2**, and its location was tentatively assigned as C-3a on the basis of the singlet nature of the C-3 H nmr signal, and was confirmed on the basis of subsequent work. A cis ring juncture would be expected for **2**, and the C-3 H was assigned an exo stereochemistry because of the similarity of its chemical shift with the C-3 H of **3**.

The 10-min carbonation reaction described above, which had yielded **2**, also yielded starting **1a**. This, together with the isolation of a butyl-containing product from the foregoing reaction, indicated that simple halogen–metal interchange might not be taking place between **1a** and butyllithium. In fact, when **1a** was treated with 1 equiv of butyllithium (−80°, 30 min) and then quenched with methanol, the nmr of the crude reaction mixture showed methoxyl signals attributable to unreacted **1a** (δ 3.42) and a monochloro derivative, **4b** (δ 3.28), in about a 1:1 ratio. Also,



4a, X = Cl; R = Li
b, X = Cl; R = H
c, X = Cl; R = D
d, X = R = H



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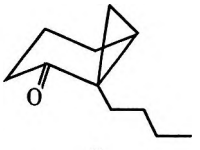

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treatment of **1a** with at least 2 equiv of butyllithium was necessary for complete reaction of the starting material. Nmr analysis indicated that **4b** was the major product of the quenched reactions, and analytical vpc also indicated a heat-sensitive, major product (70–90%) plus minor products, usually of shorter retention time. The thermal sensitivity of **4b** prevented its purification by distillation and preparative vpc. However, its structure was firmly established and rests on the following data. A rapid, positive chloride test confirmed the presence of chlorine. In the nmr spectrum, upfield from the δ 3.28 methoxyl signal, was a singlet (1 H relative to the methoxy) at δ 2.93. This was assigned as the C-7 proton, an assignment which finds a chemical shift analogy in the C-7 proton (δ 3.13) of 1-ethoxy-7-*endo*-chlorobicyclo[4.1.0]heptane.[3] By way of confirming this assignment, the δ 2.93 signal of **4b** was absent in the spectrum of **4c**, which was prepared by methanol-*O*-*d* quench of carbenoid **4a**. Reduction of a crude preparation of **4b** with sodium in liquid ammonia afforded the stable cyclopropane **4d** in over 50% yield. Compound **4d** gave a satisfactory elemental analysis and was distinguished by a high-field AB quartet at δ 0.24 and 0.40 (2 H, J_{gem} = 5.5 Hz, C-7 endo and exo, respectively) in its nmr spectrum.

Carbenoid **4a** was less thermally stable than anticipated.[1b] After the mixture was stirred at −78° for 48 min and carefully quenched, the nmr spectrum indicated that bicyclobutane **5** (methoxyl at δ 3.49, see Table I) comprised about 6% of the mixture, the

TABLE I
CHEMICAL SHIFTS (δ) OF KEY PROTONS IN SELECTED COMPOUNDS[a]

Compd	OCH_3	C-7
1a	3.42	
1b	3.43	
4b	3.28	2.93
4c	3.28	
4d[b]	3.31	0.24, 0.40
5	3.49	0.69
11b	3.22	3.3
12a	3.25	0.23 (endo)

[a] In $CDCl_3$. [b] In CCl_4.

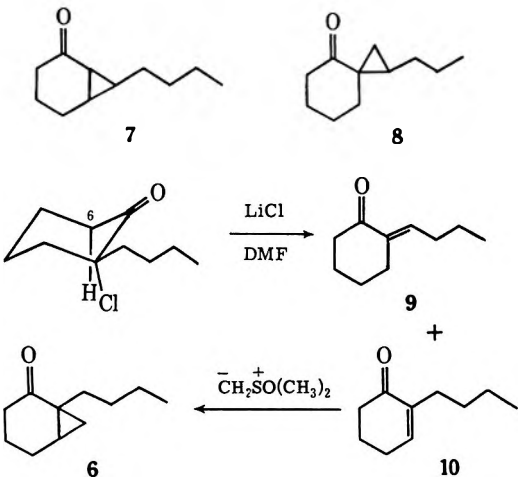
major component of which was still **4b**. After 3.5 hr at −78° and careful quenching, bicyclobutane **5** was seen to comprise 35%, and **4b** 52%, of the reaction mixture as evidenced by integration of the methoxyl region of the nmr spectrum of the mixture. Slight warming brought about rapid α elimination, and, if patience was not exercised in the addition of butyllithium solution (at room temperature) to ethereal **1a** (at −78°), crude reaction mixtures containing about equal amounts of **5** and **4b** (plus other products) resulted after stirring in a Dry Ice–acetone bath for 50 min. Either warming a solution of **4a** to room temperature or stirring at −35° for 65 min yielded the bicyclobutane **5** as the major component (>60% by vpc) of a chlorine-free, multicomponent mixture. An nmr spectrum of a crude preparation of **5** typically showed a dominant methoxyl singlet at δ 3.49 (see Table I) and smaller singlets in the δ 3.18–3.12 region. Also in the spectra of these mixtures was a narrow doublet (J = 1 Hz) at δ 0.69 which, relative to the methoxyl signal at δ 3.49, integrated for 1 H. Further, this doublet was reduced in intensity by 55–60% (relative to the δ 3.49 methoxyl) when **5** was stirred with excess butyllithium for 4 hr at room temperature and then quenched with D_2O.[4] Since the methoxyl signal at δ 3.49 was clearly associated with the major reaction product, it was assigned as the methoxyl signal of **5**, and the doublet at δ 0.69 as (tentatively) the C-7 bridgehead proton of **5**. Distillation and preparative vpc attempts resulted in the partial alteration of **5** with a concomitant increase in the complexity of the reac-

(3) W. E. Parham, F. M. Parham, J. F. Dooley, and M. K. Meilahn, *J. Org. Chem.*, **33**, 3651 (1968).

(4) The $t_{1/2}$ for exchange of the bridgehead proton of tricyclo[4.1.0.0^{2,7}]heptane is 3 hr. See L. E. Closs and G. L. Closs, *J. Amer. Chem. Soc.*, **85**, 2022 (1963).

tion mixture. The structure of **5** was proven by mild acid hydrolysis to the ketone **6**, which could be isolated in 46% yield (>90% pure) by distillation from the reaction mixture (yielded 50.4% by vpc determination). Actually, the possible structures **6**, **7**, and **8** all were consistent with the ir spectrum of **6**: 3070 (cyclopropyl CH) and 1695 cm^{-1} (cyclohexanone conjugated with a cyclopropane). Structure **6**, however, was chosen for synthesis first and its preparation is outlined in Scheme I and elaborated in the Experimental

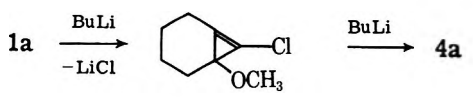
SCHEME I



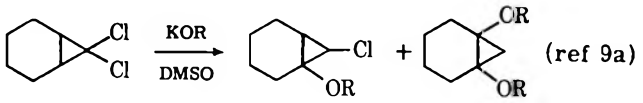
Section. The nmr spectrum of 2-butyl-2-chlorocyclohexanone was interesting in that a triplet of doublets, 1 H, appeared at δ 3.12, somewhat downfield from the main broad multiplet. First-order analysis indicated splittings of (−) 14, 14.5, and 5.5 Hz, consistent with J_{gem}, J_{ax-ax}, and J_{ax-eq} for an axial proton, most likely the one on C-6. The observed chemical shift for this proton can be explained if the conformation of 2-butyl-2-chlorocyclohexanone is as shown in Scheme I. Calculations by the method of Zurcher[5] predict that this proton should be deshielded by 0.5 ppm relative to the observed δ 2.3 chemical shift of the α protons of 2-butylcyclohexanone.[6] If a van der Waals interaction is included in the above calculation[5,7] (r_{Cl-H} = 2.8 Å) the predicted deshielding is 0.74 ppm (0.50 + 0.24). Since the observed deshielding is about δ 0.8, the above assignment of the δ 3.12 signal as that of the axial H-6 seems reasonable.

Thus, by the proof of structure **6**, the structure of the major reaction product of carbenoid **4a** was firmly established as the C–H insertion product, bicyclobutane **5**.

The formation of carbenoid **4a** from **1a** can be envisioned as occurring by way of the following reaction sequence.



Supporting this proposition are the following facts and analogies. (1) Two equivalents of butyllithium was required for complete disappearance of **1a**. (2) Methoxyl groups are known to facilitate the abstraction of cis β protons by alkyllithium reagents[8] and this structural feature of **1a** could enable the β-elimination reaction to compete favorably with chlorine–metal interchange. (3) Base-catalyzed dehydrochlorination of 7,7-dichloronorcarane proceeds as shown.[9a] (4) Magid has demonstrated that phenyllithium undergoes cis addition to cyclopropene.[9b]



The preceding results provided reasonable evidence that the carbenoid **4a** was present in the reaction mixture. While **4a** was less stable than anticipated, it still appeared to be more stable than 7-*endo*-chlorobicyclo[4.1.0]hept-7-yllithium,[10] and provided us with our first example of an electrophilic reaction which had proceeded *via* an intramolecularly stabilized carbenoid. However, the rather circuitous route of formation of **4a** and the somewhat complex and unstable nature of its thermolysis products discouraged us from examining the chemistry of **4a** further at this time. Finally, there was evidence that insertion into other C–H bonds had occurred[11] and the following only provides a partial explanation for the rather high specificity of insertion demonstrated by the formation of **5**. Moore and coworkers[12] have established a selectivity sequence of tertiary > secondary > primary C–H for the C–H insertion reaction of "cyclopropylidines." In the absence of conformational effects, insertion into a C–H bond adjacent to a cyclopropane ring would permit stabilization of the transition state by the electron-donating cyclopropane ring. This should be a favorable process and probably accounts for the high yields of bicyclobutanes from these reactions.[12] Regarding carbenoid (or "cyclopropylidine") **4a**, the C–H bond on C-5 will be more reactive than the C–H on C-2 because of the electron-withdrawing effect, on the latter hydrogen, by the C-1 methoxyl group. If insertion does indeed take place on the α CH_2 of the butyl side chain,[11] no ready explanation for the preference of insertion at C-5 relative to the side chain can be given at this time.

1-Methoxy-7-*endo*-bromobicyclo[4.1.0]hept-7-yllithium (11a).—Dibromocyclopropane **1b**, reported as being thermally unstable above 50°,[2] could be obtained satisfactorily pure by chromatography followed by low-temperature recrystallization. Reaction of **1b** with ethereal methyllithium–lithium bromide at −80°

(5) R. F. Zurcher in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. 2, J. W. Emsley, J. Feeny, and L. H. Sutcliffe, Ed., Pergamon Press, New York, N. Y., 1967, Chapter 5.

(6) B. B. Elsner and H. E. Strauss, *J. Chem. Soc.*, 588 (1957).

(7) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, Chapter 8.

(8) R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1951).

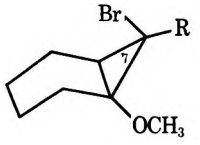
(9) (a) T. C. Shields, B. A. Shoulders, J. F. Krause, C. L. Osborn, and P. D. Gardner, *J. Amer. Chem. Soc.*, **87**, 3026 (1965); (b) J. G. Welch and R. M. Magid, *ibid.*, **89**, 5300 (1967).

(10) G. Kobrich and W. Goyert, *Tetrahedron*, **24**, 4327 (1968).

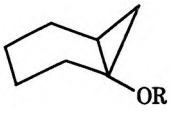
(11) A red (conjugated) DNP, isomeric with that from ketone **6**, was isolated from hydrolysis of reaction mixtures containing bicyclobutane **5**. Also, when **6** was prepared from samples of cyclohexenone **10** which contained some isomer **9**, a minor ketone product was formed which had a vpc retention time identical with that of a minor product obtained by hydrolysis of crude bicyclobutane **5**. The above data points to structure **8** as that of one of the minor products isolated when crude **5** was hydrolyzed and indicates that **4a** also yielded insertion into the α-CH_2 of the butyl side chain. One of the methoxyl signals near δ 3.12 in crude **5** may be due to the methoxyl group of this bicyclobutane.

(12) (a) W. R. Moore and B. J. King, *J. Org. Chem.*, **36**, 1877 (1971); (b) W. R. Moore and J. B. Hill, *Tetrahedron Lett.*, 4343 (1970).

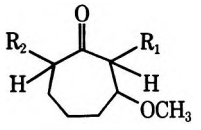
afforded carbenoid **11a** which, in contrast to **4a**, gave no evidence of decomposition at that temperature. Water or methanol quenching of **11a** gave **11b** in 70–90% yields. The monobromocyclopropane **11b** was less thermally stable than **1b** and was readily disposed toward solvolysis. As a consequence an analytical sample could not be prepared, but the weight of evidence in the chemistry cited below firmly characterized **11b**, and hence **11a**. The nmr spectrum of **11b** showed the C-7 H doublet (J = 7–8 Hz) at δ 3.22, partially obscured by the methoxyl signal. In **11c**, prepared by D_2O quenching of **11a**, the signal attributed to the C-7 H was absent and the base of the methoxyl signal was narrowed. The mass spectrum of crude **11b** gave weak molecular ions at m/e 204 and 206 in the correct intensity ratio for bromine-containing molecules and an intense base peak at m/e 125 due to $M\cdot^+-Br$. In **11c**, this base peak was moved to m/e 126.



11a, R = Li
b, R = H
c, R = D
d, R = $(C_6H_5)_2COH$



12a, R = CH_3
b, R = H
c, R = $OCC_6H_4NO_2$



13a, $R_1 = R_2 = H$
b, R_1 = D; R_2 = H
c, $R_1 = R_2$ = D

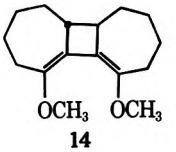
Reduction of **11b** with lithium in ethylamine gave **12a** as a minor product (11%), which was also prepared in good yield by sodium–liquid ammonia reduction of **1a** and **1b**. The major product (71%) of the Li–ethylamine reduction was, interestingly, cyclopropanol **12b**, characterized by its close nmr similarity to **12a** and by elemental analysis on it and a crystalline p-nitrobenzoate derivative **12c**.

Solvolysis of **11b** in acidic methanol–water was facile ($t_{1/2} \cong$ 3–4 hr) at room temperature, yielding 3-methoxycycloheptanone (**13a**).[3] Nmr spectra of the reaction mixture at intermediate times showed a pattern of olefinic protons which indicated the presence of 2-cycloheptenone,[3] and vpc analysis corroborated the ketone's presence. After long reaction times the unsaturated ketone had disappeared and the major product was **13a**, formed in part, presumably, by conjugated addition of methanol to 2-cycloheptenone. In ethanol–water, the 3-ethoxy derivative was formed. The solvolysis of **11b** and **11c** showed some promise as a method for the synthesis of certain deuterium analogs of **13a**. Thus, solvolysis of **11c** under mild conditions yielded **13b**. With **11b** in CH_3OD–D_2O–D^+, mild conditions gave **13c**,[13] while more vigorous acid conditions yielded 2,2,7,7-tetradeuterio-**13a**.

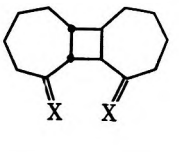
(13) D content was measured by nmr integration only. Since the C-7 protons of **13a** were not magnetically distinguishable, **13c** probably contained 7,7-dideuterio and 7,7-dihydro species as well.

Carbenoid **11a** was further characterized by reaction with benzophenone, which afforded the crystalline, relatively stable carbinol **11d** in moderate yield.

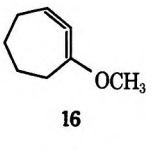
Thermolysis of 11a.—When ether solutions of **11a** were warmed from −80°, precipitation of a white solid (LiBr?) began at about −20°. Subsequent work-up yielded an oil, of which the major component (60–85%) was **14** (vpc). Diene **14** was thermally



14



15a, X = O
b, X = H, H



16

unstable, slowly dimerizing or polymerizing when kept neat at room temperature. Analytical vpc of **14** was possible and a small sample collected at low exit port temperatures showed a $M\cdot^+$ at m/e 248 in a mass spectrum recorded soon after collection. The nmr spectrum of crude **14** showed a single methoxyl peak at δ 3.60 (vinyl methoxyl) and a uv spectrum showed λ_{max} 264. Crude **14** reacted with maleic anhydride and N-phenylmaleimide with loss of its methoxyl groups, as evidenced by the nmr spectrum of the crude product. The preceding results are consistent with the (*S*)-*cis*-1,3-diene formulation of **14**. Mild acid hydrolysis rapidly converted diene **14** to the crystalline diketone **15a**, mp 78–79°, in about 50% yield. The structure and stereochemistry of **15a**, and hence **14**, rest on the following data. In addition to satisfactory elemental analysis and molecular weight determination, **15a** had a uv spectrum with λ_{max} 285 nm (ϵ 110) consistent with a diketone having isolated chromophores. The nmr spectrum of **15a** showed a two-proton doublet (J = 9 Hz) at δ 3.78 assigned as the two tertiary protons adjacent to the C=O groups. A four-proton, broadened triplet was centered at δ 2.4 and assigned as the four other α hydrogens. The chemical shift of the two remaining cyclobutane protons was determined as δ 2.2, because irradiation of the sample at that region caused the collapse of the δ 3.78 doublet to a sharp singlet. Further, diketone **15a** was configurationally stable to basic conditions which were capable of exchanging all six α hydrogens, thereby indicating cis fusion for the ring junctures. The unusually low field location of the nmr signal of the tertiary α hydrogens was more consistent with a cis–anti–cis ring system than with a cis–syn–cis ring system. Drieding models indicated that with cis–anti–cis geometry both tertiary α hydrogens lie in the plane of, and hence should be deshielded by, the nonadjacent carbonyl groups.[14] Finally, Wolff–Kishner reduction of **15a** gave hydrocarbon **15b** as a crystalline solid, mp 63–64°, different from the cis–syn–cis isomer, mp 53°, firmly characterized by Criegee and Reinhardt.[15]

The most logical precursor of diene **14** is 1-methoxycyclohepta-1,2-diene (**16**). If this is the case, then the methoxyl group of **16** causes little or no perturbation

(14) Eaton and Lin isolated **15a** [mp 79–81°, nmr δ 3.7 (2 H, d, J = 9 Hz)] as a secondary product of the thermal dimerization of *trans*-2-cycloheptenone. We thank Professor Eaton for this information. See also P. E. Eaton and K. Lin, *J. Amer. Chem. Soc. Soc.*, **87**, 2052 (1965).

(15) R. Criegee and H. G. Reinhardt, *Chem. Ber.*, **101**, 102 (1968).

of the normal stereochemistry of dimerization of cyclic, strained allenes.[16] However, the methoxyl did dramatically alter the reactivity of the carbenoid, since previously investigated "cyclopropylidines" in the bicyclo[4.1.0]heptyl series did not display any evidence of allene formation.[12a,16b]

Experimental Section

General.—All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Vapor phase chromatography (vpc) analyses were performed on an F & M Scientific Corp. instrument Model 5750 fitted with a flame ionization detector or Model 700 fitted with a thermal conductivity detector. The following columns were used: (A) 15% polytetramethylene ether glycol 3000 on Chromosorb G-NAW; (B) 10% Carbowax 20M on Chromosorb G-NAW; (C) 2% polytetramethylene ether glycol on Chromosorb G-NAW; (D) 10% silicone rubber UCW 98 on Chromosorb G-NAW; (E) 2% silicone rubber UCW 98 on Chromosorb G-NAW; (F) 2% silicone rubber UCW 98 on Diatoport S; (G) 5% UCW 98 on Chromosorb W; (H) 20% SE-52 silicone on Chromosorb G-NAW; (I) 10% Carbowax 20M on Chromosorb W 80–100; (J) 10% UCW 98 on Diatoport S; (K) Carbowax 20M on Chromosorb W-AW + DMCS, 60/80. Nmr spectra were obtained with a Varian Associates A-60A spectrometer with tetramethylsilane as an internal standard and, unless otherwise specified, deuteriochloroform was the solvent. Infrared spectra were determined on a Perkin-Elmer Model 337 grating spectrophotometer, ultraviolet spectra were obtained with a Cary Model 14 spectrophotometer, and mass spectra were obtained with an Hitachi RMU-6. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind.

All the reactions which involved the use of potassium metal, carbene addition, or the use of alkyllithium reagents were conducted in an atmosphere of dry nitrogen. The methyllithium and butyllithium reagents were titrated when required by the method of Gilman and Haubein, substituting ethylene dibromide for benzyl chloride.[17]

2-Oxo-3-chloro-3a-butyl-7a-methoxyoctahydrobenzofuran (2).—To a cooled (−80°) solution of 2.0 g (10.88 mmol) of **1a**[2] in 30 ml of ether was added butyllithium (10.88 mmol) during a period of 10 min. The solution was stirred for an additional 10 min and dry CO_2 was passed into the stirred solution for a period of 1 hr. The reaction was quenched with water, and the basic water layer was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract was dried ($MgSO_4$) and concentrated *in vacuo* to yield 0.19 g (6.7%) of an oil which solidified on standing. Recrystallization from ether–petroleum ether (bp 30–60°) yielded a white, crystalline compound: mp 76–77°; ir 1780 (C=O), 1158 (m), and 1130 cm^{-1} (w, -CO); nmr δ 4.82 (s, 1 H), 3.34 (s, 3 H), 1.6 (m, 17 H).

Anal. Calcd for $C_{13}H_{21}ClO_3$: C, 59.88; H, 8.12; O, 18.41. Found: C, 59.70; H, 7.98; O, 18.45.

6-Butyl-*endo*-7-chloro-1-methoxybicyclo[4.1.0]heptane (4b).—To a cooled (−78°), stirred solution of 0.735 g (3.80 mmol) of **1a** in 12 ml of ether was added 10 ml (10.8 mmol) of a pentane solution of butyllithium during a period of 12 min. The mixture was stirred at −78° for 45 min and quenched by the slow addition of methanol. The solution was washed with water, dried (K_2CO_3), and concentrated *in vacuo* to 1.10 g of light yellow oil. Vpc (column F) showed one major component, **4b** (74%), and two minor components of lower retention time, one of which was demonstrated to be **5** by vpc analysis (column J, 6 ft × 0.125 in., and column I, 3 ft × 0.125 in.). Analysis of the crude mixture showed the following absorptions: nmr δ 3.28 (s, 3 H, -OCH_3 of **4b**), 2.93 (s, 1 H, C-7 of **4b**), and 2.2–0.8 (multiplets, **4b**), plus a minor singlet at 3.49 (OCH_3 of **5**) having 6% of the intensity of the singlet at 3.28; ir 3045 cm^{-1} (C–H stretch, cyclopropane). Attempts at purifying **4b** by preparative vpc resulted in the collection of decomposition products.

6-Butyl-*endo*-7-chloro-*exo*-7-deuterio-1-methoxybicyclo[4.1.0]heptane (4c).—To a cooled (−78°), stirred solution of 0.785 g (4.03 mmol) of **1a** in 10 ml of ether was added 10 ml (10.8 mmol) of a pentane solution of butyllithium over a period of 13 min. After an additional 15 min of stirring at this temperature the mixture was quenched by the slow addition of 1 ml of methanol-*O-d*. After working up as for **4b** there was obtained 0.925 g of light yellow oil. Vpc using columns F, J (6 ft × 0.125 in.) and I showed one major component comprising 76, 80, and 91% of the total peak area, respectively: nmr δ 3.28 (s, 3 H, OCH_3 of **4c**) and 2.2–0.8 (m, 17 H).

6-Butyl-1-methoxybicyclo[4.1.0]heptane (4d).—To a cooled (−78°), blue solution of 0.20 g (8.7 g-atoms) of sodium in 15 ml of liquid ammonia was added, over 10 min, 0.40 g of crude **4b** (from above) in a few milliliters of pentane. After five additional minutes of stirring the cooling bath was removed and the solution was allowed to reflux for 40 min using a Dry Ice–acetone condenser. The blue color was discharged by the slow addition of ammonium chloride. There was then added 0.5 ml of methanol, the ammonia was evaporated, and 10 ml each of ether and water was added. After washing, drying (K_2CO_3), and concentrating *in vacuo* there was obtained 0.275 g of light yellow oil. Vpc (column K) showed that the major product (**4d**) comprised 61% of all the components and the estimated yield by vpc was greater than 50%. The major component was collected from column K and recollected from column J for spectra and elemental analysis: nmr (CCl_4) δ 3.31 (s, 3 H, OCH_3), 2.2–0.8 (multiplets, 17 H), 0.40 (d, 1 H, J_{gem} = −5.5 Hz), and 0.24 (d, 1 H, J_{gem} = −5.5 Hz); ir (CCl_4) 3065 cm^{-1} (C–H stretch, cyclopropane).

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.84; H, 12.00.

6-Butyl-*endo*-7-chloro-1-methoxybicyclo[4.1.0]hept-7-yllithium (4a) at −78° for 3.5 Hr.—To a stirred, cooled (−78°) solution of 0.173 g (0.89 mmol) of **1a** in 5 ml of ether was added 1.75 ml (1.89 mmol) of a pentane solution of butyllithium. The solution was stirred at −78° for 3.5 hr and remained clear. The mixture was quenched by the slow addition of an equimolar mixture of methanol and methanol-*O-d*. After washing, drying (K_2CO_3), and evaporating solvent *in vacuo* there was obtained 0.176 g of nearly colorless oil. The vpc traces (columns I and J) showed the two major components to be **4b**(c) and **5** in amounts of 45 and 22%, respectively.

Nmr analysis showed singlets at δ 3.57–3.15 and multiplets at δ 2.2–0.8 in a ratio of 1:6. The major singlets were at δ 3.49 (OCH_3 of **5**) and 3.28 (OCH_3 of **4b**) and they constituted 35 and 52%, respectively, of the total peak area in the methoxyl region. Also there was a singlet at δ 2.93 (C-7 of **4b**) integrating for $^1/_6$th of the singlet at δ 3.49. (This fact indicated that carbenoid **4a** had not abstracted H from the reaction medium during the reaction time.) Also, there was a doublet at δ 0.69 (J = 1 Hz, C-7 of **5**) with an intensity equal to $^1/_3$rd of the δ 3.49 singlet.

Stability of 4a at −35°.—To a cooled (−78°) stirred solution of 0.20 g (1.03 mmol) of **1a** in 4 ml of ether was added, over 12 min, 2.1 ml (2.27 mmol) of a pentane solution of butyllithium. The mixture was stirred at −78° for an additional 5 min, warmed over a 20-min period to −35°, and maintained at this temperature (±3°) for 65 min, by which time a heavy, white precipitate was noted. The reaction mixture was quenched by the addition of methanol. After washing, drying (K_2CO_3), and evaporating solvent *in vacuo* there was obtained 0.196 g of light yellow oil. Vpc by two columns (I and J, 6 ft × 0.125 in.) showed one major component accounting for 70% of the total peak area, two minor peaks of higher retention time, and no **4b**.

Nmr showed absorptions at δ 3.49–3.13 (singlets) and 2.5–0.6 (multiplets) in a ratio of 1:5.6. The singlet at δ 3.49 accounted for greater than 60% of all the singlet integration. There was a doublet at δ 0.69 (C-7 of **5**) which integration showed was $^1/_3$rd of the area of the singlet at δ 3.49.

Formation of 4a and 5 by Rapid Addition of Butyllithium to a −78° Solution of 1a.—To a stirred, cooled solution of 0.42 g (2.15 mmol) of **2a** in 6 ml of ether was added, over 3 min, 4.5 ml (4.82 mmol) of a pentane solution of butyllithium. Stirring was continued at −78° for 47 min. The reaction mixture was quenched with methanol, washed with water, dried (K_2CO_3), and evaporated to 0.399 g of light yellow oil. Vpc (columns I and J, 6 ft × 0.125 in.) showed the major component, **4b**, to account for 62 and 65%, respectively, of all the peak areas. Also, vpc using these columns indicated that one of the minor components in significant proportion was **5**. In the nmr, the major low field singlets were at δ 3.49 (OCH_3 of **5**), 3.28 (OCH_3 of **4b**), and 2.93 (C-7 of **4a**), in a ratio of 1.8:3:1. The ratio of high-field multiplets to the singlets at low field, exclusive of the C-7 H of **5** (δ 0.69, d) was 6.7:1. The reason for this ratio being slightly

(16) (a) W. R. Moore, R. D. Bach, and T. M. Ozretich, *J. Amer. Chem. Soc.*, **91**, 5918 (1969); (b) W. R. Moore, and W. R. Moser, *ibid.*, **92**, 5469 (1970).

(17) H. Gilman and A. H. Haubein, *ibid.*, **66**, 1515 (1944).

greater than the expected 17:3 value might be explained by the fact that a blank experiment, using only butyllithium and ether, showed absorptions in the high-field region and none in the methoxyl region of the nmr spectrum.

1-Butyl-2-methoxytricyclo[4.1.0.0^{2,7}]heptane (5).—To a cooled (−80°) solution of 9.0 g (49.1 mmol) of 1a in 150 ml of ether was added butyllithium (122.0 mmol) during a period of 5 min. The mixture was stirred at −80° for 1 hr, allowed to warm to room temperature over 25 min, and quenched by the addition of water. The ether layer was washed with two portions of water, dried ($MgSO_4$), and concentrated *in vacuo*. This yielded 10.22 g of an amber oil. Vpc (column F, 6 ft × 0.125 in.) showed one major component and three minor components with higher retention times. Attempts to purify the major component by distillation and preparative vpc (columns A, B, D, F, H, 6 ft × 0.25 in.) were unsuccessful.

Deuterium Exchange at C-7 of 1-Butyl-2-methoxytricyclo-[4.1.0.0^{2,7}]heptane (5).—To a cooled (−78°), stirred solution of 0.30 g (1.55 mmol) of 1a in 8 ml of ether was added, over 12 min, 3.8 ml (4.10 mmol) of a pentane solution of butyllithium. The solution was warmed to 25° over a 1-hr period, by which time a heavy precipitate had formed. To this mixture was added an additional 4.32 mmol of butyllithium, after which the mixture was stirred for 4 hr at room temperature (some darkening) and quenched with deuterium oxide. The usual work-up yielded 0.459 g of yellow oil. An nmr spectrum on this crude mixture clearly showed, in addition to increased absorption in the δ 2.5–0.8 region, an intensity reduction of 57 (±3)% for the doublet at δ 0.69 (C-7 of 5) relative to the singlet at δ 3.49 (OCH_3 of 5).

1-Butylbicyclo[4.1.0]heptan-2-one (6) from 5.—To a stirred ether solution of 10.22 g of the crude product containing 5 was added 4 drops of 4 *N* sulfuric acid. The reaction was followed by vpc (column F, 6 ft × 0.125 in.) by observing the disappearance of one major peak and the appearance of another at a higher retention time. The reaction was essentially complete after 18 hr. The ether solution was washed with sodium bicarbonate solution and water, dried ($MgSO_4$), and concentrated *in vacuo*. The remaining yellow oil was distilled and the fraction boiling at 80–83° (0.3 mm) was collected. This yielded 3.77 g of 6 (>90% purity) as a yellow oil or 46.5% based on starting compound 1a. The vpc (column C, 6 ft × 0.125 in.) yield was found, using an internal standard (acetophenone), to be 50.4%: ir 3070 (CH cyclopropane), 1695 cm^{-1} (C=O).

The red dinitrophenylhydrazone was prepared and recrystallized from ethanol (95%), mp 120–123°.

Anal. Calcd for $C_{17}H_{22}N_4O_4$: C, 58.94; H, 6.40; N, 16.17. Found: C, 58.85; H, 6.53; N, 16.28.

An isomeric DNP was also obtained as a minor product, mp 187–187.5°, red crystals from 95% ethanol.

Anal. Found: C, 58.95; H, 6.51; N, 16.30.

The semicarbazone was prepared with heating and recrystallized from ethanol–water, mp 189–190.5°.

Anal. Calcd for $C_{12}H_{21}N_3O$: C, 64.54; H, 9.48; N, 18.82. Found: C, 64.40; H, 9.43; N, 18.76.

2-Chloro-2-butylcyclohexanone.—To a stirred solution of 35.22 g (0.23 mmol) of 2-butylcyclohexanone[6] in 120 ml of dry carbon tetrachloride was added 33.8 g (0.25 mol) of sulfuryl chloride in 35 ml of carbon tetrachloride during a 1-hr period. The slightly exothermic reaction was moderated by cooling with a water bath at room temperature. After the addition was completed, stirring was continued for 2 hr. The clear, colorless solution was then washed successively with three portions of water, two portions of saturated sodium bicarbonate solution, and one portion of saturated salt solution, and dried ($MgSO_4$). The solvent was removed by distillation, first at atmospheric pressure and finally at reduced pressure (2.5 mm). The residue was distilled and yielded, after a small forerun, 36.6 g (85%) of a clear, colorless oil: bp 101–103° (2.5 mm); ir 1750 cm^{-1} (C=O); nmr (CCl_4) δ 3.12 (triplet of doublets, J_{gem} = −14, J_{vic} = 14.5, 5.5 Hz, H-6 axial), 1.6 (m, 16 H).

Anal. Calcd for $C_{10}H_{17}ClO$: C, 63.64; H, 9.08; O, 8.48. Found: C, 63.86; H, 8.92; O, 8.71.

2-Butyl-2-cyclohexanone (10).[18]—To 60 ml of distilled dimethylformamide was added 36.6 g (0.19 mol) of 2-chloro-2-2-butylcyclohexanone and 6.0 g of anhydrous lithium chloride. The stirred mixture was maintained, under a nitrogen atmosphere, at 100° (oil bath) for 45 min. The mixture was cooled, poured into 250 ml of ether and 250 ml of 2.5% sulfuric acid, and stirred at room temperature for 4 hr. The layers were separated and the water layer was saturated with sodium chloride, then extracted with two portions of ether. The organic layers were combined, washed with one portion of saturated sodium chloride solution and two portions of saturated sodium bicarbonate solution, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was distilled through a heated column packed with glass helices and the fraction boiling at 81.5–92° (1.6 mm) was collected. Vpc (column F, 6 ft × 0.125 in.) showed two components in about a 4:1 ratio. This material was redistilled (6.8 mm) using spinning band apparatus. The major component was collected in an overall yield of 51% as estimated from vpc: uv λ_{max} 237 nm (ε 8480), calcd λ_{max} 237; ir 1675 (-C=O) and 1630 cm^{-1} (C=C); nmr δ 6.67 (br t, J = 3–4 Hz, 1 H), 2.2 (m, 8 H), 1.4 (m, 4 H), 0.95 (~t, $J \cong 6$ Hz, 3 H).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59; O, 10.51. Found: C, 78.64; H, 10.51; O, 10.24.

The dinitrophenylhydrazone was prepared and recrystallized from ethanol (95%) to yield red-orange crystals, mp 134–135°.

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.06; N, 16.85. Found: C, 57.65; H, 6.27; N, 16.67.

2-Butylidenecyclohexanone (9).—The minor component from the above spinning band distillation was collected: uv λ_{max} 244 nm (ε 8130), calcd λ_{max} 242; ir 1695 (-C=O) and 1625 cm^{-1} (C=C); nmr δ 6.61 (triplet of triplets, J = 7 and 2 Hz, 1 H), 2.6–1.2 (m, 12 H), 0.93 (t, J = 6 Hz, 3 H).

The dinitrophenylhydrazone was prepared and recrystallized from ethanol (95%) to yield deep red needles, mp 123.5–124.5°.

Anal. Calcd for $C_{16}H_{20}N_4O_4$: C, 57.82; H, 6.06; N, 16.85. Found: C, 57.87; H, 6.26; N, 16.68.

1-Butylbicyclo[4.1.0]heptan-2-one (6) from the Reaction of 10.—Sodium hydride, 1.55 g (53.6% mineral oil dispersion), was washed three times with petroleum ether to remove the mineral oil. The remaining petroleum ether was removed under vacuum. The vacuum was released to a dry nitrogen source and 7.5 g (34.0 mmol) of dry powdered trimethylsulfoxonium iodide was added to the dry powdered sodium hydride. The mixture was stirred during the dropwise addition of 25 ml of dimethyl sulfoxide (distilled over calcium hydride). A vigorous evolution of hydrogen ensued, which ceased after 15–20 min to give a milky white reaction mixture. The reaction was submerged in a water bath and 4.7 g (31.0 mmol) of 10 in 5 ml of dimethyl sulfoxide was added. The reaction mixture was stirred at room temperature for 2 hr, then at 50° for 1 hr, poured into 80 ml of cold water, and extracted with ether. The ether extracts were washed with two portions of water, dried ($MgSO_4$), and concentrated *in vacuo* to leave a pale yellow oil. Distillation yielded 3.32 g (65.4%) of a colorless liquid, bp 97–99° (1.9 mm). The product was checked on three columns (C, E, and G, 6 ft × 0.125 in.) with the ketone 6 obtained from 5. The retention times were identical in all three cases: ir 3070 (-CH cyclopropane) and 1695 cm^{-1} (-C=O).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.90. Found: C, 79.71; H, 11.01.

The semicarbazone was prepared and recrystallized from ethanol–water, mp 189–190.5°. A mixture melting point with the previously prepared semicarbazone of 6 was undepressed.

The dinitrophenylhydrazone was prepared and recrystallized from ethanol (95%), mp 121–125°. A mixture melting point with the previously prepared dinitrophenylhydrazone of 6 was undepressed.

Anal. Calcd for $C_{17}H_{22}N_4O_4$: C, 58.94; H, 6.40. Found: C, 59.23; H, 6.66.

1-Methoxy-7,7-dibromobicyclo[4.1.0]heptane (1b).—To 300 ml of *tert*-butyl alcohol (distilled over sodium) was added 9.8 g (0.25 mol) of potassium. The mixture was heated until dissolution occurred. The excess *tert*-butyl alcohol was removed *in vacuo* with mild heating. The remaining potassium *tert*-butoxide was broken up and 30.0 g (0.25 mol) of 1-methoxycyclohexene in 90 ml of pentane was added. The resulting slurry was cooled to −20° (ice–acetone) and 56.2 g (0.22 mol) of bromoform in 75 ml of pentane was added during a period of 1 hr. The mixture was stirred for an additional 1 hr at −20° and quenched with water. The organic layer was washed with two portions of water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was placed *in vacuo* at 0.5 mm for 15 min. The remaining red oil was dissolved in pentane and passed over a column (40.0 g)

(18) E. W. Warnhoff, D. G. Martin, and W. S. Johnson, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 162, report the synthesis of 2-methyl-2-cyclohexenone by this chlorination–dehydrochlorination sequence.

of neutral alumina. The first 150 ml of eluent was collected and concentrated *in vacuo* to yield 43.52 g (70.5%) of a yellow oil. This material could be further purified by low-temperature (−80°) crystallization. The yellow oil was dissolved in pentane and cooled to −80°. The supernate was decanted from the crystals. This was repeated twice to yield 23.3 g (33.2%) of a clear, colorless oil. This oil when stored at −20° gave a white, crystalline solid which appeared to be stable indefinitely at this temperature, nmr δ 3.43 (s, 3 H), 1.8 (m, 9 H).

1-Methoxybicyclo[4.1.0]heptane (12a) from 1b.—To a cooled (−80°) solution of 0.5 g (2.17 mmol) of sodium in 75 ml of ammonia was added 2.0 g (10.8 mmol) of **1b** in 25 ml of ether during a period of 1 hr. The cooling bath was removed and the blue solution was refluxed, using a Dry Ice–acetone condenser, for 30 min. The blue color was discharged by the careful addition of ammonium chloride followed by the addition of 2 ml of methanol. The ammonia was allowed to evaporate, and an additional 30 ml of ether and 50 ml of water were added. The resulting ether layer was washed with two portions of water, dried ($MgSO_4$), and concentrated *in vacuo*. The major component was collected from preparative vpc (column D, 6 ft × 0.25 in.): ir 3070 (–CH cyclopropane) and 2825 cm^{-1} (–OCH_3); nmr δ 3.25 (s, 3 H), 1.67 (m, 10 H), 0.23 (q, J_{gem} = −5.75 and J_{trans} = 4.5 Hz, 1 H).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.36; H, 11.19.

12a from 1a.—The above procedure was repeated using **1a**. The major component was collected. The ir spectrum was identical with the one obtained from the reduction of **1b**.

***endo*-7-Bromo-1-methoxybicyclo[4.1.0]heptane (11b).**—To a stirred solution of 2.22 g (0.00783 mol) of **1b** in 30 ml of anhydrous ethyl ether cooled to −80° was slowly added 1 equiv of methyllithium–lithium bromide in ether. The mixture was stirred for an additional 30 min at −80° before quenching with water. The solution was brought to room temperature and the organic layer was separated, washed with two portions of water, and dried (K_2CO_3). Concentration of the solution yielded 970 mg of a yellow oil: a test for bromide was positive and rapid; nmr δ 3.3 (d, 1 H at C-7), 3.22 (s, 3 H, –OCH_3), 2.2–1.0 (m, 9 H); mass spectrum *m/e* 204, 206 ($M\cdot^+$), 125 (base peak, $M\cdot^+$ − Br).

***endo*-7-Bromo-*exo*-7-deuterio-1-methoxybicyclo[4.1.0]heptane (11c).**—To a stirred solution of 2.04 g (0.0072 mol) of **1b** in 30 ml of anhydrous ethyl ether, cooled to −80°, was added 9 ml of CH_3Li–LiBr in ether. The solution was stirred for 15 min, quenched with deuterium oxide, and warmed to room temperature. The organic phase was washed twice with water and then dried (K_2CO_3). Concentration *in vacuo* yielded 1.10 g of yellow oil: a silver nitrate test for bromide was positive and rapid; nmr δ 3.25 (s, 3 H), 1.0–2.7 (m, 10 H); mass spectrum *m/e* 126 (base peak, $M\cdot^+$ − Br).

Bicyclo[4.1.0]heptan-1-ol (12b) from 11b.—Five grams (17.5 mmol) of **1b** was treated with methyllithium and worked up as above.

To a blue solution of 250 ml of distilled ethylamine and 1.5 g of lithium metal (rinsed in pentane) was added the crude **11b** from above in 50 ml of pentane at such a rate to maintain the blue color. The blue solution was refluxed, using a Dry Ice–acetone condenser, for 7 hr. The blue color was discharged with ammonium chloride and the excess lithium metal was removed with tweezers. The ethylamine was distilled and 100 ml of ether was added. The ether layer was washed with two portions of saturated sodium chloride solution, dried ($MgSO_4$), and concentrated *in vacuo*. Vpc (column C, 6 ft × 0.125 in.) showed one minor and one major component. The minor component was identified as **12a** by comparing its retention time on three columns (C and F, 6 ft × 0.125 in., and G, 6 ft × 0.25 in.) with an authentic sample. The yield of **12a** was 11.3% as estimated from vpc. Collection of the major component with preparative vpc (column G, 6 ft × 0.25 in.) yielded 1.4 g (71.2%, calculated from starting **1b**) of **12b**: ir 3300 (–OH) and 3075 cm^{-1} (–CH cyclopropane); nmr δ 3.06 (s, 1 H), 1.76 (m, 10 H), 0.29 (q, J_{gem} = −5.5 and J_{trans} = 4.8 Hz, 1 H).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78; O, 14.26. Found: C, 74.81; H, 10.68; O, 14.42.

The *p*-nitrobenzoate was prepared and recrystallized from ethanol (95%), mp 153–153.5°.

Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.78; O, 24.49. Found: C, 64.60; H, 5.70; O, 24.26.

3-Methoxycycloheptanone (13a).—To a solution of 15 ml of methanol, 5 ml of water, and 1 drop of sulfuric acid was added 0.74 g of **11b**. After stirring for 24 hr at room temperature, the organic phase was separated by addition of chloroform and washed three times with water. After drying (K_2CO_3), concentration *in vacuo* gave 460 mg of amber oil. Vpc (column F, 6 ft × 0.125 in.) showed only one component, **13a**: nmr δ 3.4 (broad m, 1 H at C-3), 3.32 (s, 3 H, –OCH_3), 2.77 (m, 2 H at C-2), 2.65–2.27 (m, 2 H at C-7), 2.08–1.50 (m, 6 H); ir (neat) 1695 cm^{-1}. The nmr data were identical with those reported in the literature.[3]

3-Methoxy-2-deuteriocycloheptanone (13b).—To 0.103 g (0.000503 mol) of **11c** was added 3 ml of 0.161 *N* standardized methanol–water (3:1)–sulfuric acid solution. After stirring for 29 hr at room temperature, the organic phase was separated by addition of chloroform, washed twice with water, dried (K_2CO_3), and concentrated *in vacuo* to give 60 mg of amber oil. Preparative vpc (column F, 6 ft × 0.25 in.) of the major component gave **13b**: nmr δ 3.5 (m, 1 H at C-3), 3.35 (s, 3 H –OCH_3), 2.8 (m, 1 H at C-2), 2.65-2.30 (m, 2 H at C-7), 2.15–1.50 (m, 6 H).

3-Methoxy-2,7-dideuteriocycloheptanone (13c).—To 0.303 g (1.49 mmol) of **11b** was added a 5-ml solution of methanol-*O*-d_1–deuterium oxide (3:1) sulfuric acid-d_2 (taken from stock solution of 15 ml of methanol-*O*-d_1, 5 ml of deuterium oxide, and 1 drop of sulfuric acid-d_2). After stirring for 24 hr at room temperature the usual work-up gave 200 mg of amber oil. Vpc (column F, 6 ft × 0.25 in.) showed one major and one minor component. Preparative vpc of the major component gave **13c**: nmr δ 3.5 (m, 1 H at C-3), 3.35 (s, 3 H, –OCH_3), 2.8 (m, 1 H at C-2), 2.65-2.30 (m, 1 H at C-7), 2.0–1.55 (m, 6 H).

Preparative vpc (column F, 6 ft × 0.25 in.) of the minor component gave 2-cycloheptenone.

3-Methoxy-2,2,7,7-tetradeuteriocycloheptanone.—To 0.144 g (0.7 mmol) of **11c** was added a 3-ml solution of the methanol-*O*-d_1–deuterium oxide (3:1)–sulfuric acid-d_2 (taken from the stock solution of 15 ml of methanol-*O*-d_1–5 ml of deuterium oxide, and 1 drop of sulfuric acid-d_2). After stirring for 29 hr the usual work-up gave 85 mg of amber oil. Preparative vpc (column F, 6 ft × 0.25 in.) of the major component gave the title compound: nmr δ 3.5 (m, 1 H at C-3), 3.34 (s, 3 H, –OCH_3), 2.8 (less than 0.1 H), 2.65–2.3 (m, 0.4–0.5 H at C-7), 2.1–1.5 (m, 6 H).

***endo*-7-Bromo-*exo*-7-(diphenylmethanol)-1-methoxybicyclo-[4.10]heptane (11d).**—To 2.44 g (0.008 mol) of **1b** in 25 ml of anhydrous ethyl ether at −80° was added 4.5 ml of methyllithium–lithium bromide. The solution was stirred at −80° for 30 min and then treated with 1.57 g of benzophenone in 5 ml of ether. The reaction mixture was stirred for an additional 15 min and then quenched with 5 ml of water and warmed to room temperature. The organic phase was washed thrice with water and then dried (K_2CO_3). Concentration *in vacuo* yielded, after triturating with pentane, 860 mg of crystals mp 91–96°. Recrystallizing from hexane gave 520 mg of **11d**, mp 94–96°, ir (CCl_4) 3500 cm^{-1}.

Anal. Calcd for $C_{21}H_{23}BrO_2$: C, 65.10; H, 5.95; Br, 20.67. Found: C, 64.91; H, 6.13; Br, 20.78.

From the mother liquors there was recovered 1.4 g of **11b**.

3,14-Dimethoxytricyclo[7.5.0.0^{2,8}]tetradeca-2,14-diene (14).—To a cooled (−80°) solution of 2.0 g of **1b** in 25 ml of anhydrous ether was added 3.48 ml of methyllithium–lithium bromide (10% excess). The solution was stirred for an additional 15 min, and then warmed to room temperature and stirred for 30 min. After quenching with 5 ml of water, the orgainc layer was washed twice with 30 ml of water and dried (K_2CO_3). Concentration *in vacuo* yielded 0.570 g of amber oil. Vpc (column G) showed one major (85%) and at least one minor peak. A mass spectrum on a sample of the major peak collected from the vpc column gave *m/e* 248 ($M\cdot^+$): nmr δ 3.6 (s, 6 H, OCH_3), 2.8–1 (m, 18 H); uv λ_{max}^{EtOH} 264 nm.

Tricyclo[7.5.0.0^{2,8}]tetradeca-3,14-dione (15a).—To a solution of 55 ml of methanol, 10 ml of water, and 5 drops of sulfuric acid was added 2.7 g of **14**. After stirring for 24 hr at room temperature, the organic phase was separated by addition of chloroform, washed three times with water, dried (K_2CO_3), and concentrated *in vacuo* to give 2.2 g of amber oil. Column chromatography using acid-washed alumina and eluting with ether–pentane gave 1.16 g of crystals, mp 73–77°. Recrystallization from pentane gave white crystals: mp 78–79°; nmr δ 3.78 (d, 2 H, *J* = 9 Hz), 1.0–2.8 (m, 18 H); mol wt, 218 (Rast), 220 (mass spectrum); uv λ_{max}^{EtOH} 285 nm (ε 110).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.61; H, 8.88.

Base Stability of **15a**.—A solution of 50 mg of **15a** and 1 equiv of sodium methoxide in 3 ml of anhydrous methanol was stirred at room temperature for 17 hr. The reaction solution was then poured into water, neutralized, and extracted three times with 10-ml portions of chloroform. The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield a solid. The nmr of the solid was identical with that of **15a** before reaction.

Heating the same sample of **15a** under the above conditions at 55° for 20 hr showed no change in its nmr. Recrystallizing the resulting solid from pentane gave 15 mg, mp 74–76°. Vpc (column F) showed only **15a**.

At room temperature, treatment of **15a** with sodium methoxide in methanol-*O*-*d* resulted in the exchange of all six H's α to the carbonyl groups as determined by nmr.

Wolff–Kishner Reduction of 15a.—A solution of 103 mg (0.468 mmol) of dione **15a** and 4 ml of 99% hydrazine hydrate in 4 ml of diethylene glycol was refluxed for 2 hr. The excess hydrazine hydrate and water were distilled off and 0.4 g of sodium hydroxide was added. The temperature was then raised to 190° for 24 hr. The solution was cooled, poured into 100 ml of water, and extracted three times with 30-ml portions of pentane. After the organic phase was dried (Na_2SO_4), concentration *in vacuo* gave 80 mg of white, oily solid. Recrystallization from ethanol gave 40 mg of crystal, mp 64–65°, nmr δ 0.9–2.3. Preparative vpc gave an analytical sample, mp 64–65°.

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.20; H, 12.80.

Registry No.—**1b**, 3045-92-9; **2**, 34737-28-5; **4a**, 34737-29-6; **4b**, 34737-30-9; **4c**, 34737-31-0; **4d**, 34737-32-1; **5**, 34737-33-2; **6**, 34737-34-3; **6** 2,4-DNPH, 34737-35-4; **6** semicarbazone, 34737-36-5; **9**, 7153-14-2; **9** 2,4-DNPH, 34737-38-7; **10**, 34737-39-8; **10** 2,4-DNPH, 34737-40-1; **11a**, 34737-41-2; **11b**, 34737-42-3; **11c**, 34737-43-4; **11d**, 34739-96-3; **12a**, 34737-44-5; **12b**, 34737-45-6; **12b** *p*-nitrobenzoate, 34737-46-7; **13b**, 34737-47-8; **13c**, 34737-48-9; **14**, 34737-49-0; **15a**, 34737-50-3; **15b**, 34737-51-4; 2-chloro-2-butylcyclohexanone, 34737-52-5; 3-methoxy-2,2,7,7-tetradeuteriocycloheptanone, 34737-53-6.

Acknowledgment.—The authors wish to acknowledge the technical help of Chemistry 391 student Abel Coronel. Also, funds for the Hitachi RMU-6 mass spectrometer were provided, in part, by Grant No. GP8643 from the National Science Foundation.

Palladium(II)-Catalyzed Exchange and Isomerization Reactions. IV. The Exchange of Vinylic Chloride with Radioactive Lithium Chloride Catalyzed by Palladium(II) Chloride in Acetic Acid[1]

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Received September 20, 1971

In its simplest form the rate expression for exchange is rate = $k[Li_2Pd_2Cl_6]$[vinyl chloride]. By analogy with the kinetics of other Pd(II)-catalyzed exchanges a more meaningful form of the rate expression is believed to be rate = k $[Li_2Pd_2Cl_6]$[vinyl chloride][LiCl]/[LiCl]. This rate expression is consistent with a rapid preequilibrium to give a π complex followed by attack of chloride in the rate-determining step. Stereochemical results with *cis*- and *trans*-1-chloropropene were inconclusive because of a side reaction involving cis–trans isomerization without exchange. The mechanism most consistent with all the facts involves chloropalladation to give a σ-bonded Pd(II) intermediate. Dechloropalladation of this intermediate completes exchange. The fact that 1-chlorocyclopentene exchanges indicates that chloropalladation is not stereospecific. However, independent evidence suggests that cis chloropalladation using chloride from the coordination sphere of Pd(II) is more important than trans chloropalladation from outside the coordination sphere. Methyl substitution on the double bond retards chloride exchange but not as much as substitution retards acetate exchange of vinyl acetates. The difference is believed to be due to greater steric hindrance in trans acetoxypalladation than in cis chloropalladation.

The previous papers of this series have dealt with Pd(II)-catalyzed exchange and isomerization reactions of vinyl and allylic esters. The exchange reaction is shown in eq 1 using vinyl and allyl propionate as examples. This paper will be the first in the series to consider the reactions of another type of unsaturated substrate, namely vinylic chlorides. The reaction studied will be chloride exchange with radioactive chloride.

$$\begin{matrix}CH_2{=}CHOOCC_2H_5\\CH_2{=}CHCH_2OOCC_2H_5\end{matrix} + OAc^- \xrightarrow{Pd(II)} \begin{matrix}CH_2{=}CHOAc\\CH_2{=}CHCH_2OAc\end{matrix} + {}^-OOCC_2H_5 \quad (1)$$

The previous studies showed that these Pd(II)-catalyzed vinylic[3] and allylic[4] ester exchanges with acetate have the rate expression shown in eq 2 where k' is the rate constant for an acetate independent reaction

$$\text{rate} = \frac{[Li_2Pd_2Cl_6][\text{olefin}]}{[LiCl]}(k' + k''[LiOAc]) \quad (2)$$

and k'' the rate constant for a reaction first order in acetate.

The first step in both reactions is apparently π-complex formation between the Pd(II) dimer and the olefin portion of the unsaturated ester. This π-complex

$$Li_2Pd_2Cl_6 + >C{=}C< \underset{}{\overset{HOAc}{\rightleftharpoons}} LiPd_2Cl_5(>C{=}C<) + LiCl \quad (3)$$

formation accounts for the first-order terms in $[Li_2Pd_2Cl_6]$ and olefin, as well as the [LiCl] inhibition. The stereochemical evidence indicates that the next step in the exchange reactions almost certainly involves attack of solvent acetic acid or acetate ion to give an acetoxypalladation adduct which then undergoes deacyloxypalladation to give exchange. The allylic isomeriza-

(1) (a) Hercules Research Center Contribution No. 1563. (b) Paper III: P. M. Henry, *J. Amer. Chem. Soc.*, **94**, 5200 (1972).

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(3) P. M. Henry, *J. Amer. Chem. Soc.*, **93**, 3853 (1971).

(4) P. M. Henry, *ibid.*, **94**, 1527 (1972).

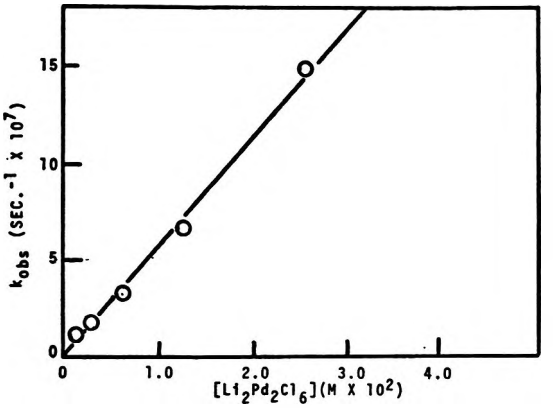
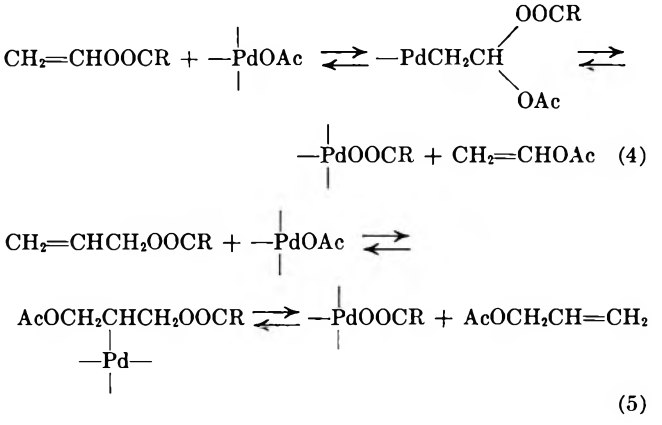
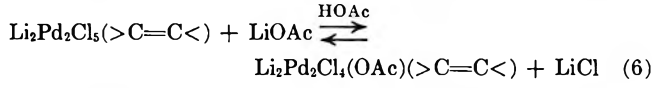


Figure 1.—Plot of k_{obsd} *vs.* $[Li_2Pd_2Cl_6]$. Vinyl chloride concentration is that of a saturated solution at 1 atm vinyl chloride or *ca.* 1.70 *M*.

tion reaction requires no external reagent after π-complex formation, since it involves internal attack of the ester group to give an acetoxonium ion type intermediate.



The rate expression for exchange (eq 1) does not involve a second [LiCl] inhibition term, which would be expected if LiOAc were coordinating before attack.



For that reason, plus other chemical evidence,[5] it is believed that LiOAc is attacking from outside the coordination sphere to give trans addition. Stereochemistry of exchange of vinyl chlorides with acetate indicates that acetoxypalladation and dechloropalladation have different stereochemistries.[6] This would suggest that dechloropalladation has cis stereochemistry. Chloropalladation, because of the principle of microscopic reversibility, would also have cis stereochemistry. This work was undertaken to determine the rate expression for chloride exchange and to interpret the rate expression in terms of stereochemical evidence.

Results

All runs were carried out at 25° in dry acetic acid containing various amounts of $PdCl_2$ and LiCl. The concentrations of the various species present under any given set of reaction conditions were calculated using

(5) P. M. Henry, *J. Amer. Chem. Soc.*, **93**, 1494 (1971).
(6) E. W. Stern, *Catal. Rev.*, **1**, 73 (1967) (see page 125); A. Sabel, J. Smidt, R. Jira, and H. Prigge, *Chem. Ber.*, **102**, 2939 (1969).

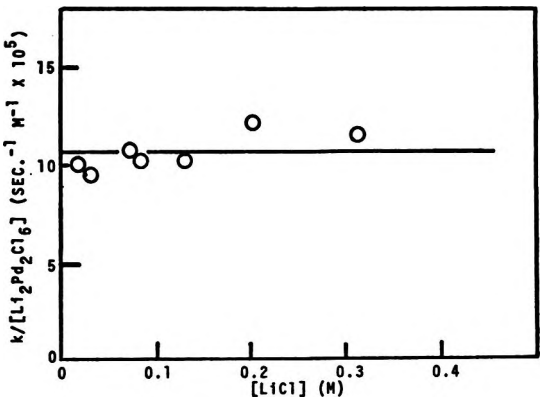
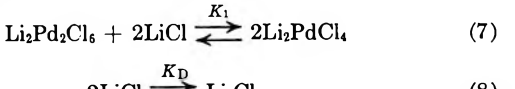


Figure 2.—Plot of $k/[Li_2Pd_2Cl_6]$ *vs.* [LiCl].

the previously determined[7] values of K_1 and K_D for the equilibria represented by eq 7 and 8. The value of K_1



is 0.1 M^{-1} and the value of K_D is 2.56 M^{-1} at 25°.

The exchange rates were measured using radioactive LiCl. A plot of k_{ex} *vs.* $[Li_2Pd_2Cl_6]$ at constant [LiCl] is shown in Figure 1. The straight line with zero intercept indicates a reaction first order in $[Li_2Pd_2Cl_6]$.

The plot of $k_{obsd}/[Li_2Pd_2Cl_6]$ *vs.* [LiCl], shown in Figure 2, is indicative of a reaction zero order in [LiCl]. LiOAc did not affect the kinetics. Rates were the same within experimental error for two runs, one of which was 1 *M* in LiOAc and one of which did not contain LiOAc.

The order in the vinylic chloride was determined using isopropenyl chloride (see Experimental Section for discussion of the kinetics of isotope exchange). As shown in Table I, the value of the experimental rate

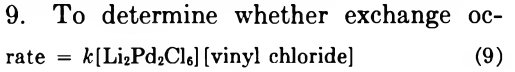
TABLE I
EFFECT OF ISOPROPENYL CHLORIDE CONCENTRATION ON THE EXPERIMENTAL RATE CONSTANT[a]

Isopropenyl chloride, *M*	k, sec^{-1} X 10^5
0.2	6.6
1.0	6.6

[a] $[Pd(II)]_t$ = 0.060 *M*; $[Cl]_t$ = 0.22 *M*.

constant, assuming a reaction first order in vinylic chloride, does not change with concentration of the vinyl chloride, indicating a first-order reaction.

The rate expression for exchange in its simplest form is thus eq 9. To determine whether exchange oc-



curred with isomerization, a sample of *trans*-propenyl chloride was isomerized in a solution containing radioactive LiCl. The activities of the *cis*- and *trans*-propenyl chlorides were determined at various times. Data are given in Table II. These results indicate that isomerization is much faster than exchange.[8]

(7) P. M. Henry and O. Marks, *Inorg. Chem.*, **10**, 373 (1971).
(8) This isomerization without exchange reaction, which was also detected in the vinyl ester exchange studies,[3] is apparently independent of the exchange reaction. A preliminary communication[9] on the isomerization reaction has appeared and it is the subject of two of the following papers in the series.
(9) P. M. Henry, *J. Amer. Chem. Soc.*, **93**, 3547 (1971).

TABLE II

ISOMERIZATION OF *trans*-PROPENYL CHLORIDE IN A REACTION MIXTURE CONTAINING INORGANIC RADIOACTIVE CHLORIDE[a]

		Specific activity of propenyl chloride, specific activity of inorganic chloride[b]	
Time, hr	% cis[c]	cis[d]	trans[d]
4:18	15.3	0.026[e]	
7:10	23.7	0.018[e]	0.008[e]
24:28	54.3	0.058	
31:04	59.0	0.044	0.026
54:53	67.1	0.046	0.046

[a] $[Pd(II)]_t = 0.01552\ M$; $[Cl]_t = 0.0524\ M$. [b] Specific activity of inorganic chloride is $1.5 \times 10^{-2}\ \mu Ci/mmol$. [c] Per cent cis at equilibrium is 74%. [d] If exchange occurred every time isomerization occurred the value of this ratio would be 1.0. [e] These values are less accurate than others because of small amounts of cis isomers present.

The rates of exchange of several substituted vinyl chlorides are given in Table III.

TABLE III

RATES OF EXCHANGE OF SEVERAL VINYLIC CHLORIDES AT 25° IN ACETIC ACID CATALYZED BY Pd(II)

Vinylic chloride	k, $M^{-1}\ sec^{-1} \times 10^5$
Vinyl chloride	10
1-Chloro-1-propene[a]	0.23
2-Chloro-1-propene	0.21
2-Chloro-2-butene[a]	0.049
1-Chlorocyclopentene	0.056

[a] Mixtures of cis and trans isomers.

Discussion

The rate expression for exchange shown in eq 9 is surprising in that it does not contain a [LiCl] term in the denominator, present in all previous rate expressions. This term arises from the coordination of the olefin to Pd(II) *via* the equilibrium represented by eq 3. Thus, either the reaction also has a first-order term in [LiCl] to give a rate expression of the form of eq 10 or

$$\text{rate} = \frac{k[Li_2Pd_2Cl_6][\text{vinyl chloride}][LiCl]}{[LiCl]} \qquad (10)$$

else the reaction must proceed without π-complex formation between olefin and Pd(II).

The experimental facts of the present study which any reaction path must explain are as follows.

(1) 1-chlorocyclopentene exchanges at an appreciable rate.

(2) Methyl substitution on vinylic carbon (Table III) does not retard the rate of chloride exchange as much as it did acetate exchange.[3]

(3) Although the result is obscured by isomerization without exchange, in the exchange of *trans*-propenyl chloride with radioactive LiCl (Table II) the radioactivity originally accumulates in the *cis*-propenyl chloride.

Other related experimental facts, some of which have been mentioned in the introduction, are as follows.

(4) Acetoxypalladation is a trans process[5] proceeding by attack of acetate from outside the coordination sphere of Pd(II).[3]

(5) If the Pd(II)-catalyzed exchange of vinyl chlorides with acetate proceeds *via* an acetoxypalladation–dechloropalladation the stereochemical results require that dechloropalladation has mainly cis stereochemistry. Thus chloropalladation would also be expected to have cis stereochemistry.

(6) In the previous exchange studies[1b,3,4] as well as in olefin oxidation studies[10] the first step in the reaction is olefin complexing.

(7) Under the reaction conditions Pd(II) is much more strongly complexed to chloride than to acetate.[7]

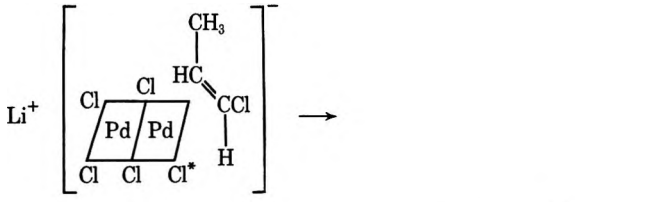
Finally, a kinetic study of the exchange of vinylic chlorides with acetate, to be reported in paper VI of this series,[11] revealed the following.

(8) The kinetic and stereochemical results are consistent with an acetoxypalladation–dechloropalladation route.

(9) Dechloropalladation is mainly cis but is not completely stereospecific.

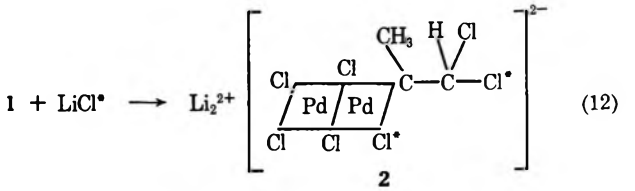
(10) Dechloropalladation requires that a vacant coordination sphere on Pd(II) be formed before it can be accomplished.

The author believes that the most plausible reaction path consistent with all the experimental facts consists of the *main* exchange route involving cis chloropalladation followed by dechloropalladation. The first step would be formation of π complex *via* an equilibria analogous to eq 3. Now, since dechloropalladation requires a vacant coordination site (see 10), the completion of the cis-chloropalladation step would be expected to require that the vacant coordination site being formed on Pd(II) by cis chloropalladation is filled by chloride from solution. The reaction scheme is thus given in eq 11–13.



(11)

1



(12)

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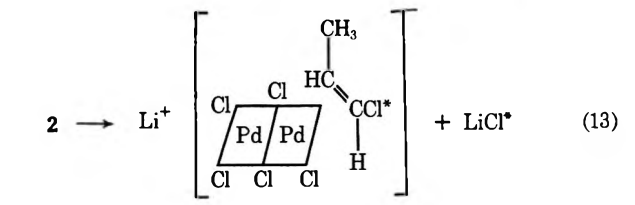
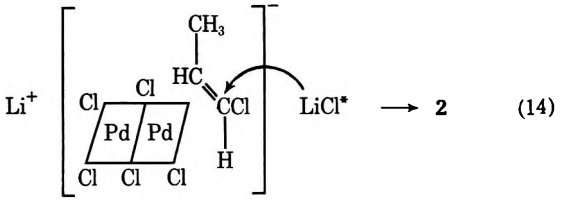


(13)

(10) P. M. Henry, *J. Amer. Chem. Soc.*, **86**, 3246 (1964); **88**, 1595 (1966).
(11) P. M. Henry, *ibid.*, in press.

The second, less important route, would involve trans attack of chloride on the π complex (eq 14) anal-

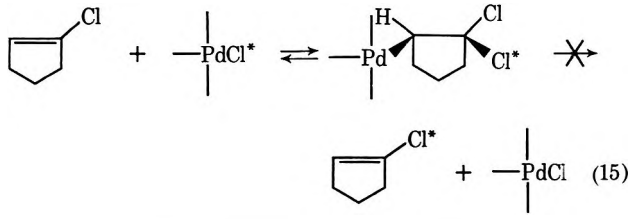


(14)

ogous to the manner in which acetate attacks the π complex in the acetate exchanges.[3,4] Exchange is then completed *via* eq 13. It is reasonable that this second route should occur to some extent, since chloride and acetate would behave in a similar fashion as nucleophiles. Thus if acetate gives trans attack chloride would be expected to also give some trans attack.

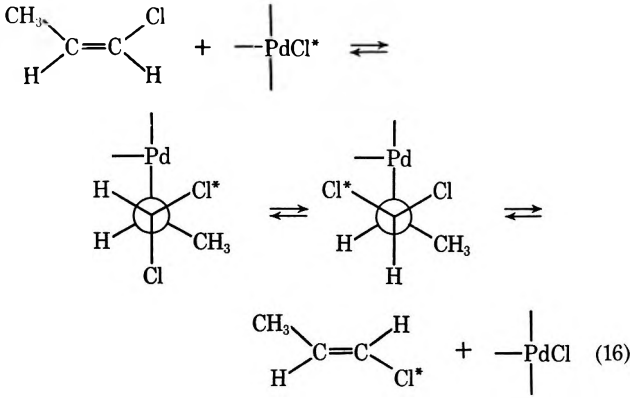
Both routes would have a first-order term in [LiCl] and a first-order inhibition term in [LiCl] because of π-complex formation *via* eq 3. Thus the rate expression for both routes would be eq 10.

The proposal that both routes occur is required by the fact (No. 1) that 1-chlorocyclopentene exchanges. As shown by eq 15, if chloropalladation–dechloropalladation were stereochemically pure, exchange should not have occurred. Note that cis chloropalladation–dechloropalladation is used for purposes of illustration. Trans stereochemistry would have given the same result. Nonstereospecific chloropalladation is also consistent with No. 9.



(15)

As shown by eq 16, stereochemically pure cis chloropalladation–dechloropalladation would be predicted to give exchange when, and only when, there is isomerization. Suggestion of *mainly* cis chloropalladation is consistent with No. 3 as is also in agreement with No. 5 and 9.



(16)

The effect of vinylic substitution on the rate of chloropalladation is qualitatively the same as that previously found for acetoxypalladation.[3,4] Qualitatively chloropalladation has much less of a steric factor than acetoxypalladation. Thus, vinyl acetate exchanges at a rate about a million times faster than 2-acetoxy-2-butene, while vinyl chloride exchanges only about 200 times faster than 2-chloro-2-butene. These results cannot be explained on different steric requirements for Cl and OAc, since the two do not have greatly different steric factors.[12] The lower steric effect for chloropalladation may result from the steric requirements for a cis addition being less than for a trans addition. This is a reasonable postulate, since in the first step a chloride from the coordination sphere of Pd(II) is being inserted. Thus the crowding about the Pd(II) is less than if a chloride from outside the coordination sphere is being added.

The fact that the reactive species is the dimeric π complex **1** rather than a monomeric π complex which could be formed by way of eq 17 deserves comment.

$$Li_2Pd_2Cl_6 + 2C_2H_3Cl \rightleftharpoons 2LiPdCl_3(C_2H_3Cl) \quad (17)$$

In both the vinyl[3] and allylic[2,4] exchanges the reactive species was also a dimeric π complex, although in the allylic case there was evidence that monomeric π complex, formed by an equilibrium analogous to eq 17, was present in much larger quantities than the dimeric π complex but was unreactive.

The reason postulated for this lack of reactivity is that the monomeric π complex has more negative charge concentrated on the Pd(II) complexed to the olefin than would the dimeric π complex. This negative charge would repulse the attacking acetate. The same argument could be used in the present case, since both eq 12 and 14 require the approach of chloride to the Pd(II) before chloropalladation can be completed.

It is interesting that 2-chloro-2-butene and 1-chlorocyclopentene exchange at about the same rate. If steric factors to chloropalladation are equal, the latter might be expected to exchange more slowly, since it can exchange only when chloropalladation and dechloropalladation have different stereochemistries. Thus the rate of chloropalladation of 1-chlorocyclopentene is probably faster than that of 2-chloro-2-butene. This is a reasonable result since the former has a more reactive double bond. Previously, the fact that 1-acetoxycyclopentene did not exchange acetate at a measurable rate while 2-acetoxy-2-butene did was taken as evidence that acetoxypalladation was stereochemically pure,[3] since the two might be expected to have approximately the same rates of acetoxypalladation. The present results support that contention.

Experimental Section

Materials.—Vinyl chloride was purchased from Matheson Gas Products. The cyclopentenyl chloride was prepared by a literature procedure.[13] A pure sample for use in the kinetic runs was obtained by preparative vapor phase chromatography (vpc) using a 20-ft 20% Carbowax 20M on ABS (70–80 mesh) programmed from 80 to 200° at 7.5°/min. The helium flow rate was 60 ml/min. The other vinylic chlorides were purchased from K & K Laboratories. Crude separation of the *cis*- and *trans*-1-chloro-1-propene isomers was by distillation. Final purification was by preparative vpc using a 20-ft 20% Lac 446 on Chromosorb W (60–80 mesh). The temperature was 50° and the helium flow rate was 100 ml/min. The radioactive LiCl was purchased from Radiochemical Center, Amersham, England. It had a specific activity of 8 μCi/mg.

(12) E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, **4**, 761 (1965).
(13) E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 1755 (1951).

The preparation and analysis of the Pd(II) stock solutions has been described previously.[1,7] All other chemicals were of reagent grade.

Kinetic Runs.—The reaction mixtures for the vinyl chloride exchange were prepared by mixing known amounts of the Pd(II) and LiCl stock solutions, adding radioactive lithium chloride, and diluting to a known volume, usually 5 ml. The reaction mixture was put into a polymerization tube. A rubber liner was fitted into the mouth and the tube was capped with a metal cap having an opening through which a syringe needle could be inserted. The tube was connected to a gas buret by means of the needle. The entire system was evacuated, flushed twice with vinyl chloride, and then pressured to atmospheric with vinyl chloride. The tube was then agitated until the gas uptake stopped, and a sample of the solution was then removed for radioactive assay. Samples (usually 0.05 ml) were then removed periodically and put in small vials which were capped with rubber stopules. The vinyl chloride was removed by evacuating the vials by means of a syringe needle inserted through the rubber stopule. The residue was then assayed for radioactivity.

The runs with isopropenyl chloride and 2-chloro-2-butene were carried out in the same fashion. Because of its higher boiling point, the runs with cyclopentenyl chloride were carried out by assaying the cyclopentenyl chloride rather than the inorganic salts. A portion of the reaction mixture was diluted with CH_2Cl_2 and the acetic acid and inorganic salts removed by washing with water. After drying and concentrating the entire organic phase was injected onto vpc and the cyclopentenyl chloride collected and assayed. Vpc conditions used were the Lac 446 column (see above) programmed from 80–200° at 7.5°/min.; helium flow rate was 100 ml/min.

The treatment of data for an isotope exchange reaction has been discussed previously.[3] In the present case, the rate expression is eq 18, where [VC] is the vinylic chloride concentration,

$$\ln \frac{A_\infty}{A_\infty - A} = \frac{R}{[\mathrm{VC}][\mathrm{Cl}]_t}([\mathrm{VC}] + [\mathrm{Cl}]_t)t \qquad (18)$$

$[Cl]_t$ is the total inorganic chloride concentration, A is the radioactivity at any given time during the run, and A_∞ is the activity at equilibrium. When the inorganic salts were assayed, A_∞ was simply calculated from the total activity A_t by the relationship

$$A_\infty = A_t \frac{[\mathrm{Cl}]_t}{[\mathrm{VC}] + [\mathrm{Cl}]_t} \qquad (19a)$$

of eq 19a, and when the organic salt is assayed the relationship is eq 19b.

$$A_\infty = A_t \frac{[\mathrm{VC}]}{[\mathrm{VC}] + [\mathrm{Cl}]_t} \qquad (19b)$$

A first-order plot, giving the first-order rate constant k_{obsd}, is obtained no matter what the order in [VC]. This observed rate constant then has the following relationship (eq 20) to [VC] and $[Cl]_t$, where R is the rate expression in vinylic chloride. If $R = k[VC]$ we have eq 21, and the first-order rate constant can be calculated from the relationship. If k remains constant with varying [VC], we have eq 22, a first-order process. As shown in Table I, k does remain constant.

$$k_{obsd} = \frac{R}{[\mathrm{VC}][\mathrm{Cl}]_t}([\mathrm{VC}] + [\mathrm{Cl}]_t) \qquad (20)$$

$$k_{obsd} = \frac{k}{[\mathrm{Cl}]_t}([\mathrm{VC}] + [\mathrm{Cl}]_t) \qquad (21)$$

$$k = k_{obsd} \frac{[\mathrm{Cl}]_t}{([\mathrm{VC}] + [\mathrm{Cl}]_t)} \qquad (22)$$

The runs with *cis* and *trans*-1-chloro-1-propene were carried out in a fashion similar to that for 1-chlorocyclopentene. However, rather than working up the reaction mixture, a 2-ml sample was injected onto vpc using same conditions as were used for purification, and the two isomers were collected in traps and assayed.

Radioactive Assay.—All assays were made using a Packard Tri-Carb Liquid Scintillation Counter made by Packard Instrument Co., Inc., La Grange, Ill. The scintillation recipe for the inorganic salts contained 1044 parts of toluene, 1356 parts of dioxane, 720 parts of ethanol, 9.69 parts of PPO (2,5-diphenyloxazole purchased from New England Nuclear Co.), and 0.24 parts of POPOP [*p*-bis(2,5-phenyloxazolyl)benzene purchased from Pilot Chemical Co.]. This recipe completely dissolved the inorganic salts at the concentrations used for assay. For the organic chlorides a recipe containing 3144 ml of toluene, 9.42 g of PPO, and 0.3144 g of POPOP was used. For both recipes, the use of an internal ^{36}Cl standard indicated counting efficiency very close to 100%; so internal standards were not used in subsequent countings.

The calculation of specific activities of the inorganic chlorides was easily done, since the volume of the aliquots of the reaction mixture was known and the concentration of inorganic chloride was known from analysis. However, in the case of the organic chloride assay, the efficiency of collection is variable; so the counting solution had to be analyzed for organic chloride content to calculate the specific activity. The same vpc procedure as was used for purification was used for analysis. With cyclopentenyl chloride the assay was simple, since only one compound was involved. However, in the runs with *cis*- and *trans*-1-chloropropene the vpc procedure did not completely separate the two isomers on the scale needed for radioactive assay and reanalysis. It was found that pure cis isomer could be collected while the trans collection always contained some cis isomer. The specific activity of the cis was determined on the pure cis isomer and then its contribution to the radioactivity in the mixture was calculated and subtracted from the total activity. The specific activity of the trans isomer could then be calculated.

Registry No.—Vinyl chloride, 75-01-4; *cis*-1-chloro-1-propene, 16136-84-8; *trans*-1-chloro-1-propene, 16136-85-9; 2-chloro-1-propene, 557-98-2; *cis*-2-chloro-2-butene, 2211-69-0; *trans*-2-chloro-2-butene, 2211-68-9; 1-chlorocyclopentene, 930-29-0; LiCl, 7447-41-8; $Li_2Pd_2Cl_6$, 31183-05-8; $PdCl_2$, 7647-10-1.

Acknowledgment.—The author gratefully acknowledges helpful discussions with Professors H. Taube and H. Goering and the following for technical assistance: Mr. A. Croes, who carried out the radioactive assays, and Mr. F. J. Kriss, who carried out the majority of the other laboratory work.

A Mechanistic Study of the Copper(II)-Catalyzed Oxidation of Fluorene with Molecular Oxygen

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Received October 28, 1971

Salts of Cu(II), containing a benzoate and a methoxide ion, in the presence of aliphatic amines, catalyze the reaction of fluorene with oxygen in pyridine–methanol solutions at 25°. Fluorenone is the major product and small amounts of bifluorenyl are formed. Kinetic studies indicate that removal of the 9 proton is the rate-determining step. With excess triethylenetetramine present spectral evidence indicates that Cu(I) complexes are not formed during catalysis and kinetic studies show that the Cu(II) catalyst system is 500 times as active as the corresponding catalysis by sodium methoxide. Oxidations in CH_3OD–pyridine solvent suggest that this marked catalysis by copper is due to an increase of greater than 10^4 in the ratio of the rate constants for reaction of fluorenyl anion by electron and proton transfer.

The reactions of a variety of organic molecules with molecular oxygen are catalyzed by copper salts and amines. Many of the reactions reported involve the breaking of an X–H bond where X is most commonly O, C, or N. Thus molecules such as phenols,[1] *p*-nitrotoluene,[2] acetylenes,[3] α,β-unsaturated ketones,[4] nitriles,[5] and aromatic amines[6] are susceptible to catalysis. Usually the major products result from coupling. However, α,β-unsaturated ketones yield oxygenated products.[7] With phenols, acetylenes, and amines it is generally observed that Cu(I) salts are more effective catalysts than Cu(II) salts. It has been shown that the autoxidation of Cu(I) salts in hydroxylic solvents forms amine complexes of Cu(II) containing a basic ligand such as OH^- or CH_3O^-[1b,6,9] and the basicity of these ligands has been assumed to be responsible for the enhanced catalytic activity of the Cu(I) salts. The catalytic activity of added methoxide ions has been demonstrated in Cu(II)-catalyzed autoxidations of unsaturated ketones.[10] In some cases it has been shown that a Cu(II) species acts directly as an oxidizing agent.[5,11] Only a limited amount of information is available on the relationship between the structures of the complexes, reactivity, and properties such as base strength, redox potential, and ability to coordinate with intermediates formed during oxidation.[1b,9,11]

In the course of searching for a representative reaction to study, a marked acceleration in rate was observed for the oxidation of the hydrocarbon fluorene when catalytic amounts of cuprous chloride or carboxylate salts and aliphatic polyamines were present in pyridine–methanol solutions at 25°. Since no report of the large catalytic effect in this system appeared to have been made, a detailed study was carried out. In this paper results are presented which allow some conclusions on the general mechanism and in particular on the relationship of catalyst structures, anionic species, and catalytic reactivity. Some general conclusions on related types of catalysis are drawn.

Results

It was first established that the only significant reaction of cuprous chloride and carboxylate salts in pyridine–methanol solutions under oxygen pressure at 25° is the formation of mixed salts of Cu(II) containing a methoxide ion and the corresponding anion of the cuprous salt in agreement with a previous report.[9]

These Cu(II) salts then were synthesized and it was observed that the catalytic rates with the cuprous salts are the same as with the cupric except that a small amount of oxygen is absorbed initially with cuprous salts to form cupric compounds, causing difficulties in kinetic measurements. Therefore, for experimental convenience the detailed mechanism studies were carried out with the Cu(II) salts. For better solubility, salts containing a benzoate ion were chosen for most of the experiments.

In all these reactions the rates of exchange of the ligands at the copper centers are many times greater than the overall reaction rates.[12] Therefore, the order of addition of the reactants will not affect the observed results. Except where specified, the solvent is a mixture of five volumes of pyridine to one volume of methanol. The temperature in all runs is 25.0°. The rates of oxygen uptake could not be described by any simple kinetic expression over the complete course of the reactions. A first-order kinetic plot was made for a typical run such as run 60B in Table I and was linear over the initial 40–60% of the reaction. The value of the rate constant is 8.5×10^{-4} sec^{-1}. During the later stages retardation of the rate appeared and first-order kinetics were no longer obeyed. The retardation is not due to appearance of the major reaction products, water and fluorenone, since addition of each of them, in amounts formed during reaction, caused no change in initial rates. To avoid the complexities of the later stages of reaction all rates were measured at 1% conversion of the fluorene.

Ligand Effects.—Significant reaction only occurs when the molar ratio of available amine groups to copper is greater than three, as shown by the plots in Figure 1, where ethylenediamine (en), diethylenetriamine

(1) (a) G. F. Endres, A. S. Hay, and J. W. Eustance, *J. Org. Chem.*, **28**, 1300 (1963); (b) E. Ochiai, *Tetrahedron*, **20**, 1831 (1964); (c) Y. Ogata and T. Morimoto, *ibid.*, **21**, 2791 (1965).

(2) H. A. Stansbury and W. R. Proops, *J. Org. Chem.*, **26**, 4162 (1961).

(3) H. A. Stansbury and W. R. Proops, *ibid.*, **27**, 320 (1962); A. S. Hay, *ibid.*, **27**, 3320 (1962).

(4) H. C. Volger and W. Brackman, *Recl. Trav. Chim. Pays-Bas*, **84**, 579, 1203 (1965).

(5) M. S. Karasch and G. Sosnovsky, *Tetrahedron*, **3**, 97 (1958).

(6) K. Kinoshita, *Bull. Chem. Soc. Jap.*, **32**, 777, 780 (1959).

(7) Coupling is reported in the absence of O_2; see ref 8.

(8) H. C. Volger and W. Brackman, *Recl. Trav. Chim. Pays-Bas*, **84**, 1233 (1965).

(9) H. Finkbeiner, A. S. Hay, H. S. Blanchard, and G. F. Endres, *J. Org. Chem.*, **31**, 549 (1966).

(10) H. C. Volger and W. Brackman, *Recl. Trav. Chim. Pays-Bas*, **86**, 244 (1967).

(11) H. C. Volger and W. Brackman, *ibid.*, **85**, 818 (1966).

(12) R. G. Pearson and R. D. Lanier, *J. Amer. Chem. Soc.*, **86**, 765 (1964).

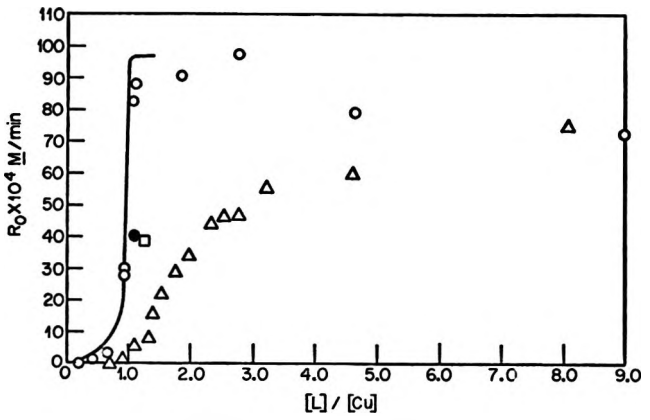

Figure 1.—Initial rate of oxygen uptake *vs.* [ligand]/[Cu(OBz)-(OCH_3)], where $[Cu(OBz)(OCH_3)] = 2.50 \times 10^{-3}$ *M*: ○, trien, $[FlH_2] = 0.200$ *M*; △, en, $[FlH_2] = 0.100$ *M*; □, dien, $[FlH_2] = 0.100$ *M*; ●, tetraen, $[FlH_2] = 0.100$ *M*. The solid line is a plot of the calculated concentration of free (trien) $Cu(OBz)(OCH_3)$ species.

TABLE I

EFFECTS OF LIGANDS AND METAL ON INITIAL OXIDATION RATES (R_0) OF 0.100 *M* FLUORENE IN 5:1 PYRIDINE–CH_3OH AT 25.0° AND 950 TORR OF O_2 WITH 0.0025 *M* CATALYST

Run	Catalyst	Amine	Amine/catalyst	R_0, *M*/min $\times 10^4$
60B	$Cu(OBz)(OCH_3)$	Trien	2.22	50
65	$Cu(OCH_3)_2$	Trien	2.20	~115[a]
96	$Cu(OBz)_2$	Trien	2.21	136[b]
49B	$Cu(OBz)OCH(CH_3)(CH_2NH_2)$	Dien	1.09	18
51A	$Cu(OBz)OCH(CH_3)(CH_2NH_2)$	Trien	1.10	33
59B	$Cu(OBz)(OCH_3)$	Dien	1.42	36
52B	$Cu(Cl)(OCH_3)$	En	2.19	32
	$Cu(OBz)(OCH_3)$	En	2.19	41[c]
96	$NaOCH_3$	Trien		0.19[b]
9	$NaOCH_3$			0.51[d]

[a] Catalyst was slow to dissolve; so the rate was taken after several per cent reaction. [b] Solution contains added $NaOCH_3$ (0.0107 *M*) and is 0.050 *M* in fluorene. Before the $Cu(OBz)_2$ was added $R_0 = 0.2 \times 10^{-4}$. After addition of the $Cu(OBz)_2$ $R_0 = 136 \times 10^{-4}$. [c] Interpolated from plot in Figure 1. [d] Solution contains added $NaOCH_3$ (0.0150 *M*). After 10 min reaction $Cu(OBz)_2$ (2.5×10^{-3} *M*) was added but a precipitate formed and the rate dropped to 0.28×10^{-4}.

(dien), and triethylenetetramine (trien) were used as ligands. Negligible rates are observed with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine and bipyridyl even in large excesses.

There is no observable oxygen uptake unless methoxide ions are present in the reaction mixture. Runs 60B, 65, and 96 (Table I) show the effects of adding methoxide in different ways. In runs 49B and 51A the alkoxide group was included as 1-amino-2-propoxide ion, a bidentate type ligand.

There appears to be no specific effect of the benzoate group. If the benzoate ion is replaced by chloride ion (compare R_0 in run 52B with the comparable value interpolated from Figure 1), R_0 decreases by about 22%, and, if benzoate is replaced by methoxide (compare run 60B with run 65), the rate approximately doubles. The benzoate group was the preferred ligand in these reactions because of the solubility it imparts to the copper compound in organic solvents compared with chloride and other inorganic ions.

Effect of Fluorene Concentration.—The initial rates of oxygen uptake depend on the fluorene concentration in a first-order manner (Figure 2). The blank reaction

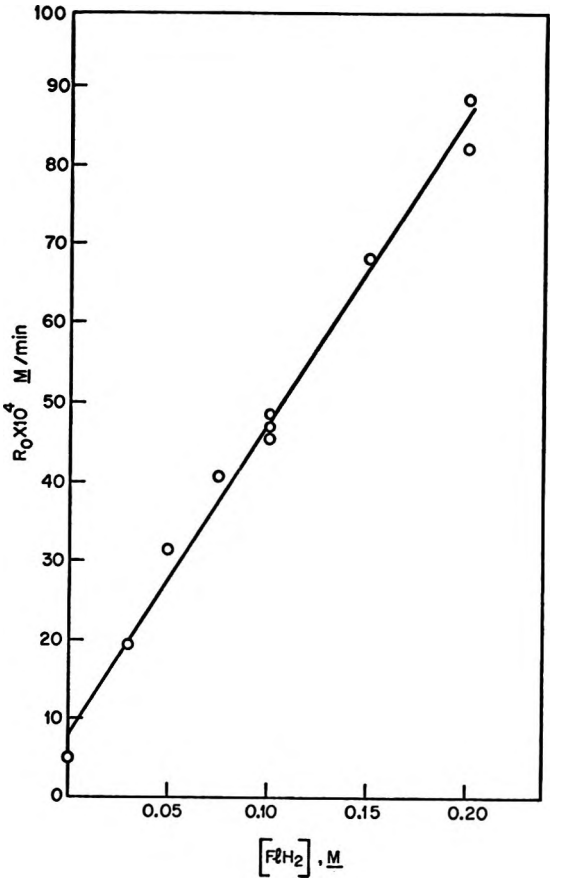

Figure 2.—Initial rate of O_2 uptake *vs.* concentration of fluorene $[Cu(OBz)(OCH_3)] = 2.5 \times 10^{-3}$ *M*, [trien] $= 2.7 \times 10^{-3}$ *M*, $P_{O_2} = 950$ Torr.

observed at zero fluorene (Figure 1) leads to a total O_2 absorption of less than 1.5 mmol per mmole of catalyst. Possibly the amine ligand groups are oxidized, causing termination of catalytic activity. From the slope the value of the pseudo-first-order rate constant is 6.6×10^{-4} sec^{-1}. On the basis that the reaction is also first order in catalyst (see below), the second-order rate constant has a value of 0.26 M^{-1} sec^{-1}.

Effect of Catalyst Concentration.—Between 2.5×10^{-3} and 7.0×10^{-3} *M* catalyst in 0.100 *M* fluorene solutions the oxygen uptake is first order in catalyst and between 0 and 2.5×10^{-3} *M* the rate falls off slightly (Figure 3). The low concentration points probably fall off because the total concentration of amine is insufficient to maintain as high a percentage of the copper in the complexed form as with the higher concentration runs. From the slope the pseudo-first-order rate constant is 3.1×10^{-2} sec^{-1}. The bimolecular rate constant is $(3.1 \times 10^{-2})/0.100 = 0.31$ M^{-1} sec^{-1}, in good agreement with the values obtained from hydrocarbon variation, 0.26, and from the value calculated from the first-order kinetic plot of the initial 50% of reaction for run 60B, 0.34.

Effect of Oxygen Pressure.—The rate of oxygen uptake is essentially independent of O_2 pressure in the range 200–1950 Torr (Figure 4).

Effect of Solvent.—When the reaction components were homogeneously mixed in CH_3OH–C_6H_6 (1.5:1.0, v/v) and CH_3OH–CCl_4 (1.5:1.0, v/v) mixtures, no O_2 uptake occurred. However, when neat pyridine was used as solvent, the reaction rates were normal. When

TABLE II

OXYGEN PRESSURE DEPENDENCE OF THE PRODUCTS OF THE OXIDATION OF 0.100 *M* FLUORENE WITH 5.0×10^{-3} *M* Cu(OBz)(OCH_3) AND 1.09×10^{-2} *M* TRIEN[a]

Run	P_{O_2}	Δ_{FlH_2}	% Reaction	Fl=O	$(FlH)_2$	F=O/$(FlH)_2$	Unaccounted fluorene
84	1950	1.07	54	1.09	5.5×10^{-3}	2.0×10^2	
88	1950	0.99	50	0.98	4.9×10^{-3}	2.0×10^2	
85	200	0.94	47	0.76	0.039	20	0.10
92	200	1.00	50	0.90	0.046	20	0.01
87	44	0.48	24	0.029	0.035	0.83	0.38
93[b]	0				6.1×10^{-3}		

[a] Product yields are given in millimoles. [b] The catalyst and trien concentrations were double those of the other runs and the reaction was run for 10 min. The other reactions in the table were run for 5–6 min.

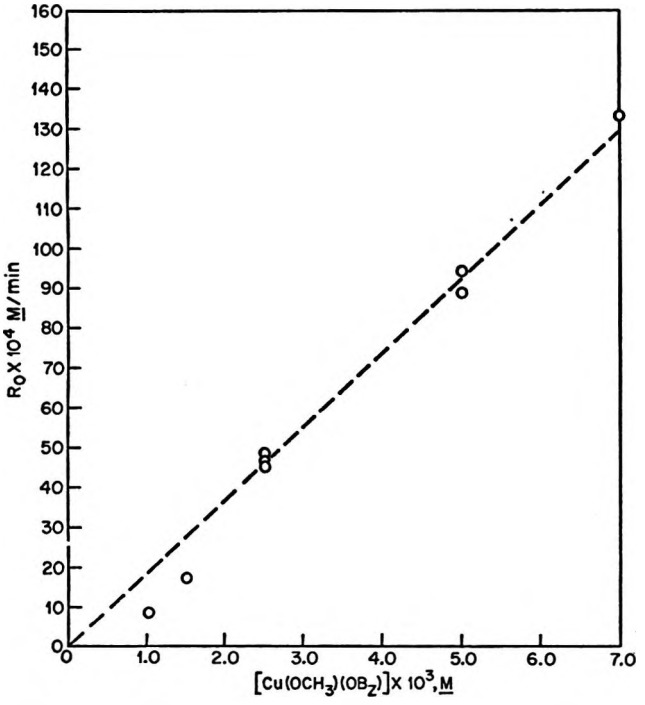

Figure 3.—Initial rate of O_2 uptake *vs.* [Cu(OBz)(OCH_3)]; [trien]/[Cu] = 1.1, P_{O_2} = 950 Torr, [FlH_2] = 0.100 *M*.

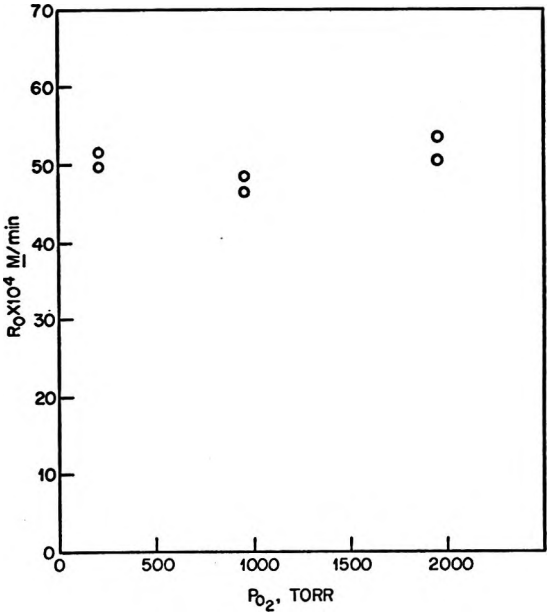

Figure 4.—Dependence of initial rate of O_2 uptake on O_2 pressure for 0.100 *M* fluorene, 2.50×10^{-3} *M* Cu(OBz) (OCH_3), and 2.78×10^{-3} *M* trien.

0.2 *M* benzene was added to a normal reaction mixture, no change in initial rate occurred.

Isotope Effect.—Duplicate runs of 0.100 *M* solutions of 9-dideuteriofluorene (96% deuterated in the 9 position) with 2.50×10^{-3} *M* Cu(OBz)(OCH_3), 2.78×10^{-3} *M* trien, and 950 Torr of O_2 gave initial rates of 6.5 and 7.0×10^{-4} *M* min^{-1}. Duplicate runs under identical conditions with fluorene gave rates of 45 and 47 $\times$ 10^{-4} *M* min^{-1}. On the basis of the 96% deuteration of the deuterated sample the average isotope effect, $R_0(H)/R_0(D)$, is 9.0.

Products.—The relative rates of product formation are oxygen pressure dependent (Table II). At the highest pressure fluorenone and 9,9′-bifluorenyl account for all the fluorene consumed within experimental error. At 200 Torr the material balance is still good but at 44 Torr the fate of much of the consumed fluorene is unknown. The unknown products are not 9-fluorenol, bifluorylidene, or 9-methoxyfluorene. In a run under N_2 (run 93, Table II) after 10 min 6.1×10^{-3} mmol of $(FlH)_2$ were recovered. Some oxygen was introduced into the final reaction mixture during manipulation. Hydrogen peroxide, a possible reaction product, cannot be observed because of its instability under the reaction conditions. When a sample is added to a reaction mixture, gas is vigorously evolved.

Exchange Reactions.—The 9 protons in fluorene are exchanged for deuterium atoms in oxygen-free pyridine–CH_3OD solutions containing $NaOCH_3$ or Cu(OBz)-(OCH_3) with excess trien. The results of nmr analysis of the recovered and recrystallized fluorene are shown in Table III. The analyses are accurate to within about 5%.

A 0.100 *M* solution of fluorene was oxidized at 950 Torr of O_2 to 50% conversion of the fluorene with 2.5×10^{-3} *M* Cu(OBz)(OCH_3) and 5.18×10^{-3} *M* trien using pyridine–CH_3OD (5:1, v/v) as the solvent. The unreacted fluorene was recovered and purified by preparative gas chromatography. Mass spectral analysis showed that 3.2% of the fluorene contained one deuterium atom. A similar run was done at 150 Torr of O_2. The mass spectral analysis showed that 2.3% of the recovered fluorene was monodeuterated at about 50% conversion. A control experiment without copper (run 18, Table III) showed 2.9% exchange for the same reaction time.

Spectra.—The visible spectra of solutions containing combinations of Cu(OBz)(OCH_3), trien, and fluorene in the presence and absence of O_2 are shown in Figure 5. The esr spectra at 77°K and room temperature of

TABLE III

DEUTERIUM EXCHANGE OF THE 9 PROTONS OF 0.200 *M* FLUORENE IN O_2-FREE PYRIDINE-CH_3OD (5:1, v/v) SOLUTION[a] AT 25.0°. ANALYSIS BY NMR AND MASS SPECTROMETER

Run	[Cu(OBz)(OCH₃)]	[trien]	[NaOCH₃]	Time, min	% Exchange	Analysis
121			1.14×10^{-2}	5.0	67	Nmr
122	1.01×10^{-2}	1.07×10^{-2}		5.0	39	Nmr
120		1.07×10^{-2}		15.0	<5–7	Nmr
18		5.2×10^{-3}		10.0	2.9	Mass spectrum

[a] All concentrations are in moles/liter.

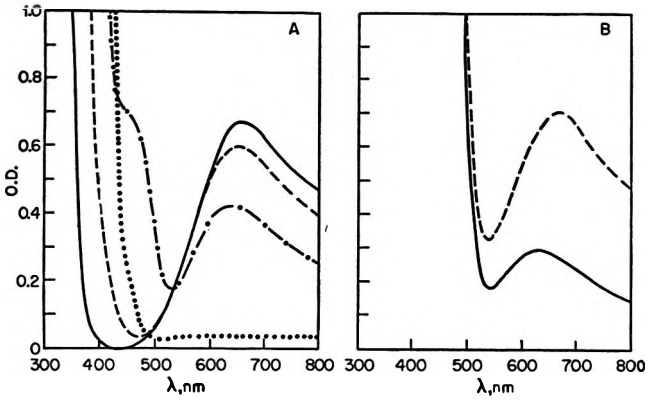

Figure 5.—Visible spectra of O_2-free and O_2-saturated Cu-catalyst solutions. A: —, no fluorene, [Cu(OBz)(OCH₃)] = 5.0×10^{-3} *M*, [trien] = 2.1×10^{-2} *M*; - - -, [FlH₂] = 0.10 *M*, [Cu(OBz)(OCH₃)] = 5.0×10^{-3} *M*, [trien] = 2.1×10^{-2} *M*, no O_2, 3 min after mixing; -·-·-, same as - - - but 2 hr after mixing; ·····, [Cu(I)OBz] = 2.5×10^{-3} *M*, [trien] = 1.5×10^{-2} *M*, no O_2. B: —, [FlH₂] = 0.10 *M*, [Cu(OBz)(OCH₃)] = 5.0×10^{-3} *M*, [trien] = 2.1×10^{-2} *M*, no O_2, 2 days after mixing; - - -, same as — but solution saturated with O_2.

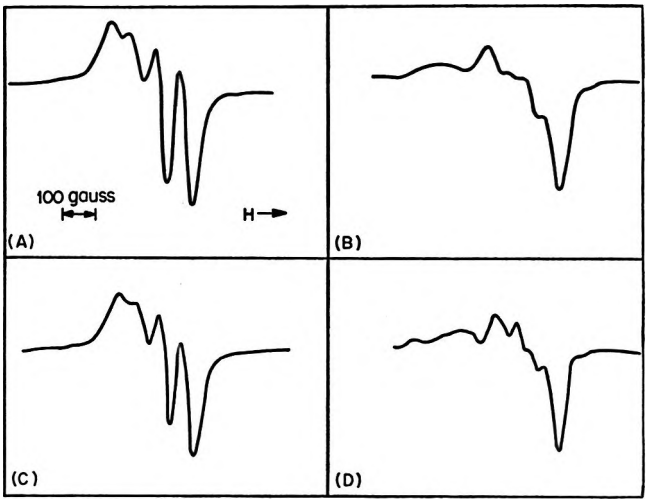

Figure 6.—The esr spectra of pyridine–methanol solutions containing 5.0×10^{-3} *M* Cu(OBz)(OCH₃) and 2.3×10^{-2} *M* trien. A and B are O_2-free solutions containing 0.10 *M* fluorene. Spectra of A and B were taken 15 min after mixing at room temperature. A and C are at ambient temperature; B and D are at 77°K.

solutions of Cu(OBz)(OCH₃) and trien with and without fluorene and O_2 are shown in Figure 6. At 2°K the values of the g and A parameters are $g_{11} = 2.21$, $g_\perp = 2.06$, $A_{11} = 554$ MHz, and $A_\perp \sim 0$.

Discussion

Kinetics.—Reactions 1–11 are proposed to explain the experimental observations. The reactive complex of Cu(II) must have three or four amine ligands, as concluded from the plots of Figure 1. Most of the kinetic data were obtained using trien as the amine ligand, so in the discussion below the active complex is $[(trien)Cu(II)]^{2+}$ which is represented by LCu(II) where L ≡ trien. Although free ions are written below, it is understood that the predominant ionic species are probably ion pairs.

$$L + Cu(II)(CH_3O^-)(BzO^-) \rightleftharpoons LCu(II) + CH_3O^- + BzO \quad (1)$$

$$FlH_2 + CH_3O^- \underset{k_{-H}}{\overset{k_H}{\rightleftharpoons}} FlH^- + CH_3OH \quad (2)$$

$$FlH^- + LCu(II) \rightleftharpoons LCu(II)(FlH^-) \quad (3)$$

$$LCu(II)(FlH^-) + O_2 \longrightarrow LCu(II)(FlH\cdot)(O_2\cdot^-) \quad (4)$$

$$LCu(II)(FlH\cdot)(O_2\cdot^-) \longrightarrow LCu(II) + FlH\cdot + O_2\cdot^- \quad (5)$$

$$FlH\cdot + O_2 \longrightarrow FlHO_2\cdot \quad (6)$$

$$FlH\cdot + O_2\cdot^- \longrightarrow FlHO_2^- \quad (7)$$

$$FlHO_2\cdot + O_2\cdot^- \longrightarrow FlHO_2^- + O_2 \quad (8)$$

$$FlHO_2^- + CH_3OH \rightleftharpoons FlHO_2H + CH_3O^- \quad (9)$$

$$FlHO_2H + CH_3O^- \longrightarrow Fl{=}O + CH_3OH + OH^- \quad (10)$$

$$2FlH\cdot \longrightarrow (FlH)_2 \quad (11)$$

The general scheme is based on those proposed earlier by Russell and coworkers[13,14] for the base-catalyzed oxidation of fluorene. It appears that the present data are best explained on the basis that the effect of the copper salt is to supply a base (the methoxide ion) and a Cu(II) species which acts as an electron transfer catalyst. These points now will be discussed in detail.

A fluorenyl anion is produced in the forward step of reaction 2. The required methoxide ion can be associated either with a copper ion (see Figure 3 and run 65, Table I) or an inert sodium ion (see run 96, Table I). The fluorenyl anion, after complexing with LCu(II), can react by electron transfer with an oxygen molecule (*via* reactions 3 and 4), or by proton transfer from solvent (reverse step of reaction 2). Electron transfer to a fluorenyl peroxy radical (reaction 12) is a possible

$$FlO_2\cdot + FlH^- \longrightarrow FlO_2^- + FlH\cdot \quad (12)$$

reaction in this system. However, this reaction has been shown to be negligible in the base-catalyzed autoxidation of fluorene in the presence of *m*-trifluoromethylnitrobenzene, a very active one-electron oxidizing agent.[14] In this case[14] the kinetics were zero order in catalyst and oxygen. In analogy with these observations reaction 12 is assumed to be negligible in the present discussion. Oxidation of the fluorenyl anion by direct electron transfer to Cu(II) (reaction 13) is excluded by spectral evidence (see below). The

$$LCu(II)(FlH^-) \longrightarrow LCu(I)(FlH\cdot) \quad (13)$$

(13) G. A. Russell, *et al.*, *Advan. Chem. Ser.*, **51**, 122 (1965).
(14) G. A. Russell, *et al.*, *ibid.*, **75**, 174 (1968).

formation of low concentrations of a reactive, transient Cu(III) species which can act as an oxidizing agent for FlH^- is consistent with the observed data (reactions 14 and 15). However, since there is no direct evidence

$$LCu(II) + O_2 \rightleftharpoons LCu(III) + O_2\cdot^- \quad (14)$$

$$LCu(III) + FlH^- \longrightarrow LCu(II) + FlH\cdot \quad (15)$$

for Cu(III) at present (see below), reactions 3 or 4 are preferred. The results (see below) of deuterium exchange experiments indicate that protonation is much slower than electron transfer; thus in terms of the rate scheme

$$r_{ox} \ll k_{-H}[CH_3OH]$$

where

$$r_{ox} = \frac{k_3k_4[LCu(II)][O_2]}{(k_{-3} + k_4)}$$

The quantity r_{ox} represents the total psuedo-first-order rate constant for the oxidation of the fluorenyl anion. With the above inequality the complete steady state rate expression reduces to

$$\frac{-d[FlH_2]}{dt} = k_H[FlH_2][CH_3O^-] \quad (16)$$

and proton loss becomes rate determining. Since fluorenone is the major product observed, $-d[O_2]/dt \equiv R_0 \cong -d[FlH_2]/dt$ (one fluorene is consumed per oxygen), and eq 16 then agrees with the observed kinetics (Figures 2, 3, and 4). The experiments with added sodium methoxide (see above) imply that the observed first-order dependence on total Cu(OBz)(OCH$_3$) added (Figure 3) is due to the methoxide ion released in reaction 1. It follows then that the overall rate is independent of [LCu(II)] over the concentration range studied (>1 × 10^{-3} M) as required by the theoretical rate expression.

From the plots of Figures 2 and 3, values of 0.26 and 0.31 M^{-1} sec^{-1} are obtained respectively for k_H. In the absence of O_2, exchange of the 9 protons with deuterium atoms from CH_3OD occurs at similar rates for the copper catalyst system and sodium methoxide (Table III). On the basis that exchange is first order each in hydrocarbon and base,[14,15] the value of k_H calculated from run 122, Table III, is 0.2 M^{-1} sec^{-1}, in reasonable agreement with the above values. The observed isotope effect of $k_H/k_D \sim 9.0$ is in reasonable agreement with the value of 10 measured by Russell, *et al.*, for fluorene in *tert*-butyl alcohol using potassium *tert*-butoxide.[14]

The assumption that capture of the fluorenide ion complex by oxidizing agent is faster than capture by proton is valid, since no more than 3% deuterium exchange is found at the 9 position of unreacted fluorene remaining in a 50% conversion oxidation at 950 and at 150 Torr of oxygen. It follows then that at 950 and 150 Torr

$$r_{ox}/r_{-H} > 97/3 \sim 32$$

where r_{ox} is as defined previously and

$$r_{-H} = k_{-H}[CH_3OH]$$

Quantitative determination of the ratio is limited by the blank reaction exchange (Table III).

(15) D. Bethell and R. J. E. Talbot, *J. Chem. Soc. B*, 638 (1968).

The internal electron transfer step, reaction 13, can be ruled out as an important path in the oxidation by visible and esr spectral measurements. The broad band at 650 nm is characteristic of the d–d transitions in Cu(II) complexes and is absent in Cu(I) complexes (Figure 5).[16] Very similar bands have been observed in $[(en)_2Cu(II)]^{2+}$ complexes.[17] The rate of disappearance of this band in an oxygen-free reaction mixture (Figure 5) is slower than both exchange under comparable conditions and oxidation in the presence of oxygen. During the initial 2-hr life of a freshly mixed, oxygen-free solution containing 0.100 M fluorene, 4.92 × 10^{-3} M Cu(OCH$_3$)(OBz), and 2.31 × 10^{-2} M trien at 24.3° the intensity of the 650-nm band only decreased by 37%. The rate of decrease does not follow any simple first- or second-order kinetic dependence but the average rate over this period is roughly 1.5 × 10^{-5} M min^{-1} or about 400-fold slower than the rate of oxidation. The shoulder which slowly appears between 450 and 480 nm may be due to $\Delta^{9,9'}$-bifluorenyl, which has a reported maximum (CCl_4) at 460 nm (log ϵ 4.1).[18] An absorbance of unity would correspond to a concentration of 8 × 10^{-5} M. The esr signal observed in this same solution 15 min after mixing at room temperature (Figure 6) has roughly the same intensity and appearance as a similar solution without fluorene. Since Cu(I) is diamagnetic no significant change in oxidation state could have occurred.

The observed similarities of the visible and esr spectra of oxygenated and degassed solutions of the copper complexes suggests that Cu(III) species, if formed (perhaps by reactions 14 or 15), are present in small amounts. The solubility of oxygen in the solvent system was measured and found to be the same within a few per cent whether or not copper was present (in concentrations up to several times the solubility of oxygen), in agreement with the above conclusion.

Comparison of Sodium and Copper.—It is of interest to compare catalysis with sodium methoxide to catalysis by Cu(OCH$_3$)(OBz). The overall rates of oxygen uptake can be compared by calculating the rates in runs 96 and 9 (Table I) for 0.200 M fluorene and 2.5 × 10^{-3} M $NaOCH_3$ on the basis of the known first-order dependence of rate on each of these reactants.[14,15] On this basis the average value of R_0(Na) is 0.20 × 10^{-4} M min^{-1} at 950 Torr of O_2. Comparing this to the maximum rate at 950 Torr of O_2 with the (trien)Cu(II) complex in Figure 1 gives a ratio $R_0(Cu(II))r/R_0(Na)$ = 4.9 × 10^2. The base-catalyzed oxidation of fluorene in *tert*-butyl alcohol is known to be approximately first order each in base, oxygen, and hydrocarbon[14,15] and the known mechanism requires reaction 2 in conjunction with reaction 17.

$$FlH^- + O_2 \longrightarrow FlH\cdot + O_2\cdot^- \quad (17)$$

The kinetics thus require $r_{-H}^{Na} \gg r_{ox}^{Na}$ where $r_{-H}^{Na} = k_{-H}^{Na}[CH_3OH]$ and $r_{ox}^{Na} = k_{17}^{Na}[O_2]$. Since fluorenone is the only product reported

$$R_0(Na) = \frac{r_{ox}^{Na}k_H^{Na}[FlH_2][CH_3O^-]}{r_{H^-}^{Na}} \quad (18)$$

(16) The slight absorption of (trien)Cu(I) complex in Figure 5 is due to a small amount of oxidation of the sample during handling.

(17) I. M. Procter, B. Hathaway, and P. Nicholls, *J. Chem. Soc. A*, 1678 (1968).

(18) J. Schuyer, *Recl. Trav. Chim. Pays-Bas*, **72**, 933 (1953).

From the above rate comparison and dividing equations 16 and 18 we obtain

$$\frac{R_0(\mathrm{Cu})}{R_0(\mathrm{Na})} = \frac{k_H^{Cu} r_{-H}^{Na}}{r_{ox}^{Na} k_H^{Na}} = 490$$

Since the rates of exchange of the 9 protons catalyzed by $NaOCH_3$ and the (trien)Cu(II) catalyst are equal within a factor of two (Table III), $k_H^{Cu} \sim k_H^{Na}$ and $r_{-H}^{Na}/r_{ox}^{Na} \sim 500$. Thus in the sodium methoxide catalyzed autoxidation, protonation of the fluorenyl anion occurs 500 times as often as reaction with oxygen. From the deuterium exchange during oxidation in the Cu(II) system at 950 Torr $r_{ox}^{Cu}/r_{-H}^{Cu} > 32$ and therefore

$$(r_{ox}^{Cu}/r_{-H}^{Cu})/(r_{ox}^{Na}/r_{-H}^{Na}) > 1.5 \times 10^4$$

The special catalytic effect of Cu(II) is thus due to the large change in the above anion capture ratios. It follows then that if reaction 12 is indeed negligible the catalytic effect of the copper is specifically due to a decrease in the protonation rate (reaction 2) and/or an increase in the electron transfer rate (reactions 3 and 4) by a total factor of 10^4 or greater.

Catalyst Structures.—Some conclusions can be drawn as to the structures of the copper complexes. The physical evidence suggests that the initial complex has a tetragonal structure with the anions weakly attached to the axial positions or in outer coordination spheres. A pyridine–methanol solution of $Cu(OBz)(OCH_3)$ in the presence of excess trien gives the esr spectra shown in Figure 6. The spectrum was also taken at 2°K and the spin parameters calculated from this spectrum are $g_{11} = 2.21$, $g_\perp = 2.06$, $A_{11} = 554$ MHz, and $A_\perp \sim 0$. These parameters are typical of a symmetrical square planar structure with bonding by four nitrogens[19] and the g tensors are very similar to those found in complexes of the type $(en)_2Cu(II)X_2$ where X represents a variety of anions such as chloride and nitrate.[17] It is believed that the anions are very weakly coordinated in the axial positions. Volger and Brackman[20] have reported that in methanol–pyridine solutions the species $[(pyridine)_4Cu(II)]^{2+}$ readily coordinates a methoxide ion as a fifth ligand. However, in the case of the aliphatic amines, the coordination must be very similar to loose ion pairing, since Davis and Patel[21] have observed a 20-fold rise in the conductance of an aqueous solution of copper malonate when 2 mol of ethylendiamine are added for each mole of copper. On the other hand, methoxide ions are strongly coordinated in the absence of amine ligands and in the case of $Cu(OCH_3)_2$ dissolution in pyridine–methanol solvent does not occur readily until polydentate aliphatic amine is added. In the absence of ligands methoxide bridging undoubtedly occurs.

The kinetic evidence is in accord with the above structure. The similar values of k_H for $NaOCH_3$ and $(trien)Cu(OBz)(OCH_3)$ show that the reactivity of the methoxide ion is only slightly affected by the cation and suggest a very weak coordination of the methoxide ion. The fact that pyridine is necessary for oxidation suggests that replacement of the axial ligands by pyridine takes place, and that in the active catalyst complex these ions may exist as outer sphere ligands. The similar rate with benzoate and chloride ions (Table I) is in accord with this description. The rate of oxidation with the copper catalyst is roughly proportional to the total concentration of methoxide ion added regardless of the cation. Thus, comparing runs 60B, 65, and 96 (Table I) the ratios of total methoxide concentration are 1.0:2.0:4.3 and the respective rates are 1.0:2.3:5.5. However, when the alkoxide ion is connected to an amine group in a bidentate type structure as in the case of the 1-amino-2-propoxide ligand, the oxidation rates are lowered, suggesting that increased coordination of the base group lowers the rate of proton removal. Thus as the amine ligand is changed from dien to trien (runs 49B and 51A, Table I) the rate nearly doubles and the latter rate is nearly that for $Cu(OBz)(OCH_3)$ with dien (run 60B, Table I).

The unusually steep rise in oxidation rate when the ratio of trien concentration to Cu(II) concentration is slightly below unity may be due to additional coordination of the methoxide ion of a reactive catalyst molecule by an uncomplexed Cu(II) species leading to a loss in reactivity of the methoxide ion.

$$(trien)Cu(OBz)(OCH_3) + Cu(OBz)(OCH_3) \overset{K}{\rightleftharpoons} \text{inactive species}$$

Different values of the equilibrium constant ranging from 10 to 10^5 were assigned, and using the conditions of 0.100 M fluorene and 2.5×10^{-3} M total Cu the equilibrium concentration of $(trien)Cu(OBz)(OCH_3)$ as a function of the trien/Cu ratio was calculated. Assuming that $R_0 = k[(trien)Cu(OBz)(OCH_3)]$, k was calculated by equating the observed maximum rate in Figure 1 with the maximum calculated concentration. The calculated plot of R_0 for $K = 10^4$ is shown in Figure 1 and has a fair fit to the observed rate curve.

As regards the structure of the proposed intermediate fluorenide–copper complex, the fluorenide anion is probably a weakly bonded axial ligand similar to methoxide. However, additional stabilization is possible by π backbonding from the electron-rich d orbitals of the copper analogous to the proposed bonding of benzene to copper(II) dimethylglyoxime in benzene solutions of the complex.[22] It is possible that such a structure could lead to a very facile electron transfer from the axial fluorenide ion *via* the copper atom to an O_2 molecule located in the other axial position (reaction 4). The fluorenide ion protonation rate constant may also be lowered for such a structure. Both possibilities are in agreement with the experimental observations.

Product Formation.—The products and their dependence on oxygen pressure (Table II) are qualitatively in accord with the postulated mechanism (reactions 1–11). Since an increase in oxygen pressure will increase reaction 6 but not 11 the yield of fluorenone should increase relative to bifluorenyl as is observed. However, bifluorenyl has not been reported as a product in other catalyzed autoxidations of fluorene in basic media[13,14] under similar conditions. One possible explanation may be that the fluorenyl radicals (and other intermediates as well) are associated with a Cu(II) species in such a way as to alter the rates of their reactions.

Related Copper-Catalyzed Reactions.—There are other copper-catalyzed reactions in which polyamines

(19) D. Kivelson and R. Nieman, *J. Chem. Phys.*, **35**, 149 (1961).

(20) H. C. Volger and W. Brackman, *Proc. Int. Conf. Coord. Chem.*, *8th*, 38 (1964).

(21) C. W. Davis and V. C. Patel, *J. Chem. Soc.*, 4716 (1963).

(22) K. Falk, E. Ivanova, B. Roos, and T. Vanngard, *Inorg. Chem.*, **9**, 556 (1970).

have an accelerating effect on the rate. The autoxidation of 2,6-di-*tert*-butylphenol[1b] by CuCl in pyridine reaches a maximum rate when the ratio of [en]/[cu] ~ 3. At zero and very high concentrations of ethylenediamine the rate is about 0.125 times as rapid. Roughly the same acceleration is shown by diethylenetriamine when [dien]/[Cu] ~ 1 but at high ratios the rate does not fall off. Triethylenetetramine inhibits the reaction. Thus for maximum reactivity three amine ligands should be coordinated to the copper. It has been reported that the decomposition of H_2O_2 is catalyzed by a bis(2,2-bipyridyl)copper complex, although the 1:1 complex is the most reactive.[23] The present work suggests that in cases where the copper catalyst has three or four aliphatic amine groups strongly coordinated, Cu(II) does not act as an oxidizing agent because of the unfavorable change of the redox potential between Cu(I) and Cu(II) with increasing coordination by polydentate aliphatic amines. This is supported by the observation of Janes and Williams[24] that the oxidation potential of the half reaction $L_4Cu(I) = L_4Cu(II) + e$ changes by about 0.66 V when the four ligand sites change from coordination with four pyridines to two ethylenediamines. Thus the bis(ethylenediamine)Cu(II) complex is a substantially weaker oxidizing agent. The Cu(II)-containing enzymes, amine oxidase[25] and galactose oxidase,[26] appear to function as oxidation catalysts without intervention of a Cu(I) state. However, in these cases the exact nature of the ligands is uncertain.

Experimental Section

Materials.—Standard reagent grade pyridine and methanol were used fresh from well-stoppered bottles without further purification. Deuteriomethanol (99% CH_3OD) was obtained from the Isomet Corp. Ethylenediamine (en), diethylenetriamine (dien), and triethylenetetramine (trien) were distilled from CaH_2 and stored in well-stoppered bottles. Fluorene was recrystallized from hot ethanol to constant melting point (116.5–117.5°).

9-Dideuteriofluorene.—The 9-deuterated fluorene was prepared by repeated exchange in pyridine–CH_3OD mixtures using $NaOCH_3$. Each exchange was run under N_2 for 2 hr, then quenched by pouring into 1 *M* HCl solution. The precipitated fluorene was collected by suction filtration, washed several times with water, and dried *in vacuo*. The final sample was 96% deuterated at the 9 position by nmr analysis. After recrystallization from hot aqueous ethanol the melting point was 115.5–116.5°.

Preparation of Copper Compounds. CuCl.—Cuprous chloride was prepared by the method of Walton.[27] A white, crystalline powder was obtained.

CuOBz.—Cuprous benzoate was prepared by modifying the method of Cohen and Lewin.[28] Benzoic acid (0.11 mol) was dissolved in 200 ml of xylene. Cuprous oxide powder (0.025 mol) was added and the mixture was refluxed under N_2 overnight with a Dean–Stark trap connected to remove water. After reaction, only a trace of red oxide remained and after cooling in ice a white solid formed. The xylene was filtered off under N_2 pressure and the solid was washed with 50 ml of xylene and 25 ml of ether. The solid was then freed of remaining solvent by pumping at 0.2 Torr, leaving 8.5 g of a whitish-gray solid (42% yield). The material discolors in air and must be stored in the dark in a well-stoppered bottle. *Anal.* Calcd for $CuC_7H_5O_2$: Cu, 34.4. Found: Cu, 34.1.

Cu(Cl)(OCH_3).—The method of Finkbeiner, *et al.*,[10] was followed, giving a 92% yield. *Anal.* Calcd for $CuCH_3OCl$: Cu, 48.8. Found: Cu, 48.7.

Cu(OBz)(OCH_3).—The above method for preparation of Cu(Cl)(OCH_3) was used except that CuOBz was substituted for CuCl. *Anal.* Calcd for $CuC_8H_8O_3$: Cu, 29.5; C, 44.5; H, 3.74. Found: Cu, 29.0; C, 44.2; H, 3.74.

(Trien)Cu(OBz)(OCH_3).—To a stirred mixture of 650 mg (3.0 mmol) of Cu(OBz)(OCH_3) in 50 ml of dry ether under N_2 was added 450 mg (3.08 mmol) of trien. After a few minutes the color of the slurry darkened and became bluish. After stirring for 3.5 hr the dark green slurry was filtered under N_2 pressure and washed twice with dry ether and the excess solvent was removed by pumping at 0.2 Torr. The dark green powder collected (520 mg) was very hygroscopic and formed a sticky green solid on contact with air. For this reason it was not characterized further.

Cu(OCH_3)$_2$.—A modification of the methods of Finkbeiner and coworkers[9] and Brubaker and Wicholas[29] was used. Into 100 ml of methanol was added 753 mg (2.03 mmol) of $Cu(ClO_4)_2 \cdot 6H_2O$. Then with continuous stirring 340 mg (6.28 mmol) of $NaOCH_3$ was added. A blue precipitate immediately formed and was filtered off under N_2 pressure, and washed twice with methanol and twice with ether. Solvent was removed *in vacuo*, leaving 250 mg of blue powder. *Anal.* Calcd for $CuC_2H_6O_2$: Cu, 50.6. Found: Cu, 51.5.

($CH_3CHOCH_2NH_2$)Cu(OBz).—A solution containing 170 mg (2.26 mmol) of 1-amino-2-propanol in 50 ml of ether was added to 387 mg (2.05 mmol) of CuOBz and stirred under 760 Torr of O_2 for 2.5 hr. The blue solid which formed was filtered off and washed twice with ether. Excess solvent was removed *in vacuo*, leaving 475 mg of product (89% yield). *Anal.* Calcd for $CuC_{10}H_{13}NO_3$: Cu, 24.6. Found: Cu, 24.0.

Oxidation Runs. Kinetics. Apparatus.—The apparatus for measurement of oxygen was designed to measure small changes in pressure under conditions of nearly constant total pressure. The apparatus consisted of a Pyrex glass reaction vessel equipped with a magnetic stirring bar, an electrically operated solenoid valve, a 3-l. stainless steel gas cylinder, a Wallace and Tierman precision pressure gauge, a Pace-Wianko differential pressure transducer with full scale deflection adjusted to follow a pressure drop of 10 Torr, and a recorder connected to the transducer. The reaction vessel was connected to one port of the transducer and *via* the solenoid valve to the 3-l. reservoir, pressure gauge, and reference port of the transducer. The reaction vessel, transducer, and reservoir were immersed in a constant-temperature bath. A pair of micro switches on the recorder were used to turn the solenoid valve off and on. Whenever 10.0 Torr of oxygen was consumed in the reaction vessel the solenoid opened and allowed the vessel to equilibrate with the reservoir. When zero differential pressure was reestablished the solenoid closed. The times for equilibration were generally small compared to the consumption times. The gas volume in the reactor was calibrated so that the moles of oxygen consumed and the rates of oxygen uptake were calculated from the slopes of the recorder plots. The slopes were much more accurate than total oxygen consumption, since the errors in each pressure cycle accumulated in the total consumption. In duplicate experiments maleic anhydride was hydrogenated very slowly and the total hydrogen consumption was exactly the theoretical within ±0.4%. However, in the oxidation experiments where consumption was fast, the total consumption usually fell short of theoretical.

Procedure.—All runs were at 25.0°. Pyridine–methanol (5:1, v/v) was the solvent in all cases except where mentioned. The hydrocarbon and amine were dissolved in the solvent. The catalyst was placed in a polyethylene boat which was suspended above the solution. The vessel was sealed and pumped and filled four times with pure O_2 at the desired pressure. After the reservoir was connected, the solution was then stirred until no more pressure change occurred; the solution then had attained the equilibrium oxygen concentration. The catalyst was added and the rate of pressure drop was followed. During a typical run the total pressure was 1000 Torr and pressure changes of 10.0 Torr were followed per cycle. After complete reaction the total drop in the reservior was about 1–2 Torr. The vapor pressure of the solvent was measured and found to be 50 (±1) Torr. Thus the

(23) R. Griesser, B. Prijs, and H. Sigel, *J. Amer Chem. Soc.*, **91**, 7758 (1969).

(24) B. R. James and R. J. P. Williams, *J. Chem. Soc.*, 2007 (1961).

(25) S. Nara and K. T. Yasunobu in "The Biochemistry of Copper," J. Peisach, P. Aisen, and W. E. Blumberg, Ed., Academic Press, New York, N. Y., 1966, p 423.

(26) W. E. Blumberg, *et al. Biochim. Biophys. Acta*, **96**, 336 (1965).

(27) H. F. Walton, "Inorganic Preparations," Prentice-Hall, Englewood Cliffs, N. J., 1962, p 154.

(28) T. Cohen and A. Lewin, *J. Amer. Chem. Soc.*, **88**, 4521 (1966).

(29) C. H. Brubaker and M. Wicholas, *J. Inorg. Nucl. Chem.*, **27**, 59 (1965).

total pressure of O_2 above the reaction was just the total pressure minus 50 Torr. The stirring speeds were adjusted to avoid making the rates diffusion controlled. In rates higher than about 150 M min^{-1} diffusion rates of oxygen begin to compete as rate-limiting steps. All kinetic studies were done below this limiting rate.

Products.—Reaction solutions were quenched by pouring into cold 1 M HCl. The mixture was extracted with two portions of benzene and the benzene extracts were washed several times with water. The benzene solutions were dried and analyzed by gas chromatography. Fluorene, fluorenone, and fluorenol were determined on an XE-60 column at 230° using chloronaphthalene as an internal standard. No fluorenol was found in any reactions. 9,9′-Bifluorenyl was analyzed on an XE-60 column (seasoned overnight at 275°) at 245°.

Spectra.—Visible spectra were done using a Cary 14 spectrophotometer. A Varian Aerograph instrument was used for esr spectra except for liquid helium temperatures, where a super heterodyne spectrometer operating near 9200 MHz was used.

Registry No.—Fluorene, 86-73-7; CuOBz, 14604-51-4; $Cu(Cl)(OCH_3)$, 2850-63-7; $Cu(OBz)(OCH_3)$, 34825-83-7; $(trien)Cu(OBz)(OCH_3)$, 34825-62-2; $Cu(OCH_3)_2$, 1184-54-9; $(CH_3CHOCH_2NH_2)Cu(OBz)$, 34825-84-8.

The Chemistry of Blocked Isocyanates. II. Kinetics and Mechanism of the Reaction of Dibutylamine with Phenyl and 2-Methylphenyl Oxime Carbamates[1]

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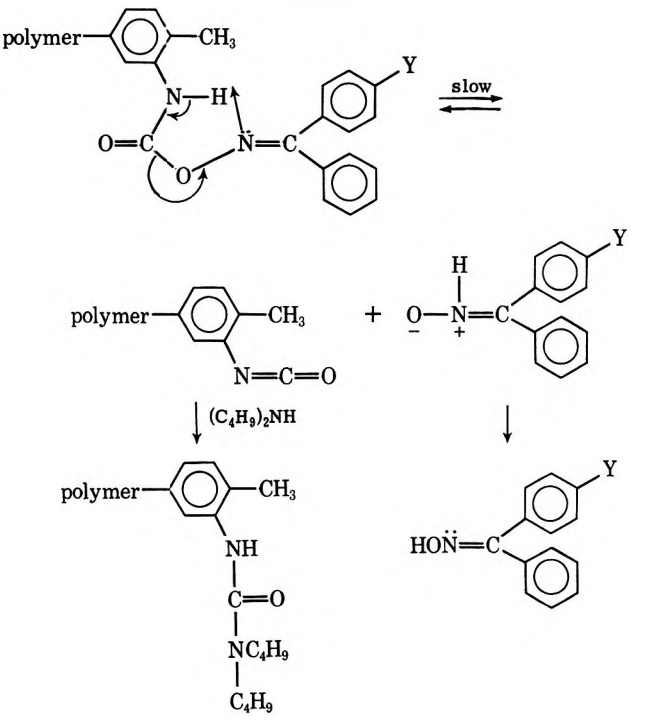
Received January 24, 1972

Dibutylamine reacts with carbamates derived from substituted benzophenone oximes and phenyl isocyanates. The reactions follow first-order kinetics and the products are the corresponding substituted phenyldibutylureas and the oximes. The rate constants for reaction of para-substituted phenyl carbamates are insensitive to added excess amine. Activation parameters for the unsubstituted compound are $\Delta H^{\pm} = 25.7 \pm 0.3$ kcal mol^{-1} and $\Delta S^{\pm} = -0.24 \pm 0.39$ eu. The reaction is facilitated by electron-withdrawing isocyanate substituents ($\rho = +0.296 \pm 0.012$, $r = 0.995$, correlation with σ) and by electron-donating oxime substituents ($\rho^{+} = -0.401 \pm 0.011$, $r = 0.997$, correlation with σ^{+}). The rate constants for carbamates derived from 2-methylphenyl isocyanate and substituted benzophenone oximes also increase with increased electron-donating ability of the substituents ($\rho = -0.512 \pm 0.034$, $r = 0.979$, correlation with σ). The difference in mode of the substituent effect is interpreted as indicating the intervention, in the former case, of a zwitterionic intermediate in the otherwise concerted carbamate dissociation.

In a previous communication,[1] we reported on the unblocking of benzophenone oxime-blocked polyurethanes using dibutylamine as coreactant. It was found that the reaction followed first-order kinetics and was not subject to base catalysis. Unlike the similar reaction of phenol-blocked polyurethanes[2,3] whose rates are favored by electron-withdrawing substituents on the blocking group, the reaction studied was found to be accelerated by electron-donating oxime substituents. On the basis of this evidence and the near-zero entropy of activation for this reaction, we postulated a five-center cyclic, intramolecular transition state for the decomposition as shown in Chart I.

In order to investigate further the postulated mechanism, we undertook to study oxime unblocking of model compounds. Two series of compounds, based on phenyl and 2-methylphenyl isocyanate (Charts II and III) were synthesized. Rate constants were determined for reaction of these compounds with dibutylamine in toluene solution. This paper discusses the results of these experiments and their bearing on the intramolecular transition state.

CHART I



Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared (ir) spectra were taken in KBr using a Perkin-Elmer Model 457 instrument. Nuclear Magnetic Resonance (nmr) spectra were recorded on a Joelco Minimar at ambient temperature in perdeuterioacetone solution. Tetramethylsilane (also deuterated solvents from Stohler Isotope Chemicals) was used as internal standard. Microanalyses were by Micro-Analysis, Inc., Wilmington, Del.

Benzophenone, substituted ketones, hydroxylamine hydrochloride, phenyl isocyanate, and 2-methylphenyl isocyanate were used as received from Eastman Organic Chemicals. Pyridine and dibutylamine were distilled from KOH. All inorganic

(1) Part I: A. W. Levine and J. Fech, Jr., *J. Org. Chem.*, **37**, 1500 (1972). The present paper was presented in part at the 163rd National Meeting of the American Chemical Society, Boston, Mass., April 9–14, Abstract ORGN-160.

(2) S. Peterson, *Justus Liebigs Ann. Chem.*, **562**, 205 (1949).

(3) G. R. Griffin and L. J. Willwerth, *Ind. Eng. Chem., Prod. Res. Develop.*, **1**, 265 (1962).

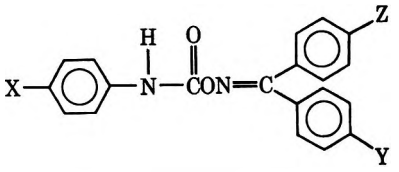
TABLE I

SYNTHESIS OF BENZOPHENONE OXIMES

Para substituent	Yield, %	Recrystn solvent	Mp, °C Found[a,b]		Mp, °C Lit. (ref)[c]	Estimated syn/anti[a] (by nmr)
H	95	Methanol	143.5–144.5		144	
NO_2	51	Aqueous ethanol	115–116	syn	115	40/60
			136–143	anti	158	
Cl	36	Ethanol	94	syn	95	5/95
			156–159	anti	155–156	
CH_3	85	Aqueous methanol	118–120	syn	115–116	15/85
			138–145	anti	153–154	
OCH_3	79	Methanol	116–120	syn	115–116	50/50
			137–142	anti	137–138	
$(CH_3)_2N$	87	Methanol	156–159	syn	163	
				anti	176 (6)	40/60
				mixture	153.5	
4,4-Bis$(CH_3)_2N$	74	Benzene	216–219		216–217 (4)	

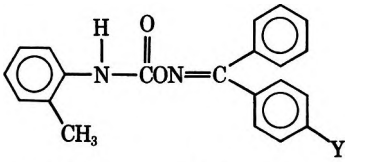
[a] Syn and anti with respect to the substituted aromatic ring. [b] Two distinct melting ranges were frequently observed. [c] Unreferenced values taken from Beilstein.

CHART II



Compd	Substituents X	Y	Z
1	H	H	H
2	NO_2	H	H
3	Cl	H	H
4	OCH_3	H	H
5	H	NO_2	H
6	H	Cl	H
7	H	CH_3	H
8	H	OCH_3	H
9	H	$N(CH_3)_2$	H
10	H	$N(CH_3)_2$	$N(CH_3)_2$
11	NO_2	OCH_3	H

CHART III



Compd	Substituent Y
12	H
13	NO_2
14	Cl
15	CH_3
16	OCH_3
17	$N(CH_3)_2$

reagents were the purest grade available from Matheson Coleman and Bell. Solvents were reagent or electronic grade and were dried prior to use.

Synthesis of Oximes.—The following procedure is illustrative of the general method used to prepare all oximes with the exception of 4,4′-bis(dimethylamino)benzophenone oxime.[4] A stirred solution of ketone and hydroxylamine hydrochloride (1 equiv each) in pyridine (100 ml) and anhydrous ethanol (200 ml) was heated under reflux for 2 hr. The cooled solutions were concentrated and poured into 600 ml of faintly alkaline (NH_3) water. The product was collected, washed well with water, dried, and recrystallized to constant melting behavior. In the case of the monosubstituted oximes, two distinct melting ranges were frequently observed. Table I lists the oximes prepared. Since the carbamates prepared from these oximes underwent smooth first-order reaction, isomer separation was not considered necessary. This observation confirms a report[5] that both isomers of substituted benzophenone oximes give the same compound upon treatment with phenyl isocyanate.

Preparation of Oxime Carbamates.—The following procedure is illustrative of the general synthesis of compounds 1–17. Tables II and III list the compounds prepared and some of their properties.[7] Benzophenone oxime (20.0 g, 0.1014 equiv) was dissolved in 50 ml of anhydrous diethyl ether. The solution was stirred magnetically and 12.7 g (0.1068 equiv) of phenyl isocyanate was added dropwise at a rate which maintained a gentle reflux. All glassware had previously been baked dry. After

TABLE II

SYNTHESIS OF BENZOPHENONE OXIME PHENYL CARBAMATES[a]

Compd	Mp, °C	Recrystn solvent	Yield, %	Ir max, cm^{-1} ν_{NH}	Ir max, cm^{-1} $\nu_{C=O}$
1	178–180	Acetone	85	3278	1733
2	162–164	*b*	70	3260	1734
3	151–153	Ether	60	3300	1735
4	126–127	Ether	60	3260	1728
5	184–188	*b*	33	3275	1739
6	207–210	Acetone	85	3290	1733
7	198–200	Dioxane	70	3290	1732
8	179–181[c]	*b*	50	3288	1732
9	149–150	Acetone	75	3293	1726
10	*d*	*b*	91	3340	1733
11	*e*	Acetone	70	3350	1738

[a] See footnote 7. [b] Analytical material obtained directly from reaction. [c] Phase transition at 170–173°. [d] Very unusual behavior. Decomposition began for this compound at 99° and, before finally liquefying at 185°, it suffered two color changes and gas evolution. [e] Photochemically active, approximate melting range 78–88°.

(4) Prepared by the method of R. D. Morin, J. S. Warner, and R. H. Poirer, *J. Org. Chem.*, **21**, 616 (1956).

(5) O. L. Brady and R. P. Mehta, *J. Chem. Soc.*, **125**, 2297 (1924).

(6) J. Meisenheimer and A. Kuppler, *Justus Liebigs Ann. Chem.*, **539**, 99 (1939).

(7) Satisfactory microanalyses (±0.4% for C, H, and N) were reported for all compounds listed in Tables II and III with the following exceptions: Calcd, **11**: C, 66.45; H, 4.38; N, 10.72. Found: C, 66.40; H, 4.62; N, 10.02. Calcd, **13**: C, 67.19; H, 4.57; N, 11.19. Found: C, 67.69; H, 4.81; N, 11.16.

TABLE III
SYNTHESIS OF BENZOPHENONE OXIME 2-METHYLPHENYL CARBAMATES[a]

Compd	Mp, °C	Recrystn solvent	Yield, %	Ir max, cm⁻¹ νNH	Ir max, cm⁻¹ νC=O
12	127–130	Ether	75	3385	1760
13	122–130	Acetone	43	3380	1758
14	148–152	Acetone	60	3390	1757
15	97–110	Acetone	50	3390	1755
16	127–129	Acetone	73	3380	1757
17	138–140	Acetone	77	3375	1750

[a] See footnote 7.

addition was complete, the mixture was held at reflux for 20 min, cooled, and diluted with 50 ml of ether. The solid was collected on a Buchner funnel, washed with ether, and recrystallized repeatedly from acetone to give 28 g (87.4%) of benzophenone oxime phenylcarbamate. Generally, compounds were repeatedly recrystallized to constant melting behavior.

While ether was a satisfactory solvent for the majority of the syntheses, significant improvement in the yield was obtained when 11 was prepared in benzene and when 13 was made in acetone. In all but two cases, reactions were exothermic and the product began to precipitate shortly after beginning the isocyanate addition. In the cases of compounds 12 and 13, however, catalysis was needed and one drop of triethylamine was used.

A number of the oxime carbamates were readily degraded by light. This was especially true of compound 11, which rapidly darkened even on exposure to an incandescent source. Since all the compounds prepared were thermally unstable, it was not surprising that some analytically pure materials exhibited very wide melting ranges, particularly in the less heat-stable 2-methylphenyl series.

Kinetics Experiments.—The reaction system and procedure have previously been described.[1] Initial concentrations were in the range of 0.02–0.03 *M*. Regressions of first-order plots and correlations of the data using the Eyring and Hammett equations were performed by computer.

Product Isolation and Identification.—In addition to our previous establishment[1] of the products of reaction, two experiments were performed on the compounds used in this study. A reaction mixture which had been used to determine the rate constant for compound 11 was cooled to room temperature. After it had stood for 3 days, a white solid had separated which was collected, washed, and dried *in vacuo* to give crystals of *p*-nitrophenyldibutylurea, mp 127–129°, identified by peak matching of its ir spectrum with that of an independently synthesized sample of the urea.

Anal. Calcd for $C_{15}H_{23}N_3O_3$: C, 61.42; H, 7.91; N, 14.32. Found: C, 61.21; H, 8.02; N, 14.56.

A second reaction mixture, from a rate determination on compound 12, was concentrated under reduced pressure. Upon cooling to −70°, crystals of benzophenone oxime separated, mp 142–144°. Identification was made by peak matching of the ir spectrum with that of an authentic sample.

Reversibility of Reaction of 17.—Dibutylamine (0.490 g, 3.79 mequiv) and 2-methylphenyl isocyanate (0.50 g, 3.76 mequiv) were dissolved in 37 ml of toluene and the solution (total volume 38 ml) was heated at 70° for 1 hr. A 10-ml aliquot of this solution of 2-methylphenyl dibutylurea was added to 100 ml of 2-propanol and titrated with 0.1 *N* aqueous HCl to a bromcresol green end point. The titration required 0.11 ml of HCl solution, indicating a residual amine concentration of $1.1 \times 10^{-3} M$. The calculated excess of amine was $0.95 \times 10^{-3} M$.

To a second 10-ml aliquot of the urea solution was added 0.24 g (1.0 mequiv) of 4-dimethylaminobenzophenone oxime. The solution was held at 70° for 10 min and then added to 100 ml of 2-propanol. The quenched solution required 0.50 ml of 0.1 *N* aqueous HCl to reach the bromocresol green end point.

The difference in titrations was 0.39 ml corresponding to an increase in amine concentration of $3.9 \times 10^{-3} M$. Since the original concentration of urea in the 10-ml aliquot was $9.74 \times 10^{-2} M$, the increase in dibutylamine concentration corresponded to 4.0% reaction.

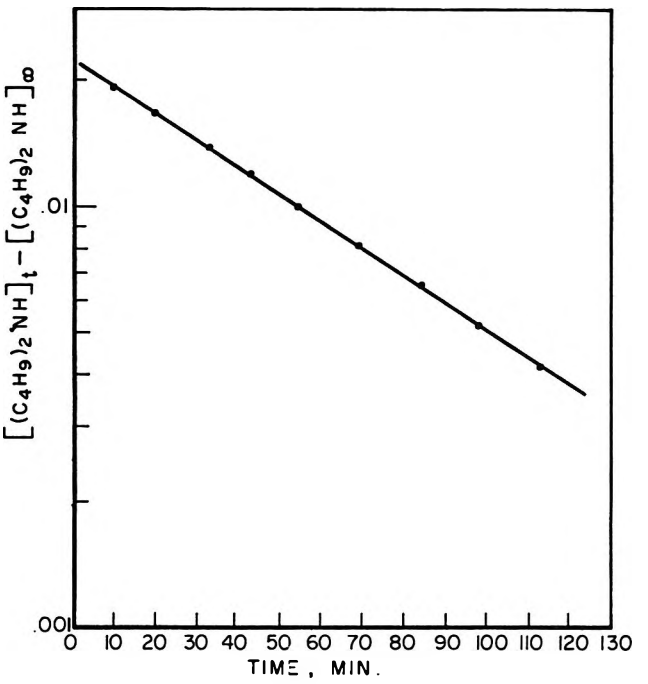


Figure 1.—Reaction of benzophenone oxime phenylcarbamate (1) with dibutylamine at 70.0° and 1/1 reactant ratio.

Results and Discussion

The oxime carbamates studied react smoothly with dibutylamine, producing the corresponding dibutylureas. In all but one case, the reactions are irreversible and quantitative conversion occurs in from 80 to 1100 min at 70° depending upon substitution. The stoichiometry of the reaction is 1 equiv of amine used per equiv of carbamate reacted. A typical kinetics experiment is presented in Figure 1. Attempts to fit the data to higher order kinetic expressions did not provide straight lines. Since there are two species taking part in the reaction and first-order kinetics are observed, either the carbamate or the amine becomes involved only after the rate-determining step of the reaction. Tables IV and V list first-order rate constants for the compounds studied under a variety of conditions.

Phenyl Carbamates.—From the values in Table IV, it is clear that the rate of reaction of 1 with dibutylamine is independent of amine concentration. It is thus the amine which does not participate in the rate-determining step. The overall pathway of reaction, therefore, requires a unimolecular decomposition of the carbamate followed by reaction of the isocyanate thus formed with dibutylamine. The latter reaction is known[8] to be very rapid.

Activation parameters[2] for the reaction of the phenyl carbamates were determined by plotting the appropriate rate constants from Table IV according to the Eyring equation ($r = 0.999$). The calculated value of enthalpy of activation ($\Delta H^{\pm}$) was 25.7 ± 0.3 kcal/mol and the entropy of activation ($\Delta S^{\pm}$) was −0.24 ± 0.39 cal/deg mol. These values are consistent with a unimolecular rate-determining decomposition[9] and compared quite well with those determined[1] for the similar macromolecular oxime carbamates where $\Delta H^{\pm}$ was 24.8 ± 0.5 kcal/mol and $\Delta S^{\pm}$ was −1.86 ± 0.8 cal/deg

(8) E. H. Dyer, H. A. Taylor, S. J. Mason, and J. Sampson, *J. Amer. Chem. Soc.*, **71**, 4106 (1949).

(9) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963).

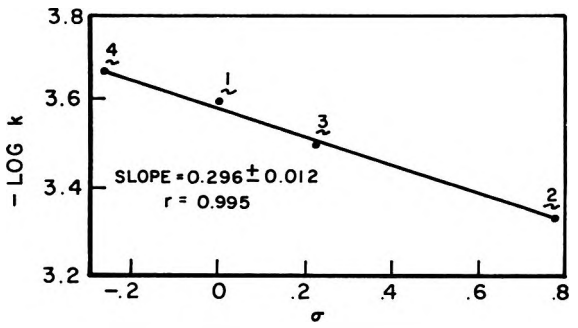


Figure 2.—Reaction of compounds 1–4 with dibutylamine at 70.0° and 1/1 equivalent ratio. Solution of the Hammett equation for position X.

TABLE IV
FIRST-ORDER RATE CONSTANTS FOR REACTION OF BENZOPHENONE OXIME PHENYL CARBAMATES WITH DIBUTYLAMINE IN TOLUENE SOLUTION

Compd	Reactant ratio[a]	Temp, °C, ± 0.05	$10^4 k$,[b,c] sec^{-1}
1	1.0	70	2.507 ± 0.016
1	2.0	70	2.316 ± 0.017
1	5.0	70	2.219[d]
1	10.0	70	2.740 ± 0.040
1	1.0	80	7.785 ± 0.101
1	1.0	60	0.811 ± 0.001
2	1.0	70	4.323 ± 0.101
3	1.0	70	3.115 ± 0.023
4	1.0	70	2.142 ± 0.001
5	1.0	70	1.058 ± 0.003
6	1.0	70	2.367 ± 0.023
6	1.45	70	2.123[d]
7	1.0	70	3.347 ± 0.022
8	1.0	70	4.888 ± 0.068
9	1.0	70	11.20 ± 0.10
10	1.0	70	14.59 ± 0.07
11	1.0	70	7.771 ± 0.285

[a] $[Amine]_0/[carbamate]_0$. [b] Average of at least two runs with different initial concentrations. [c] Limits are average deviations of the means. [d] Single experiment.

mol. It thus appeared that the mechanism for both reactions is the same.

The rate constants for the substituted phenyl carbamates were fitted to the Hammett[10] equation. The correlation is shown for position X in Figure 2 and that for position Y in Figure 3. The electronic effect of substituents at position X ($\rho = +0.296 \pm 0.012$) may be interpreted in a manner similar to that used to explain ρ values for acid-catalyzed ester hydrolyses.[11] For the reaction to proceed, the N–H bond must be broken. This process would be facilitated by an electron-withdrawing substituent, X. However, the pair of electrons forming the N–H bond does not remain localized on the nitrogen atom and instead forms part of the N=C bond in the isocyanate intermediate. The formation of the N=C bond requires nucleophilic displacement to break the existing C–O bond. The nucleophilicity of an electron pair on the nitrogen atom would be increased by an electron-releasing substituent, X. One would thus predict a small absolute value of ρ. The overall rate acceleration by electron withdrawal at position X suggests that the N–H bond

(10) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(11) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).

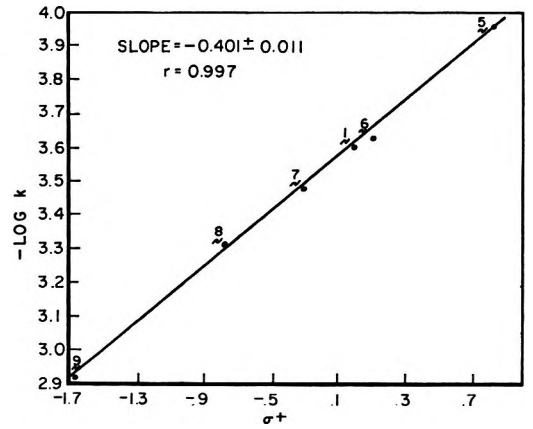


Figure 3.—Reaction of compounds 1 and 5–9 with dibutylamine at 70.0° and 1/1 equivalent ratio. Solution of the Hammett equation for position Y.

breaking is more important in the transition state of the rate-determining step than is the C–O bond breaking.

As in the case of the macromolecular compounds previously reported,[1] the electronic effect at position Y ($\rho^+ = -0.401 \pm 0.011$) indicated involvement of the –C=N:– electrons in the transition state for decomposition. Unlike the macromolecular compounds, however, the rate constants in this case are correlated by σ^+ rather than σ. The implication[12] of a σ^+ correlation is that a positive charge is generated in the rate-determining transition state. The location of this charge must be one which allows direct conjugation with the substituted aromatic ring. For the most part, reactions correlated by σ^+ occur in highly ionizing media and involve carbonium ions where the cationic center is α to the substituted aromatic ring. There are several exceptions, however, involving thermal reactions in hydrocarbon solvents and free-radical reactions.[13]

2-Methylphenyl Carbamates.—The overall similarity between the reactions of the large molecules[1] and the phenyl carbamates seemed to indicate a similar mechanism. The difference in response of the rate constants to the electronic effect of substituents, however, demonstrated that the modes of reaction for the two series of compounds were not identical. The only structural difference in the isocyanate portion of the two series of compounds was that the macromolecular compounds were derived from 2,4-toluenediisocyanate (TDI) rather than phenyl isocyanate. The 4-isocyanate group of TDI is considerably more reactive than is the 2-isocyanate group under the conditions of synthesis.[14] It is thus reasonable to assume that the structure of the macromolecular carbamates is as shown in Chart I; *i.e.*, there is a methyl group adjacent to the carbamate linkage. In order to determine the effect of such substitution, compounds **12–17** were prepared and treated with dibutylamine.

An examination of the rate constants in Table V is revealing. Comparing similarly substituted compounds, *e.g.*, **12** and **1**, it is clear that the 2-methylphenyl carbamates react considerably more rapidly

(12) Y. Okamoto and H. C. Brown, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).
(13) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963, pp 208–209.
(14) M. E. Bailey, V. Kirss, and R. G. Spaunburgh, *Ind. Eng. Chem.*, **48**, 794 (1956).

TABLE V
FIRST-ORDER RATE CONSTANTS FOR REACTION OF BENZOPHENONE OXIME 2-METHYLPHENYL CARBAMATES WITH DIBUTYLAMINE IN TOLUENE SOLUTION AT 70.0 AND 1/1 REACTANT RATIO

Compd	$10^4 k$,[a,b] sec^{-1}
12	5.175 ± 0.057
13	1.695 ± 0.023
14	4.689 ± 0.017
15	6.396 ± 0.039
16	6.248 ± 0.068
17	12.29[c] ± 0.14

[a] Average of two runs with different initial concentrations. [b] Limits are average deviations of the means. [c] Initial rates; see text.

than do the phenyl carbamates. This difference, however, is far less for compounds bearing highly electron donating substituents. Correlation of the data in Table V using the Hammett equation shows (Figure 4) that the rate constants follow σ (r = 0.979) much more closely than σ^+ (r = 0.932). The value of ρ is −0.512 ± 0.034. All of the compounds in the 2-methylphenyl series underwent smooth, first-order reaction with dibutylamine with the exception of **17**. For this material, there was a decrease in rate constant with time which became noticeable as curvature in the first-order plot after about 60% reaction (10–15 min).

Since behavior of this type can result from reversibility of a reaction, a test of the stability of the product in this reaction was made. 2-Methylphenyldibutylurea was synthesized and allowed to react at 70° with 4-dimethylaminobenzophenone oxime. An increase in the volume of aqueous HCl needed to bring aliquots of this solution, quenched in 2-propanol, to a bromcresol green end point was observed. Equilibrium was apparently reached at approximately 4% reversion to carbamate. Therefore, the rate constant for **17** was taken from the initial points in the first-order plot.

Mechanistic Implications.—The change in response of the reaction to electronic effects of substituents on the oxime moiety which attends a change in structure of the isocyanate portion of the molecule is unusual. The fact that all of the compounds studied undergo first-order reactions whose rates are insensitive to amine concentration supports the intramolecular cyclic dissociation as the rate-determining step. It appears that the presence of an ortho methyl group on the isocyanate-derived portion of the molecule changes the manner in which the azomethine group interacts with the carbamate hydrogen atom. That a rate increase is observed when 2-methylphenyl isocyanate is used suggests a steric effect. The similarity of the rate constants for TDI and 2-methylphenyl isocyanate derived carbamates on the one hand and the similarity of activation parameters of the phenyl isocyanate and TDI derived carbamates on the other imply that a single but modifiable mechanism is followed by all of the compounds studied. We originally hypothesized[1] (Chart I) that the dissociation proceeded *via* a concerted, intramolecular transition state. Clearly, this is not possible for all compounds in view of the substituent effects. The intramolecular nature of the transition state is, however, required by the gross effect that the rate in all cases is favored by an electron-donating substituent Y. The possibility, then, that the reaction is not always concerted presents itself.

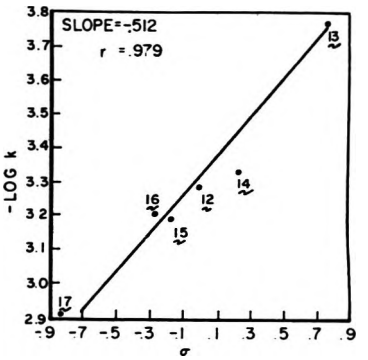


Figure 4.—Reaction of compounds 12–17 with dibutylamine at 70.0° and 1/1 equivalent ratio. Solution of the Hammett equation.

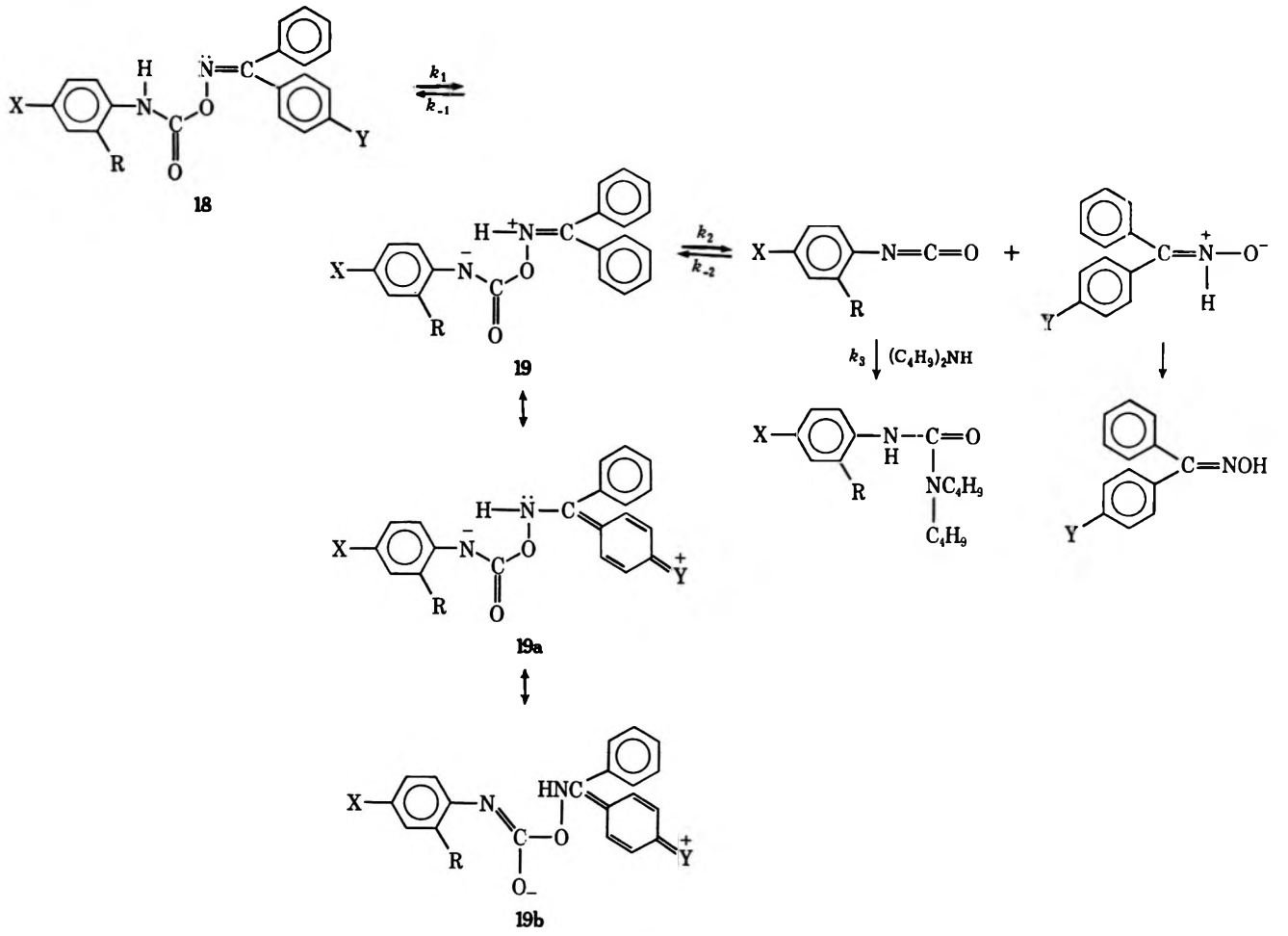
From the positive value of ρ_x, the implication may be drawn that proton transfer in the rate-determining transition state is more important than C–O bond cleavage. If these processes are formally separated, then the scheme shown in Chart IV results. The generalized compound **18** may intramolecularly transfer its carbamate proton, producing the zwitterion **19**. If **19** has a finite lifetime, then the positive center may enter into resonance with the substituent Y. Structure **19a** is one canonical form of such an interaction. One might expect that if the lifetime of **19** is sufficient to obtain σ^+ correlation at position Y then the effect of substituent X should be correlated by σ^-. The center of negative charge in **19**, however, is cross-conjugated and stabilization in the manner of structure **19b** is possible and may be energetically preferable to extended overlap with X in view of the resulting loss in rotational freedom of the aromatic nucleus. Under conditions where the lifetime of **19** is very short or nonexistent, the transformation becomes concerted and the involvement of substituent Y takes the form of inductive effects only and correlation with σ would be observed.

For the overall process to follow first-order kinetics, k_3 must be greater than either k_2 or k_1. The high reactivity of dibutylamine for isocyanates easily satisfies this requirement. The ratio of k_1 to k_2 will then determine whether σ or σ^+ best correlates the effect of substituent Y. When k_2 is smaller than k_1, as appears to be the case for R = H, **19** may be sufficiently long-lived to be resonance stabilized. When k_2 is increased so that it becomes larger than k_1, as due to the steric interaction when R = CH_3, then **19** does not intervene as an intermediate in the reaction and correlation with σ is observed.

The absolute value of ρ_y is quite small for a reaction which follows σ^+. This may be due to the orthogonality of the azomethine lone pair and the π-electron system of the benzophenone oxime moiety which obviates direct resonance interaction with Y. Only after the azomethine double bond electrons begin to effect charge delocalization can the ring electrons become involved. In effect, then, Y does not stabilize the primary positive charge but only the charge induced at the azomethine carbon atom. Thus, while σ^+ correlation is observed, the magnitude of stabilization is much lower than, for example, that found[15] for substituted benzylic cations, and the value of ρ is correspondingly small.

(15) N. C. Deno, J. J. Jaruzelski, and A. Schriesheim, *J. Amer. Chem. Soc.*, **77**, 3044 (1955).

CHART IV



The small value of ρ thus argues against an alternative mechanism to that presented in Chart IV wherein proton transfer is to the azomethine double bond electrons. Such an alternative is also unlikely in that it would lead most reasonably to a product derived from a phenylarylnitrosomethane. Such products have not been detected in the reaction mixtures, whereas oximes have been isolated.

Conclusion

It appears that benzophenone oxime carbamates dissociate *via* a five-center intramolecular transition state to oximes and isocyanates. The pathway is supported by the kinetic order of the reaction, activation parameters, and the overall substituent effect. Depending upon the degree of steric crowding in the transition state, the decomposition may be synchronous. In the case of uncrowded molecules, a zwitterionic intermediate is detectable using Hammett equation correlations. The nature of the transition state is such that steric crowding may be introduced at a location far removed from the seat of positive charge. The net effect thus appears to be a steric effect on the electronic effect of substituents 11 bonds removed from the bulky substituent.

Registry No.—**1**, 25151-09-1; **2**, 34804-53-0; **3**, 34804-54-1; **4**, 34804-55-2; **5**, 34792-32-0; **6**, 34804-56-3; **7**, 34804-57-4; **8**, 34804-58-5; **9**, 34792-33-1; **10**, 34804-59-6; **11**, 34804-60-9; **12**, 34804-61-0; **13**, 34804-62-1; **14**, 34804-63-2; **15**, 34804-64-3; **16**, 34804-65-4; **17**, 34804-66-5; dibutylamine, 111-92-2.

Kinetically Controlled Protonation of the Enol from Deoxypicropodophyllin

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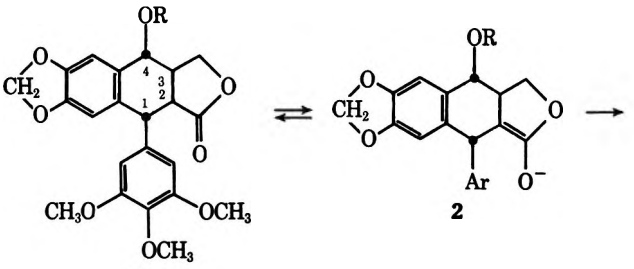
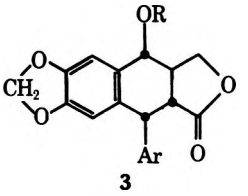
Received February 7, 1972

Under a variety of conditions, kinetically controlled protonations of the enolate or enol common to the epimers, deoxypodophyllotoxin and deoxypicropodophyllin, gave mixtures of the two compounds. In one series of experiments, the enolate was prepared by removing a proton with triphenylmethylsodium. In a second series, the enol was formed by decarboxylating 2-carboxydeoxypicropodophyllin. Conversion to the thermodynamically unstable deoxypodophyllotoxin ranged from 13 to 43% and so fell short of reaching the higher conversions anticipated on the basis of postulated transition states and *a priori* arguments. Possible explanations are advanced.

An earlier total synthesis of the anticancer lignan podophyllotoxin (**3**, R = H) calls for enolate formation from a picropodophyllin derivative (**1**, R = tetrahydropyranyl), followed by rate-controlled protonation



1 ⇌ **2** →



3

of the enolate **2**.[1] The resulting separable mixture of epimers **1** and **3**, although much richer in the thermodynamically unstable podophyllotoxin compound than the equilibrium mixture,[2] still contained more of the thermodynamically preferred picropodophyllin than we had anticipated. The present investigation examined this kind of uphill epimerization with the aim in mind of improving the yield. However, using the closely related enolate **5** from deoxypicropodophyllin (**6**) as substrate, we found under a variety of protonation conditions that the process consistently falls short of giving deoxypodophyllotoxin (**4**) in the proportions expected.[1]

Results

In the work described here, enolate **5** was generated by removing the proton from the 2 position of deoxypicropodophyllin (**6**) or deoxypodophyllotoxin (**4**). Also, the corresponding enol[3] was formed by decarboxylating 2-carboxydeoxypicropodophyllin (**7**).[4] The necessary starting materials were derived from deoxypodophyllotoxin (**4**), which in turn was available by catalytic hydrogenolysis of the podophyllotoxin 4-hydroxy group. Deoxypicropodophyllin (**6**) was prepared by epimerizing deoxypodophyllotoxin under mild basic catalysis[5] while 2-carboxydeoxypicropodophyllin (**7**) was prepared by carbonating enolate **5**.

In one series of experiments, titrating tetrahydrofuran solutions of deoxypodophyllotoxin (**4**) or deoxypicropodophyllin (**6**) with triphenylmethylsodium also in tetrahydrofuran gave the sodium enolate **5**. Introducing a proton source cleanly furnished mixtures of **4** and **6**, which were analyzed by an isotope dilution procedure with the help of deoxypodophyllotoxin (**4**) and deoxypicropodophyllin (**6**) carrying carbon-14 in their 4′-methoxy group. Table I summarizes the yields of deoxypodophyllotoxin with various proton donors. Comparing the results from replicate runs (A-1, B-1, and C-1) showed that the reproducibility was satisfactory, and allowed us to accept the outcome of single runs with more confidence. Our concern about incomplete conversion of substrates to enolate before protonation was allayed when starting with either deoxypicropodophyllin or deoxypodophyllotoxin was found to give the same results (expt A-1 and C-1). Adding enolate to protonating agent or vice versa makes little difference in yields (expt C-1 and C-2). At least with concentrated sulfuric acid, whether the solvent is tetrahydrofuran (A-3) or diethyl ether (E-1) has little effect; the same is true when the enolate is in solution or is present as a suspension.

Sterically hindered protonating agents such as 2,6-di-*tert*-butylphenol (expt B-3) and 2,4,6-trimethylpyridinium (collidinium) hydrochloride (expt D-1) failed to raise the yield of deoxypodophyllotoxin. In this connection, applying the procedure in expt D-3 showed that the sodium 2,6-di-*tert*-butylphenoxide–2,6-di-*tert*-butylphenol system epimerizes deoxypodophyllotoxin to an extent of about 8% in a period as short as 30 sec, a result that was also demonstrated qualitatively in a separate experiment. Experiment C-3 showed that, when a suspension of collidinium hydrochloride in tetrahydrofuran is added to the enolate, the product mixture consists largely of deoxypicropodophyllin and, in fact, probably falls close to the equilibrium mixture.[6] That this result may be a consequence

(1) W. J. Gensler and C. D. Gatsonis, *J. Org. Chem.*, **31**, 4004 (1966).

(2) W. J. Gensler and C. D. Gatsonis, *ibid.*, **31**, 3224 (1966).

(3) *Cf.* Jack Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 303, especially the contributions of Pederson and of Westheimer. A good review is given also by H. H. Wassermann in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 351.

(4) W. J. Gensler, J. F. X. Judge, and M. V. Leeding, *J. Org. Chem.*, **37**, 1062 (1972).

(5) Acid-catalyzed epimerization is not effective. Deoxypodophyllotoxin in methanol containing some concentrated sulfuric acid does undergo change to other compounds (see Experimental Section), but these do not include deoxypicropodophyllin.

(6) By comparison with the very similar picropodophyllin–podophyllotoxin system,[2] we assume that the equilibrium mixture will contain deoxypicropodophyllin to an extent of *ca.* 97%. Space-filling models (Courtauld) show that the 4-hydroxy group in podophyllotoxin (**3**, R = H) has plenty of room, and that the same is true in the several possible conformations for the more flexible picropodophyllin (**1**, R = H). Replacing the 4-hydroxy group with hydrogen should therefore not effect the equilibrium point substantially. Qualitatively, it has been recognized for some time that deoxypodophyllotoxin can be epimerized to deoxypicropodophyllin in high yield.

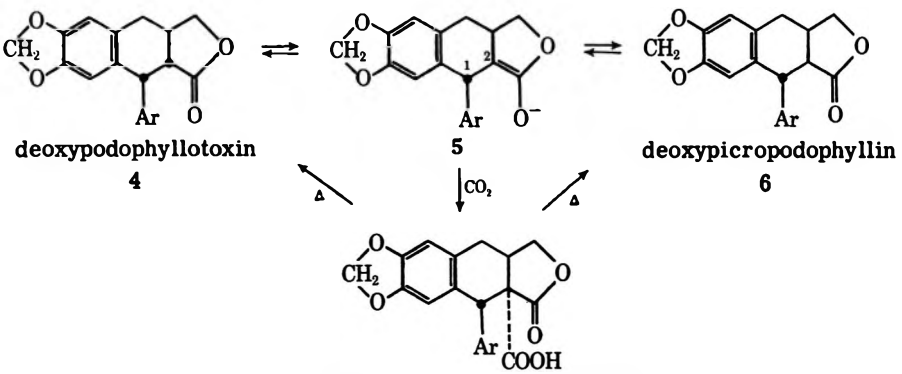


TABLE I

DEOXYPODOPHYLLOTOXIN (4) AND DEOXYPICROPODOPHYLLIN (6) FROM THE PROTONATION OF THEIR COMMON SODIUM ENOLATE (5)

Expt[a]		Protonating agent (amount)	Yield of deoxypodophyllotoxin,[b] %
A[c]	1	Acetic acid (20 ml)	40
	2	Trifluoroacetic acid (20 ml)	39
	3	Concentrated sulfuric acid (2 ml in 50 ml of tetrahydrofuran)	40
B[c]	1	Acetic acid (20 ml)	43
	2	Aqueous sulfuric acid (50 ml of 0.25 *N*)	17
	3	2,6-Di-*tert*-butylphenol (20 g of solid)[d,e]	22[d,e]
C[f]	1	Acetic acid (20 ml)	41
	2	Acetic acid (20 ml)[d]	42[d]
	3	Collidinium hydrochloride (10 g with 80 ml of tetrahydrofuran)[g]	3[g]
D[h]	1	Collidinium hydrochloride[i] with 50 ml of tetrahydrofuran	33[i] (35)[j]
	2	Collidinium hydrochloride plus ^{14}C deoxypodophyllotoxin with 50 ml of tetrahydrofuran[i,j]	*j*
	3	2,6-Di-*tert*-butylphenol (20 g) plus ^{14}C deoxypodophyllotoxin[d,k]	22 (24)[k]
E[l]	1	Concentrated sulfuric acid (1 ml in 20 ml of ether)[l]	38

[a] The capital letter designates a single batch of enolate solution, different portions of which were used as indicated. [b] The yield figure depends on the measured amounts of *both* deoxypodophyllotoxin (5) and deoxypicropodophyllin (7). [c] Enolate was prepared from 2.0 g of deoxypicropodophyllin in 250 ml of tetrahydrofuran. [d] The protonating agent was added to the enolate solution instead of vice versa. [e] To minimize equilibration due to unnecessarily prolonged exposure to the sodium 2,6-di-*tert*-butylphenoxide, aqueous sulfuric acid (50 ml of 0.25 *N*) was added 0.5 min after the phenol protonating agent had been introduced. [f] Enolate was prepared from 1.4 g of deoxypodophyllotoxin in 180 ml of tetrahydrofuran. [g] The collidinium hydrochloride was introduced as a suspension. With the solubility at room temperature determined to be approximately 0.002 *M*, calculation showed that the hydrochloride in solution and thus available for proton delivery corresponded to no more than *ca.* 10% of the initial enolate. Actually, the red color from the small excess of triphenylmethylsodium faded only slowly after mixing the hydrochloride suspension and the enolate solution. [h] Enolate was generated from 1.92 g of deoxypicropodophyllin in 150–200 ml of tetrahydrofuran. [i] The enolate solution was added slowly by drops over a 0.5-hr period to the vigorously stirred suspension of hydrochloride, which had been prepared before by bubbling anhydrous hydrogen chloride into a solution of collidine (0.03 mol) in 50 ml of tetrahydrofuran until the mixture contained approximately 0.02 mol of collidinium hydrochloride and 0.01 mol of collidine. [j] In expt D-2, the radioactivity originally introduced with the protonating agent in the form of labeled deoxypodophyllotoxin (23.53 mg at 28.9 nCi/mg) was recovered as labeled deoxypodophyllotoxin (2.64 nCi/mg) and deoxypicropodophyllin (0.100 nCi/mg). No additional amounts of labeled materials were added for the isotope dilution procedure. From the observed specific activities together with the assay results of experiment D-1, it can be shown that about 7% of the protonation deoxypodophyllotoxin isomerized to deoxypicropodophyllin *after* protonation. Accordingly, the 33% yield observed in this conversion of enolate to deoxypodophyllotoxin should be corrected to 35%. [k] To minimize equilibration due to contact with sodium 2,5-di-*tert*-butylphenoxide, glacial acetic acid was added 0.5 min after the phenol protonating agent had been introduced. Other than the labeled deoxypodophyllotoxin (39.42 mg at 28.9 nCi/mg) added together with the phenol, no additional radioactivity was involved in this experiment. The percentage of protonation deoxypodophyllotoxin recorded in the table is based on the measured activities of recovered deoxypodophyllotoxin (6.60 nCi/mg) and deoxypicropodophyllin (0.222 nCi/mg) as well as on the total amount of enolate used in experiment D-3. The last quantity was obtained by taking the difference between the weight of starting material originally used for enolate formation in the D series[h] and the sum of the weights of protonation deoxypodophyllotoxin and deoxypicropodophyllin recovered in expt D-1 and D-2 as determined by the standard isotope dilution assays. A further result emerging from the data is that 8.5% of the labeled deoxypodophyllotoxin added with the protonating agent is isomerized to deoxypicropodophyllin, so that the apparent 22% protonation conversion to deoxypodophyllotoxin should be corrected to 24%. [l] Enolate was generated from deoxypodophyllotoxin (0.504 mg) in 175 ml of ether by titrating with ethereal triphenylmethylsodium: C. R. Renfrew and C. F. Hauser, "Organic Syntheses," Collect. Vol II, Wiley, New York, N. Y., 1943, p 607; C. R. Hauser and B. E. Hudson, Jr., *Org. React.*, 1, 286 (1942). The ethereal sulfuric acid was added in a single portion to the vigorously stirred, heterogeneous enolate mixture.

of the slow dissolution of solid hydrochloride permitting only a gradual protonation and so providing time for equilibration between the slowly disappearing enolate and its two protonated forms is supported by expt D-1. Here, instead of adding the hydrochloride suspension to the enolate, the enolate was added slowly and with vigorous stirring to the suspension, a simple change that raised the yield of deoxypodophyllotoxin from 3% to over 30%. Where enough collidinium hydrochloride is given a chance to dissolve and always to be available in excess for protonating the enolate, the desired irreversible proton transfer from hydrochloride

to enolate competes successfully with the undesired reversible proton transfer from either **4** or **6** to enolate **5**, so that the complication of equilibration is minimized. Even with this technique, equilibration resulting in a net conversion of deoxypodophyllotoxin to deoxypicropodophyllin is not wholly blocked (*cf.* expt D-1 and D-2).

In the decarboxylation experiments using 2-carboxypicropodophyllin (**7**) as starting material, with the exception of equilibration at higher temperatures, the results are not far different from the direct enolate protonation experiments. In the decarboxylation runs, however, polarimetry instead of isotope dilution was relied on for product analysis. Table II shows that, in the absence of solvent, replicate experiments at 159 and at 170° give satisfactory reproducibility. The pair of results at 199° prove that the presence of added thermodynamically unstable deoxypodophyllotoxin (**4**) affects neither the deoxypodophyllotoxin initially present nor that formed. Also, separate experiments showed that deoxypodophyllotoxin is stable at 200° even in the presence of decarboxylating malonic acid. Temperatures higher than 200° lead to a net conversion of deoxypodophyllotoxin to deoxypicropodophyllin, and so are not applicable for the present purpose.

TABLE II

DECARBOXYLATION OF 2-CARBOXYDEOXYPICROPODOPHYLLIN (**7**) IN THE ABSENCE OF SOLVENT

Temp, °C	Time, min	Yield of deoxypodophyllotoxin, %
159	25[a]	27
159	25[a]	30
159	25[a]	36
159	25[a]	34
170	25	35
170	25	33
170	25	32
199	15[b]	30
199	15[b]	28[c]
210	10	22[d]
250	5	9[d]
300	5	4[e]

[a] Bubbling was observed after 5 min when the sample began to melt, and continued for another 10 min. [b] The solid melted with bubbling after 2 min; bubbling continued thereafter for another 5 min. [c] The decarboxylation mixture here consisted of 2-carboxydeoxypicropodophyllin (**7**) (6.890 mg) plus deoxypodophyllotoxin (2.050 mg). The measured composition of the mixture after decarboxylation indicated 46% deoxypodophyllotoxin. Calculation assuming the originally added deoxypodophyllotoxin to persist unchanged shows that 28% of the 2-carboxydeoxypicropodophyllin goes to deoxypodophyllotoxin. This value is close to the 30% obtained in the preceding companion run in which no deoxypodophyllotoxin had been present initially. [d] This figure should be taken as a minimum value, since epimerization of deoxypodophyllotoxin to deoxypicropodophyllin is probably occurring (see text). [e] This value reflects an equilibrium more than a kinetic result (see text).

When decarboxylations are performed with diglyme as solvent (Table III) at temperatures ranging from 90 to 160°, the proportions of deoxypodophyllotoxin vary but little. With tetraglyme as solvent at 95–210° the yields are somewhat lower, but again the variation is small. In the tetraglyme run at 200°, we found that mixing deoxypodophyllotoxin with the starting 2-carboxydeoxypicropodophyllin has no effect on the results. The procedure in the 160° run in diglyme and also in the 210° run in tetraglyme attempted to minimize the time required to bring the sample to the indicated temperatures. However, as the yields show, no difference was detected. The bottom part of Table III records the results of decarboxylation experiments using a variety of solvents. Here, in preliminary pilot experiments, the effect of heating deoxypodophyllotoxin or deoxypicropodophyllin in these solvents with or without decarboxylating malonic acid at various temperatures was found to be minimal. The yields in Table III show clearly that the nature of the solvent has only a secondary

TABLE III

DECARBOXYLATION OF CARBOXYDEOXYPICROPODOPHYLLIN (**7**) IN SOLUTION

Solvent	Temp, °C	Time, min	Yield of deoxypodophyllotoxin,[a] %
Diglyme	90	30	32
Diglyme	110	30	31
Diglyme	154	10	31
Diglyme	155	10	34
Diglyme	155	4[b]	34[b]
Diglyme	160	2[c]	29[c]
Tetraglyme	95	30	26
Tetraglyme	160	10	22
Tetraglyme	200	4	22
Tetraglyme	200	4	25[d]
Tetraglyme	210	2[c]	22[c,e]
Collidine	150	15	31
Diphenyl ether	190	5	25
Tetralin	190	5	23
Ethylene glycol	190	5	26
Acetophenone	190	5	21
Hexamethyl phosphoramide	190	5	29[e]
Dimethyl sulfoxide[f]	190	5	24[e]
Methyl benzoate[f]	190	5	13

[a] Repeat exposures of the decarboxylation mixtures to the conditions specified did not change the observed rotation, so that decarboxylations could be taken as complete. [b] That the reaction was actually complete even after as short a time as 4 min was shown by the constancy of rotation on further heating. [c] This experiment was performed to see whether the *rate* of temperature increase affected the composition of the decarboxylated product mixture. The sample of 2-carboxydeoxypicropodophyllin (**7**) was dissolved in about 15% of the eventual total volume of solvent. The stirred solution was plunged into the hot oil bath at the same time that the rest of the solvent, preheated to the temperature of the bath, was added. Thin layer chromatographic check showed that no starting material remained after the 2-min reaction period, and that only the expected products were present. The yield of deoxypodophyllotoxin in this experiment is seen to be about the same as from all the others in which the same solvent was used. [d] The starting decarboxylation mixture contained not only 2-carboxydeoxypicropodophyllin (5.863 mg) but also deoxypodophyllotoxin (2.240 mg). The mixture after decarboxylation showed a total content of 47% of deoxypodophyllotoxin. On the assumption that the initially added deoxypodophyllotoxin is not affected in any way, the yield of deoxypodophyllotoxin from the decarboxylation process itself may be calculated as 25%, a value about the same as that obtained in the absence of added deoxypodophyllotoxin. [e] No thin layer chromatography check was made here. [f] Although, as soon as the mixture became hot, it was homogeneous, the starting mixture at room temperature contained undissolved 2-carboxydeoxypicropodophyllin. The solution of products, however, remained in one phase even after returning to room temperature.

effect on the proportion of decarboxylation products formed.

Table IV summarizes the results of decarboxylations

TABLE IV

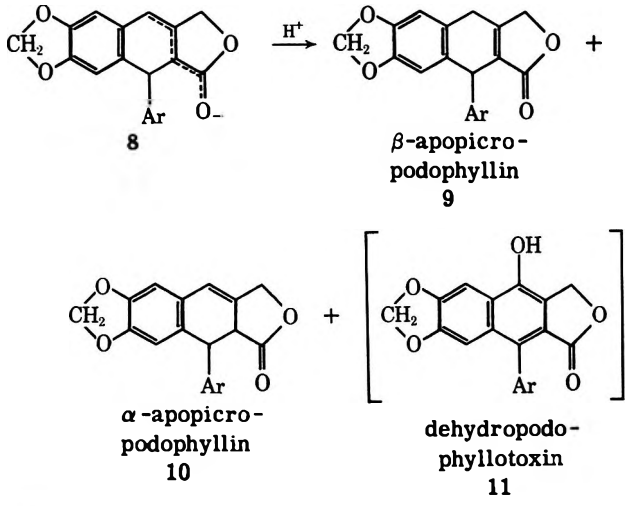
DECARBOXYLATION OF 2-CARBOXYDEOXYPICROPODOPHYLLIN (7) IN THE PRESENCE OF PROTON DONORS[a]

Solvent	Proton donor	Yield of deoxypodophyllotoxin, %
	None	27
	Phenol	27
Tetraglyme	Trichlorophenol	27
	Tribromophenol	27
	2,6-Di-*tert*-butyl-4-methylphenol	27
	None	25
	Pivalic acid	22
Diphenyl ether	Picric acid	25
	Trichlorophenol	24
	p-Toluenesulfonic acid	31

[a] All experiments were carried out over a period of 5 min at 190°.

in the presence of large excesses of various protonating agents with tetraglyme and diphenyl ether as solvents. Again, the resulting proportions of products are remarkably alike even when the proton donors are as different as, for example, phenol in tetraglyme (27% yield of deoxypodophyllotoxin) and *p*-toluenesulfonic acid in diphenyl ether (31%).

As part of this investigation, a small series of protonation experiments was performed with the lithium enolate **8**, which was derived from different though closely related substrates, namely α- and β-apopicropodophyllin (**10** and **9**). With glacial acetic acid containing a little concentrated sulfuric acid as the proton source and with air rigorously excluded, the product was a mixture of β-apopicropodophyllin (**9**) and α-apopicropodophyllin (**10**) in the ratio of about 6:1. Although α-apopicropodophyllin (**10**) is unstable with respect to β-apopicropodophyllin (**9**),[7] until the point of equilibrium is known, the question of whether the product mixture is the result of kinetic or equilibrium control cannot be answered. In experiments carried out with only routine care taken to exclude air, substantial amounts of a dehydrogenation product, dehydropodophyllotoxin (**11**), were observed.



(7) A. Robertson and R. B. Waters, *J. Chem. Soc.*, 83 (1933). See also A. W. Schrecker and J. L. Hartwell, *J. Amer. Chem. Soc.*, **74**, 5676 (1952).

Discussion

Our earlier picture of the transition state for protonation had the proton donor positioned above or below the planar enolate portion of the substrate.[1] With this geometry, models suggested convincingly that it would be easier to find room for the donor on the side of the enolate plane *away* from the bulky, quasiaxially disposed 1-trimethoxyphenyl group than on the same side, cis to this group. Accordingly, kinetically controlled protonation was expected to give more deoxypodophyllotoxin than deoxypicropodophyllin. The facts have not borne out these *a priori* arguments. Thus, although the protonations gave deoxypodophyllotoxin in amounts considerably more than in the equilibrium mixture,[6] in no case did the proportions go as high as 1:1. Variation in conditions, *e.g.*, solvent, acid strength of the proton source as well as its type and bulk, reaction temperature, and substrate either as enol or enolate, had relatively minor effects. Generally falling in the 20–40% range, the yields of deoxypodophyllotoxin appear more noteworthy in their similarity than in their difference, and, in terms of kinetic activation parameters, they point to very small energy differences for formation of the two products. The lowest uncomplicated conversion to deoxypodophyllotoxin was 13% (decarboxylation of 2-carboxydeoxypicropodophyllin dissolved in methyl benzoate); the highest conversion was 43% (quenching the sodium enolate with acetic acid). This range corresponds to a difference in Gibbs energy of activation of 1.8–0.2 kcal/mol, with the transition state for the picropodophyllin configuration always at the lower energy level.

The data in Table III allow an estimate of the difference in Arrhenius energies of activation, $\Delta E_a = E_{a(\text{deoxypodo})} - E_{a(\text{deoxypicro})}$. In diglyme solvent at decarboxylation temperatures ranging from 90 to 160°, the yields of deoxypodophyllotoxin average 32 ± 1% (uncertainty given as the mean of deviations from the mean); in tetraglyme solvent at temperatures of 95–210°, the yields, although lower (23 ± 2%), again show the same lack of variation. No trend is obvious in either series. Using these numbers and assigning an arbitrary value of +2 kcal/mol for the difference ΔE_a, in Arrhenius energies, the observed 32% yield of deoxypodophyllotoxin in diglyme at 90° would be expected to increase to 42% at 160° (*cf.* Table V). If, oppositely, ΔE_a is taken as −2 kcal/mol, the 32% yield would have to drop to 23%. In the tetraglyme series, with the same assigned values for ΔE_a, the 23% yield at 95° would have to change to either 36 or 14% at 210°. Since the uncertainty in the experimental values is in the order of 1–2%, these predicted changes of about 10% should be easily detectable, but, as reference to Table III will show, they are not. Accordingly, ΔE_a must be quite small, well within the arbitrary limits of ±2 kcal/mol and possibly close to zero.

In seeking to rationalize these results, we were led to reexamine the basis for choosing our model of the protonation transition state as we did. It developed that the earlier views are far from unanimous in their picture

TABLE V

CALCULATED EFFECT OF TEMPERATURE ON YIELD OF DEOXYPODOPHYLLOTOXIN IN THE DECARBOXYLATION OF 2-CARBOXYDEOXYPICROPODOPHYLLIN

Solvent	ΔE_a[a]	Temp, °C	Calcd yield of deoxypodophyllotoxin, %
Diglyme	+2 kcal/mol	90	[32 kcal/mol][b]
		160	42
	−2	90	[32][b]
		160	23
Tetraglyme	+2	95	[23][b]
		210	36
	−2	95	[23][b]
		210	14

[a] Arbitrarily assumed difference, ΔE_a, in Arrhenius activation energies for the processes leading, respectively, to deoxypodophyllotoxin and deoxypicropodophyllin. [b] Observed value.

of the transition state for protonization or enolization,[8] and that a single generalization for systems involving different enolates, protonating agents, solvents, etc., is not warranted. If in our case, the transition state for development of the picropodophyllin configuration were in fact somewhat removed from the planar starting material, or in other words had moved along the reaction coordinate with development of appreciable off-planar sp^3 geometry of the product, the steric influence of the bulky trimethoxyphenyl group would be weakened,[1] and with it so would the essence of our original argument. The intramolecular energies of the two epimeric products could then play a more determining role in the relative rates of protonation than the intermolecular steric interactions, and, as we actually observed, greater proportions of the thermodynamically more stable picropodophyllin form would emerge.[9] Interestingly, the same kind of interpretation could serve to explain formation of only one stereoisomer, 2-carboxydeoxypicropodophyllin, in the carbonation of enolate **5** as well as formation of only the corresponding ester in the reaction of the same enolate **5** with methyl chloroformate.[4]

From the preparative point of view, in the synthesis of physiologically active though thermodynamically unstable podophyllotoxin compounds from the corresponding picropodophyllin stereoisomers, we have as yet not found a way to improve the key epimerization step. The process, while remaining quite practical and furnishing a quantitative *corrected* yield, still gives only a modest conversion. From the theoretical point of view, the need for caution is reinforced in assuming a near-planar transition state for enolizations or ketonizations, especially where steric effects are appreciable.

(8) *Cf.*, *inter alia*, H. E. Zimmerman in P. de Mayo, "Molecular Rearrangements," Part 1, Interscience, New York, N. Y., 1963, on the "Stereochemistry of Carbanion and Related Reactions," p 352; also F. Johnson, *Chem. Rev.*, **68**, 398 (1968). An overview is given by F. G. Bordwell and K. C. Yee, *J. Amer. Chem. Soc.*, **92**, 5939 (1970). Also see G. S. Hammond, *ibid.*, **77**, 334 (1955); C. G. Swain and A. S. Rosenberg, *ibid.*, **83**, 2154 (1961); C. G. Swain and E. R. Thornton, *ibid.*, **84**, 817 (1962); S. K. Malhotra and H. J. Ringold, *ibid.*, **85**, 1538 (1962); **86**, 1997 (1964); H. Schechter, M. J. Collins, R. Dessy, Y. Okuzumi, and A. Chen, *ibid.*, **84**, 2905 (1962); J. Hine, J. G. Houston, J. H. Jensen, and J. Mulders, *ibid.*, **87**, 5050 (1965); J. Fishman, *J. Org. Chem.*, **31**, 520 (1966).

(9) Johnson[8] prefers another interpretation, namely, that enolate **5** is itself not planar, so that the difference in intermolecular steric hindrance becomes of secondary importance no matter where the transition state is found.

Experimental Section

General.—The general practice described before[1,2,4] was followed here.

Absence of Acid-Catalyzed Epimerization of Deoxypodophyllotoxin (4) to Deoxypicropodophyllin (6).—A solution of deoxypodophyllotoxin[4] (0.2 g) and concentrated sulfuric acid (0.7 ml) in 10 ml of anhydrous methanol was allowed to stand at room temperature for 1 day. Thin layer chromatography (ether–methylene chloride, 6:1) showed a spot at R_f 0.73, corresponding to deoxypodophyllotoxin, plus spots at R_f 0.23 and 0.0. After the solution had been allowed to stand for another day, the same three spots persisted, with the R_f 0.23 spot now dominant. No spot developed at R_f 0.52, where deoxypicropodophyllin appeared in a control run on the same plate. The R_f 0.0 material might be the opened deoxypodophyllic acid, while the R_f 0.23 material is probably methyl deoxypodophyllate.[10]

Labeled Deoxypodophyllotoxin and Deoxypicropodophyllin.—The 4-hydroxy group of podophyllotoxin carrying ^{14}C in its center methoxy group[2] was removed by hydrogenolysis essentially according to the hydrogen-bubbling method reported before.[4] The hydrogenolysis product, diluted with unlabeled deoxypodophyllotoxin, was purified and the colorless needles were finally dried at 100° (0.1 min) over phosphorus pentoxide. This product melted at 165–166° either with or without admixture of authentic deoxypodophyllotoxin, showed a single spot on thin layer chromatography (R_f 0.75 with ether–methylene chloride, 6:1), and was radioactive to the extent of 28.9 nCi/mg.

Labeled deoxypodophyllotoxin was epimerized to labeled deoxypicropodophyllin essentially according to the directions for the unlabeled material.[4] After a 2-day drying period *in vacuo* at 100° over phosphorus pentoxide, the recrystallized white needles (84%) showed mp 170.5–171.5°, gave a single spot on thin layer chromatography (R_f 0.54 with the same solvent as above), and contained 28.2 nCi/mg of ^{14}C.

Enolate Formation, Protonation, and Analysis.—When a red solution of triphenylmethylsodium in tetrahydrofuran[1] was added dropwise to a stirred solution of deoxypodophyllotoxin (or deoxypicropodophyllin) in the same solvent, the red color is discharged quickly, so that the process may be described as a titration. Also, since the time for disappearance of the red color from 1 drop of reagent after a molar proportion has been introduced goes up abruptly, development of a "permanent" red can be taken as a rough end point. The fact that the volume of standardized reagent added in order to reach this end point routinely compared well with the molar amount required bolsters our assumption that the substrate is completely converted to enolate. In any case, a small excess of reagent generally was added past the end point to ensure conversion. With tetrahydrofuran a solvent, the reagent, substrates, and enolate all gave homogeneous solutions. In the few experiments in which ether was the solvent, we noted that homogeneous triphenylmethylsodium in ether reacted rapidly with homogeneous deoxypodophyllotoxin in ether to give a suspension. The red color was discharged relatively slowly when deoxypicropodophyllin, which formed a suspension in ether, was taken as substrate.

To provide more significant comparisons, it was important to be able to protonate portions of the very same batch of enolate with different protonating agents, and for this purpose a manifold gently sloped downward and provided with several stopcocks was sealed to the bottom of the titration flask. Vessels containing carefully weighed quantities of protonating agent were provided with a magnetic stirring bar and were fitted to the stopcocks through ground glass joints. Where needed, pure solvent that had been distilled over lithium aluminum hydride and condensed directly into the still empty titration flask was distributed through the manifold to the several protonation flasks, where homogeneous solutions resulted. Deoxypodophyllotoxin or deoxypicropodophyllin was then added to the titration flask, more solvent was condensed in as desired, and the titration with triphenylmethylsodium was performed as described above. Portions of the enolate solution were added rapidly through the manifold to each of the well-stirred proton sources, which were always in excess. The temperature was held variously at 0–30°. Where desired, the last portion of enolate solution was retained in the titration flask, so that a protonating agent could be added to the enolate instead of vice versa.

(10) *Cf.* J. Renz, M. Kuhn, and A. von Wartburg, *Justus Liebigs Ann. Chem.*, **681**, 207 (1965).

After enolate and proton source were combined, standard chloroform solutions of radioactive deoxypodophyllotoxin and deoxypicropodophyllin were added, and the mixture was stirred further. Water, sometimes with acid, was added, and the aqueous system was concentrated under reduced pressure at temperatures no higher than 50°. The concentrated mixture, containing much precipitate, was extracted with three 60-ml portions of chloroform, and the combined extracts were washed twice with water before drying with sodium sulfate and stripping volatiles off. In some runs, the chloroform extract was also shaken with 3% aqueous bicarbonate. Thin layer chromatography showed that the protonation was clean cut, with the only products being the two expected isomers. Also, control experiments showed that deoxypodophyllotoxin did not epimerize at any stage between protonation and isolation of pure products.

The separation of deoxypodophyllotoxin and deoxypicropodophyllin was accomplished by column chromatography and crystallization. The mixture in 5 ml of chloroform was placed on a 20 × 2.6 cm column of neutral alumina. Elution with 200 ml of chloroform–ether (4:1), 100 ml of ether, ether–methanol (49:1), and finally 250 ml of ether–methanol (1:1) gave various fractions. As shown by thin layer chromatographic monitoring, the 49:1 ether–methanol contained the highest concentration of deoxypodophyllotoxin, while the 1:1 ether–methanol removed most of the deoxypicropodophyllin. The deoxypodophyllotoxin-rich fractions were freed of solvent and then recrystallized from methanol; the deoxypicropodophyllin-rich fractions were recrystallized from aqueous ethanol. In a qualitative though representative run, quenching the enolate with 2,4,6-trimethylbenzoic acid gave deoxypodophyllotoxin (*ca.* 40%), which after two crystallizations showed mp 165–167° and $[\alpha]_D$ −115° (*c* 1, $CHCl_3$) as well as deoxypicropodophyllin, which after two crystallizations showed mp 170–171° and $[\alpha]_D$ +48° (*c* 0.5, C_2H_5OH). In the quantitative runs, as soon as the thin layer chromatography results together with constancy in melting point indicated homogeneity, a sample was retained, which, together with a sample from one additional crystallization, was submitted for radioactivity assay.

To exemplify the results obtained, a sample set of data from an experiment in which the starting substrate was deoxypicropodophyllin and the protonating agent was acetic acid is given here as follows. In the isotope dilution procedure, the weight of radioactive materials introduced was 40.04 mg of deoxypodophyllotoxin (28.9 nCi/mg) plus 33.968 mg of deoxypicropodophyllin (28.2 nCi/mg). The homogeneous protonation products from consecutive crystallizations showed the following activities: deoxypodophyllotoxin, 4.821 and 4.803 nCi/mg[11] (mean, 4.812); deoxypicropodophyllin, 2.944 and 2.963 nCi/mg (mean 2.954). Accordingly, the deoxypodophyllotoxin protonation product weighed [(28.9 − 4.81) = 4.81] × 40.04 = 200 mg, and the deoxypicropodophyllin protonation product correspondingly weighed 290 mg. Thus acetic acid as a proton donor gave rise to a mixture containing 41% of the less stable deoxypodophyllotoxin. In this particular experiment, the same batch of enolate was used in three portions with different protonating agents, each product mixture being analyzed separately. The sum of the weights of the protonation products came to 1.421 g, so that the total recovery checked well with the original weight of deoxypicropodophyllin (1.417 g) taken as starting substrate. The same kind of recovery was noted in other runs.

Table I summarizes the results from the various experiments.

Epimerization of Deoxypodophyllotoxin (4) to Deoxypicropodophyllin (6) with Sodium 2,6-Di-*tert*-butylphenoxide.—With careful exclusion of moisture, 100 mg (0.25 mmol) of deoxypodophyllotoxin was added to a mixture of 5 g (24 mmol) of 2,6-di-*tert*-butylphenol plus 2.5 ml (0.27 mmol) of 0.11 *N* triphenylmethylsodium in tetrahydrofuran in 10–15 ml of the same solvent. Small aliquots of the faintly yellow solution were removed at 1-min intervals, quenched with glacial acetic acid, and analyzed directly by thin layer chromatography (ether–CH_2Cl_2, 6:1). After 1 min, the initial single-spot deoxypodophyllotoxin showed a faint second spot whose R_f value corresponded to deoxypicropodophyllin; after 3 min the spot was more pronounced; and after 5 min the deoxypodo and deoxypicro spots were about the same in appearance.

Polarimetric Assay of Mixtures of Deoxypodophyllotoxin (4) and Deoxypicropodophyllin (6).—Optical rotation measurements of known mixtures of deoxypodophyllotoxin, with $[\alpha]_{589}^{20}$ −112° (*c* 1.0, $CHCl_3$), and deoxypicropodophyllin, with $[\alpha]_{589}^{20}$ +31° (c 1.0, $CHCl_3$), showed that the rotation is directly proportional to percentage composition. The determinations, made initially at the sodium line on a Faraday electro-optic effect polarimeter, were subsequently made more conveniently with a Cary recording spectropolarimeter. At 420 nm, deoxypodophyllotoxin shows $[\alpha]_{420}^{20}$ −280° (*c* 0.20, $CHCl_3$) and deoxypicropodophyllin shows $[\alpha]_{420}^{20}$ +100° (*c* 0.20, $CHCl_3$), so that at 420 nm the difference in specific rotations is more than double that at 589 nm. Also, the slopes of the ORD curves at 420 nm were still small. Just as at 589 nm, the rotation of mixtures at 420 nm varied linearly with composition. When decarboxylations were performed in a solvent, the same solvent was used in the rotation measurements as in the decarboxylations. Linearity for the rotation–composition relation was demonstrated with diglyme, tetraglyme, and collidine; linearity was assumed for the remaining solvents.

The uncertainty in specific rotation values attributable to uncertainty in the rotation readings was estimated to range over $[\alpha] = \pm 0.2°$, and so was negligible. A series of four replications of decarboxylation experiments at 159°, by giving yields of deoxypodophyllotoxin varying from 27 to 36% (Table II), suggested that the decarboxylation results can be uncertain to an extent of up to 28% (maximum range of percentage yields divided by the mean) or, from a different viewpoint, up to 10% (mean deviation from the mean divided by the mean). Replicate experiments at 170° gave more reproducible results (Table II), with the same kind of uncertainties estimated at 10 and 3%, respectively.

Decarboxylation of 2-Carboxydeoxypicropodophyllin (7) in the Absence of Solvent.—A 4-in. test tube containing an accurately weighed sample of 2-carboxydeoxypicropodophyllin (8.116 mg) was evacuated and sealed. The glass had been cleaned by soaking it first in hot nitric–sulfuric acid and then in alkaline detergent. After repeated rinsings with distilled water, the tubes were dried at 110°. On placing the sealed tube in an oil bath at 158–160°, no change was seen for about 5 min. Thereafter, over the next 10 min, the material melted and bubbled. After a total heating time of 25 min, the tube was thoroughly cleaned and carefully opened, and the tan glassy contents were dissolved quantitatively in 3.65 ml of chloroform, *i.e.*, in a volume calculated on the basis of quantitative decarboxylation to furnish a solution containing 2 mg/ml. In this particular experiment, dilution was based on a calculated quantitative yield of 7.308 mg; the actual yield as determined by weight difference was 7.410 mg, and so was within 1.4% of the expected. A similar weight check in the other runs showed that the discrepancy between the actual and the calculated weight loss generally was no more than 1%. Thin layer chromatographic analysis of the chloroform solution (CCl_4–ether, 4:1) confirmed that the product consisted only of deoxypodophyllotoxin (4) and deoxypicropodophyllin (6). Polarimetric assay showed that the mixture contained 27% of deoxypodophyllotoxin.

Table II summarizes the results of a series of such decarboxylation experiments. The lowest temperature used was 159°; little decomposition was seen when 2-carboxydeoxypicropodophyllin in quantities greater than capillary samples was exposed to temperatures below 159° for periods of up to 0.5 hr.

A preliminary series of experiments was performed in order to eliminate the possibility that deoxypodophyllotoxin and deoxypicropodophyllin would interconvert after their formation during the heating period. As shown qualitatively by thin layer chromatography and quantitatively by polarimetric assay, deoxypodophyllotoxin alone is unchanged after heating for 35 min at 160° or for 15 min at 250°; deoxypicropodophyllin is similarly stable after heating for 15 min at 250°, or for 10 min at 300°. With the possible catalytic effect of the carboxy group in mind, several experiments were run on mixtures of deoxypodophyllotoxin as well as of deoxypicropodophyllin with about 15% by weight of malonic acid. Rough titration curves taken in 1:1 water–tetrahydrofuran showed that malonic acid (K_A *ca.* 14 × 10^{-5}) is a slightly stronger acid in a water system than the substrate, 2-carboxydeoxypicropodophyllin (K_A *ca.* 2.2 × 10^{-5}). Deoxypodophyllotoxin in the presence of malonic acid (or the

(11) In the counts serving as the basis for the specific activity values, differences between observed counts for two consecutively recrystallized samples generally came to less than 0.5%—only once as high as 1%—of the mean of the two counts. Accordingly, radioactivity purity as well as count reproducibility appeared satisfactory, and uncertainty entering from the radioactivity determinations could be neglected.

acetic acid derived from it), although stable for 35 min at 160° or 15 min at 200°, shows signs of epimerization (32%) to deoxypicropodophyllin after 15 min at 225°, and is almost completed epimerized (90%) after 15 min at 250°. After 10 min at 300°, deoxypodophyllotoxin, either alone or with malonic acid, epimerizes to an extent of *ca.* 93%. Deoxypicropodophyllin in the presence of malonic acid is unchanged after heating for 10 min at 300°.

Decarboxylation of 2-Carboxydeoxypicropodophyllin (7) in Solution.—To an accurately weighed sample (*ca.* 8 mg) of pure 2-carboxydeoxypicropodophyllin in a 4-in. Pyrex test tube was added a volume of distilled solvent calculated to provide a concentration of 2 mg/ml of decarboxylation product assuming complete reaction. The test tube was connected by rubber tubing to a small toy balloon, and the gas space was flushed thoroughly with argon. With the balloon flacid, the tube was dipped into a hot oil bath, and the homogeneous reaction mixture was stirred with the help of a tiny Teflon-covered magnetic bar for the desired time. The optical rotation of the solution at room temperature was measured without delay and without change of solvent. A routine check showed that no solvent was lost by evaporation in these manipulations. That the reaction had gone to completion was proved by returning the solution to the oil bath, repeating the heating procedure, and remeasuring the rotation. In all cases, the rotation remained constant to within 1%. Thereafter, slow removal of solvent by vacuum evaporation at 40° left a residue, which as shown by thin layer chromatography (CCl_4–ether, 4:1) consisted entirely of the expected deoxypodophyllotoxin (4) and deoxypicropodophyllin (6). Table III summarizes the results.

A test of the possibility that the acid group of 2-carboxydeoxypicropodophyllin might catalyze product interconversion was made by heating solutions of the products at various temperatures in the presence of malonic acid. The molar ratio of malonic acid to either product was at least 2:3. In no case under the conditions of the several decarboxylations was more than 4% conversion (generally 1–2%) of deoxypodophyllotoxin (4) to deoxypicropodophyllin (6) observed, nor more than 1% conversion of deoxypicropodophyllin to deoxypodophyllotoxin.

In the same kind of decarboxylation system, either with or without solvent, both the interval before the sample started to bubble and the period during which bubbles were released became shorter as the reaction temperature was raised. So long as the same temperature was used, these periods in experiments with different solvents, either with or without protonating agents present, varied only slightly.

Decarboxylation of 2-Carboxydeoxypicropodophyllin (7) in the Presence of Added Proton Donors.—Dilute, homogeneous solutions of 2-carboxydeoxypicropodophyllin in redistilled tetraglyme or in redistilled diphenyl ether containing a large excess of protonating agent (10 molar proportions) were heated essentially according to the procedure used with the other solution decarboxylations. The quantities of starting material and solvent were taken so that the final summed concentration of deoxypodophyllotoxin and deoxypicropodophyllin, on the basis of a quantitative decarboxylation, would be 2 mg/ml. The unchanged optical rotation observed on repeating the exposure of each mixture to the decarboxylation temperature, as well as the thin layer chromatographic evidence, was consistent with uncomplicated, complete decarboxylations. Also, separate experiments showed that the two decarboxylation products were stable under the conditions of decarboxylation, and that the presence of proton donors had no effect on the rotation–composition line. Table IV gives the results.

Protonation of the Enolate from α-Apopicropodophyllin (10) or β-Apopicropodophyllin (9).—The lithium enolate was prepared from 126 mg (0.32 mmol) of α-apopicropodophyllin[7,12] onto which 15 ml of tetrahydrofuran had been condensed directly from a distillation over lithium aluminum hydride. By liberal use of argon, special care was exerted throughout this experiment to eliminate air. A 0.176 *N* tetrahydrofuran solution of triphenylmethyllithium[4] (2.0 ml or 0.35 mmol) was introduced into the heterogeneous mixture by dropwise addition from a syringe through a serum cap. The red color from each drop of the reagent at first disappeared quite rapidly, but at the end required at least 5 min to fade. The enolate solution, which was now homogeneous, was taken up in a syringe and injected rapidly under the surface of a vigorously stirred mixture of glacial acetic acid (5.0 ml) containing a little concentrated sulfuric acid (*ca.* 0.8 mmol). The acetic acid had been deoxygenated previously by passage of a stream of argon. Thin layer chromatographic analysis of the reaction mixture (CCl_4–CH_3OH, 10:1) showed the presence of β-apopicropodophyllin (9) as a large spot and α-apopicropodophyllin (10) as a faint spot. No spot corresponding to dehydropodophyllotoxin (11) was detected. The ultraviolet absorption curve of the reaction mixture suitably diluted with acetic acid compared closely with the curve taken with a mixture of authentic α-apopicropodophyllin (14%) and β-apopicropodophyllin (86%). The absence of extraneous materials was further substantiated by noting that the ultraviolet absorption curves for the protonation mixture and for the synthetic mixture changed in a closely parallel way when each solution was treated with a drop of piperidine and kept at 55° for 5 hr in order to isomerize α-apopicropodophyllin to β-apopicropodophyllin.[7]

When a similar procedure was applied to 51.8 mg of β-apopicropodophyllin (9), the results were about the same, although here thin layer chromatography revealed α-apopicropodophyllin in the product mixture more as a bulge on the main β-apopicropodophyllin spot than as a discrete spot. The ultraviolet absorption curve compared closely with that of a mixture of 12% α-apopicropodophyllin and 88% β-apopicropodophyllin.

In another experiment starting with α-apopicropodophyllin (112 mg), evidently air was inadvertently admitted. Also, no sulfuric acid was present in the quenching acetic acid. The residue obtained by stripping volatile material under reduced pressures was separated into three fractions by preparative layer chromatography (CCl_4–CH_3OH, 10:1). The fastest moving band was identified by thin layer chromatography as a mixture of triphenylmethane and triphenylmethyl alcohol. The next band consisted of β-apopicropodophyllin (80 mg, 72%) as shown by ultraviolet, infrared, and thin layer chromatographic comparisons. The slowest moving band (16 mg, 14%) proved to be essentially all dehydropodophyllotoxin[13] (mp >250° dec) as shown by ultraviolet, infrared, and thin layer chromatographic comparisons.

To check the effect of oxygen, the lithium enolate was generated in tetrahydrofuran from 124 mg of α-apopicropodophyllin. Then, instead of quenching in acetic acid, the enolate solution was treated with a stream of tank oxygen for 0.5 hr. Preparative layer chromatography as above furnished 15 mg of β-apopicropodophyllin (9) as well as 36 mg of dehydropodophyllotoxin (11). Trace impurities detected in the dehydropodophyllotoxin were not identified.

Registry No.—**4**, 19186-35-7; **5**, 34825-26-8; **6**, 24150-39-8; **7**, 33369-69-6.

Acknowledgment.—We are grateful for the support of this work by the National Cancer Institute, United States Public Health Service, under grants CA2891 and CA10529. One of us (J. F. X. J.) was the recipient of a National Aeronautics and Space Administration Traineeship. We also wish to acknowledge with appreciation the gifts of podophyllotoxin and radioactive podophyllotoxin received through the courtesy of Albert von Wartburg and Emil Schreier of Sandoz Ltd., Basle, Switzerland.

(12) *Cf.* W. J. Gensler, Q. A. Ahmed, Z. Muljiani, and C. D. Gatsonis, *J. Amer. Chem. Soc.*, **93**, 2515 (1971).

(13) *Cf.* W. J. Gensler, F. Johnson, and A. D. B. Sloan, *ibid.*, **82**, 6074 (1960).

A Novel Synthetic Approach to the Eudesmane Class of Sesquiterpenes

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Received November 23, 1971

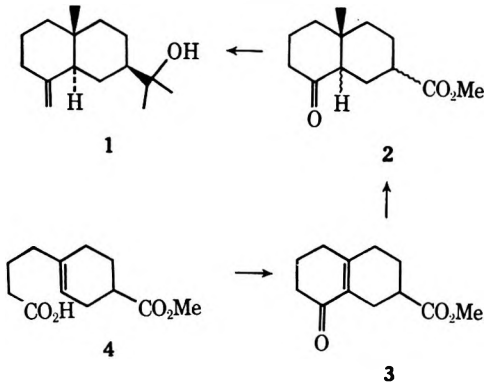
An efficient synthetic approach to the eudesmane class of sesquiterpenes is described. The key intermediate in the synthetic sequence is 7-carbomethoxy-$\Delta^{9,10}$-octal-1-one (**3**), which is prepared by an intramolecular acylation reaction. Addition of lithium dimethylcopper(I) to **3** produces a mixture of keto esters from which keto acid **14b** is readily obtained. This material has previously been converted to β-eudesmol.

Within the past two decades tremendous strides have been taken in the development of methods for the total synthesis of members of the decalin sesquiterpene class.[3] Indeed, the synthetic methodology currently available allows the synthesis of most compounds within this family of sesquiterpenes almost at will. Central to the preparation of the majority of these compounds has been the Robinson annelation reaction.[4] Although this is an extremely useful weapon in the arsenal available to the synthetic chemist, the yields for the sequence are often low and stereochemical complications arise when substituents are present on either the Michael donor or Michael acceptor. In connection with our interest in the development of general methods for the formation of carbocyclic ring systems[5] we have developed a synthetic approach to the eudesmane class of sesquiterpenes which is not dependent upon the traditional Robinson annelation sequence.[6,7]

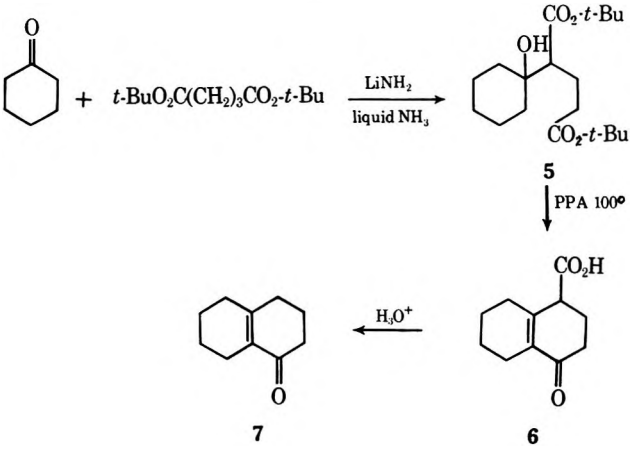
Our synthetic strategy, like that of other workers,[6c] centered on the development of an efficient synthesis of a keto ester of the type **2**. This compound is an extremely attractive synthetic goal because the ketone function at C-1 and ester function at C-7 allow epimerization at C-7 and C-9 and should permit the preparation of the stereoisomer required for conversion to β-eudesmol **1** (Scheme I). In contrast to other approaches to keto esters of the type **2**, we sought to prepare this key intermediate by the addition of lithium dimethylcopper(I)[8] to the unsaturated keto ester **3**. Although there are a number of possible routes to **3** from properly substituted naphthalene or tetralin derivatives, we chose to examine the intramolecular acylation of a cyclohexene derivative such as **4**. Compounds such as **4** are potentially available from the very useful, but seldom employed, Puterbaugh[9] extension of the Stobbe condensation.

In order to test the feasibility of this route, the model study outlined in Scheme II was carried out. The di-

SCHEME I



SCHEME II



tert-butyl glutarate adduct of cyclohexanone **5** was readily obtained by the addition of the lithium salt of di-*tert*-butyl glutarate to cyclohexanone in liquid ammonia. The ready acid-catalyzed conversion of *tert*-butyl esters to the free acids suggested that the adduct **5** might undergo dehydration, deisobutylation, and cyclization to the octalone derivative **8** in a single step on treatment with polyphosphoric acid. When **5** was heated with polyphosphoric acid at 100° all of these transformations occurred and the keto acid **6** was obtained in 51% yield.[10] When **6** was heated at reflux in aqueous acid it underwent a smooth decarboxylation to give the octalone **7**.

This sequence of reactions was then applied to 4-carbomethoxycyclohexanone (**8**) as outlined in Scheme III. Condensation of di-*tert*-butyl glutarate with **8** gave the oily hydroxy triester **9**. Attempts to convert **9** directly to the unsaturated keto acid **11** by the method described above gave only a low (18%) yield of **11**. A

(1) Alfred P. Sloan Foundation Research Fellow, 1970–1972.

(2) Taken from the Ph.D. dissertation of E. G. Zey, University of Kansas, Sept 1968 [*Diss. Abstr. B*, **30**, 2623 (1969)].

(3) For a review see J. M. Mellor and S. Munavalli, *Quart. Rev., Chem. Soc.*, **18**, 270 (1964).

(4) E. C. du Feu, F. J. McQuillin, and R. Robinson, *J. Chem. Soc.*, 53 (1937); E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179 (1959).

(5) R. G. Carlson and R. G. Blecke, *Chem. Commun.*, 93 (1969).

(6) For previous syntheses of members of the eudesmane class see (a) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966); (b) D. C. Humber, A. R. Pinder, and R. A. Williams, *J. Org. Chem.*, **32**, 2335 (1967); (c) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968); (d) J. A. Marshall and M. T. Pike, *J. Org. Chem.*, **33**, 435 (1968).

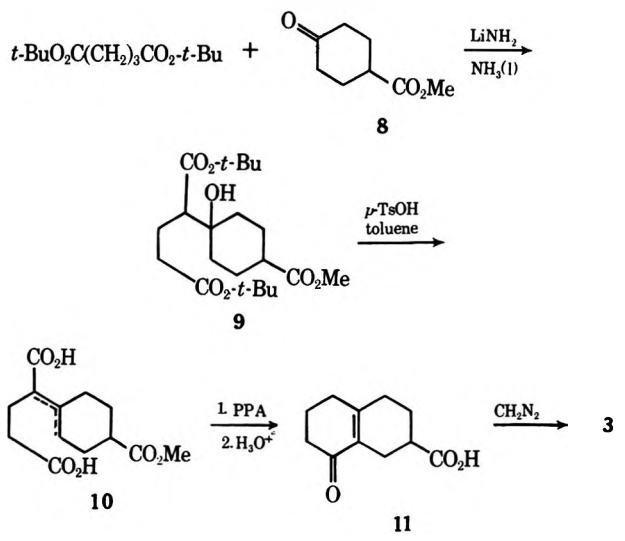
(7) Subsequent to the completion of this work[2] a report appeared of another route to **3**: J. W. Huffman and M. L. Mole, *Tetrahedron Lett.*, 501 (1971).

(8) H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966); H. O. House and W. F. Fischer, Jr., *ibid.*, **33**, 949 (1968).

(9) W. H. Puterbaugh, *ibid.*, **27**, 4010 (1962).

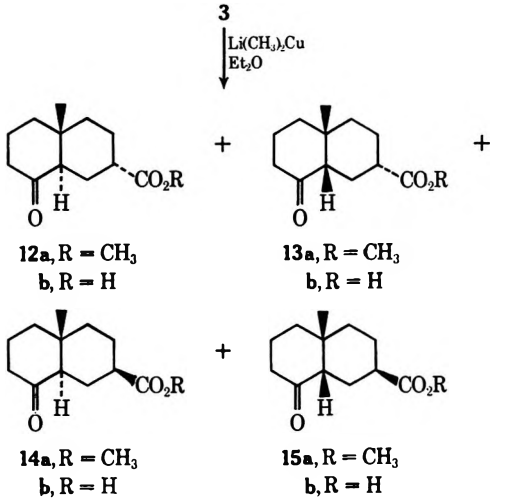
(10) No attempt was made to optimize the yields in this sequence.

SCHEME III



more efficient route to **11** was developed which involved conversion of the hydroxy triester **9** to the unsaturated diacid **10** by reaction with *p*-toluenesulfonic acid in toluene. Treatment of **10** with polyphosphoric acid and subsequent decarboxylation of the cyclized product afforded the unsaturated keto acid **11** in 58% yield. Esterification with diazomethane gave **3**.

Treatment of **3** with lithium dimethylcopper(I) gave a high yield of the conjugate addition product as a mixture of isomers. Although the exact distribution of isomers varied somewhat from run to run, the approximate relative percentages of the esters **12a–15a** in the crude product were 24% **12a**, 48% **13a**, 11% **14a**, and 17% **15a**. The stereochemistry of these products was established in the following manner. Hydrolysis of the mixture of esters and chromatography of the resulting mixture of keto acids produced four acids, two of which were identical with authentic samples of **14b** and **15b**[6c,11] and two new acids, mp 131° and 159°.



Stereochemical assignments for the two new acids and the corresponding esters were based upon nuclear magnetic resonance (nmr) spectral data. The angular methyl groups in both the acid with mp 131° and its methyl ester appear in the nmr spectra at δ 0.82, whereas the angular methyl groups in the acid with mp 159° and its methyl ester appear at δ 0.95. Based upon the useful generalization[12] that the angular methyl group of a trans-fused decalin system appears at higher field than the corresponding cis isomer, the acid with mp 131° must be **12b** and the acid with mp 159° must be **13b**. Further confirmation of these stereochemical assignments was obtained by an examination of the $\Delta W_{1/2}$ values[13] for the angular methyl groups in the esters **12a–15a** (Table I). These values for $\Delta W_{1/2}$ are consistent with the stereochemical assignments made above.

TABLE I

NMR DATA FOR ANGULAR METHYL GROUPS IN ESTERS **12a–15a**

Ester	Chemical shift, ppm	$\Delta W_{1/2}$,[a] Hz
12a	0.82	0.64 ± 0.01[b]
13a	0.95	0.47 ± 0.01
14a	0.82	0.73 ± 0.01
15a	1.17	0.46 ± 0.03

[a] The $\Delta W_{1/2}$ values were determined[13a] by using the formula $\Delta W_{1/2} = CH_3\ W_{1/2} - TMS\ W_{1/2}$, where $CH_3\ W_{1/2}$ is the half band width of the angular methyl group and TMS $W_{1/2}$ is the half band width of the TMS signal. [b] Deviations are given as average deviations.

It is clear, then, that there is a marked preference (~70%) for the introduction of the new angular methyl group from the side opposite the carbomethoxy group. The reason for this preference is not readily apparent from a conformational analysis of the various possible transition states in this reaction.

Because the keto ester **14a**, having the stereochemistry required for conversion to β-eudesmol (**1**), is not obtained in appreciable yield in the kinetically controlled methylation of **3**, we turned our attention to the equilibration of the esters **12a–15a**. When the mixture of esters obtained in the conjugate addition reaction was equilibrated with sodium methoxide in methanol, the equilibrium mixture consisted of 10% **12a**, 14% **13a**, 58% **14a**, and 18% **15a**. Saponification of the equilibrium mixture and chromatography of the resulting mixture of keto acids gave the pure keto acid **14b**. As this compound has been previously converted into β-eudesmol,[6c] this constitutes a formal total synthesis of this sesquiterpene.

Experimental Section[14]

2-(1-Hydroxycyclohexyl)di-*tert*-butyl Glutarate (5).—Following the procedure of Puterbaugh,[9] 74.6 mmol of lithium amide was generated and used to condense 10.0 g (56.8 mmol) of di-*tert*-butyl glutarate with 5.58 g (56.8 mmol) of cyclohexanone. Work-up afforded 13.6 g (87%) of the crude hydroxy diester **5**, ir 3500 (OH), 1730 cm^{-1} (ester C=O).

$\Delta^{9,10}$-Octal-1-one (7).—Polyphosphoric acid (PPA) (150 g) and 10.0 g (36.5 mmol) of the hydroxy diester **5** were blended by

(11) We are indebted to Professor Heathcock for kindly providing us with authentic samples of **14b** and **15b**.

(12) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963).

(13) (a) K. L. Williamson, T. Howell, and T. A. Spencer, *J. Amer. Chem. Soc.*, **88**, 325 (1966); (b) M. J. T. Robinson, *Tetrahedron Lett.*, 1685 (1965); (c) C. W. Shoppee, F. P. Johnson, R. E. Lack, and S. Sternhell, *Chem. Commun.*, 347 (1965).

(14) All boiling points are uncorrected and all melting points are corrected. The infrared spectra were recorded on a Beckman IR-8 spectrophotometer and the nuclear magnetic resonance spectra were recorded on a Varian A-60, A-60A, or HA-100 instrument using tetramethylsilane as an internal standard. Gas chromatography studies utilized an Aerograph A-90P or F & M Model 700 gas chromatograph and a Beckman 10-in. recorder equipped with a Disc Integrator. Unless otherwise stated, magnesium sulfate was employed as the drying agent.

hand with a stirring rod. The mixture was heated for 1.5 hr on the steam bath, which effected immediate evolution of carbon dioxide. Ice (37 g) and 11 ml of water were added. The aqueous mixture was extracted with four 15-ml portions of ether, which were combined and washed with two 10-ml portions of saturated sodium bicarbonate solution. The combined aqueous fractions were acidified, extracted with ether, dried, and concentrated to afford 2.54 g (51%) of the crude keto acid **6**, ir ($CHCl_3$) 3550 (COOH), 1700 (acid C=O), and 1660 cm^{-1} (conjugated C=O). The crude sample of keto acid **6** (2.54 g, 13.1 mmol) was refluxed in a mixture of 15 ml of PPA, 18.5 ml of acetic acid, and 125 ml of water for 5 hr. After addition of 37 g of ammonium sulfate and enough sodium chloride to saturate the solution, the mixture was extracted with four 15-ml portions of ether. The combined ether layers were washed with three 10-ml portions of saturated sodium bicarbonate solution and brine, dried, concentrated, and distilled to afford 1.21 g (62%) of the ketone **7**: bp 130–145° (9 mm); $n^{10}D$ 1.5322; ir 1670 (conjugated C=O), 1640 cm^{-1} (C=C); uv max (95% EtOH) 248 mμ (ε 12,500) [lit.[15] uv max (95% EtOH) 246 mμ (ε 12,400)]; nmr δ 2.2 (m, 8, CH adjacent to unsaturated). A 2,4-dinitrophenylhydrazone derivative was prepared in 68% yield, mp 266.5–267° [lit.[15] mp 266–266.5°]; vpc analysis (6 ft × 0.25 in., 15% DEGS on 60–80 mesh Chromosorb W, 170°) indicated the presence of only one component.

4-Carbomethoxycyclohexanone (8).—A mixture of 50.0 g (0.329 mol) of methyl *p*-hydroxybenzoate,[16] 2.0 g of 5% rhodium on alumina, and 100 ml of freshly distilled ethanol was shaken in an atmosphere of hydrogen (60 psi) until the hydrogen uptake ceased. The catalyst was removed by filtration, the solvent was removed under reduced pressure, and the residue was distilled to afford 50.1 g (96%) of 4-carbomethoxycyclohexanol (stereochemistry not determined), bp 80–85° (0.06 mm) [lit.[16] bp 96–98° (0.35 mm)].

An acetone solution of the hydroxy ester (50.0 g, 0.316 mol) was treated at 15° with 77 ml of a 2.67 *M* solution of chromium trioxide in aqueous sulfuric acid.[17] After 1 hr, 2.5 ml of isopropyl alcohol was added, the acetone solution was decanted, and the chromium salts were dissolved in brine. The aqueous layer was extracted with ether and the ether extracts were combined with the acetone solution. The organic layers were dried and concentrated, and the residue was distilled to afford 38.1 g (76%) of keto ester: bp 94–95° (0.65 mm) [lit.[16] bp 80–81° (0.40 mm)]; ir 1730 (ester C=O) and 1715 cm^{-1} (ketone C=O); nmr δ 3.7 (s, 3, OCH_3) and unresolved absorption in the region 2.5–1.2 (9 H).

2-(1-Hydroxy-4-carbomethoxycyclohexyl)di-*tert*-butyl Glutarate (9).—The lithium salt of 86.2 g (0.352 mol) of di-*tert*-butyl glutarate was prepared from 0.410 mol of lithium amide in 2 l. of anhydrous ammonia in a flask fitted with a Vibromixer. A solution of 48.2 g (0.308 mol) of keto ester **8** was added over a 30-min period with agitation. After an additional 1 hr, a mixture of 22.1 g of ammonium chloride and 400 ml of ether was added and the solution was brought to reflux to expel excess ammonia. The mixture was cooled to 0° and treated with 206 ml of water. The aqueous phase was separated, acidified (pH 2), saturated with sodium chloride, and extracted with ether. The combined ether layers were washed with 5% hydrochloric acid, saturated sodium carbonate solution, and brine. The ether solution was dried and concentrated, and the unreacted starting materials were removed by distillation (70–85°, 0.06 mm). The residue consisted of 78 g (64%) of the hydroxy triester **9** as a thick, viscous oil: ir 3500 (OH), 1730 (ester C=O), and 1385 and 1365 cm^{-1} (*gem*-dimethyl); nmr δ 3.65 (s, 3, OCH_3), 1.51 [s, 9, $-C(CH_3)_3$], 1.53 [s, 9, $-C(CH_3)_3$], and unresolved absorption in the region 1.1–2.8 (15 H).

Anal. Calcd for $C_{21}H_{36}O_7$: C, 62.98; H, 9.06. Found: C, 62.87; H, 9.16.

2-(4-Carbomethoxy-1-cyclohexenyl)glutaric Acid (10).—A solution of 78 g (0.194 mol) of the hydroxy triester **9**, 292 ml of toluene, and 3.9 g of *p*-toluenesulfonic acid in a flask fitted with a Dean–Stark apparatus was refluxed for 3 hr. The solution was concentrated, diluted with 292 ml of ether, and extracted with three 30-ml portions of saturated sodium carbonate solution. The combined sodium carbonate solutions were acidified, saturated with sodium chloride, and extracted with ether. The combined ethereal extracts were dried and concentrated to afford 50.2 g (95%) of the diacids **10** as a viscous oil: ir ($CHCl_3$) 3600–2500 (acid –OH), 1735 (ester C=O), 1710 (acid C=O), and 1620 cm^{-1} (C=C); nmr δ 8.56 (s, 2 H, $-CO_2H$), 5.75 (m, –C=CH), and 3.74 (s, 3 H, $-OCH_3$).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.77. Found: C, 57.79; H, 6.97.

$\Delta^{9,10}$-Octal-1-one-7-carboxylic Acid (11).—The mixture of diacid **10** (33 g, 0.12 mol) and 400 g of PPA was blended by hand with a glass rod and heated for 2.5 hr at 65°. After cooling, the mixture was treated with 600 ml of crushed ice and diluted with water to 700 ml. The aqueous solution was refluxed for 1.25 hr, cooled to room temperature, saturated with sodium chloride, and continuously extracted with ether for 48 hr. Saturated sodium carbonate solution was added to the ethereal extract until the aqueous phase had pH 8. This solution was cooled and the precipitated inorganic salts were removed by filtration. The aqueous phase was acidified (pH 2) and extracted with five 100-ml portions of ether. The combined ethereal extract was dried and concentrated and the residue (23 g) was subjected to chromatography (Mallinckrodt Silic AR, CC-4, 230 g) using hexane–ether and 400-ml fractions were collected. Fractions 9–17 (hexane–ether, 1:1) afforded 8.02 g (34%) of the keto acid **11**. Fractions 19–24 (ether, 400-ml fractions) afforded 12.8 g of a material believed to be a mixture of uncyclized triacids. Recycling this material by the above procedure afforded an additional 5.90 g of **11** (total yield 58%). Although this material was pure enough (mp 140–145°) for subsequent reactions, a sample was recrystallized from aqueous acetonitrile to give the pure keto acid **11** as white needles: mp 146–147°; ir ($CHCl_3$) 3600–2300 (COOH), 1700 (acid C=O), 1660 (conjugated C=O), and 1640 cm^{-1} (C=C); uv max (95% EtOH) 244 mμ (ε 10,520); nmr ($CDCl_3$) δ 11.2 (s, 1, COOH) and unresolved absorption in the region 2.7–1.7 (13 H).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.75; H, 7.08.

7-Carbomethoxy-$\Delta^{9,10}$-octal-1-one (3).—An ethereal solution of keto acid **11** (6.74 mmol) was treated with excess diazomethane for 1 hr at 0°. The resulting ether solution was washed with sodium carbonate solution and brine, dried, and concentrated to afford 1.29 g (93%) of the crude keto ester **3**: ir 1730 (ester C=O), 1660 (conjugated C=O), and 1640 cm^{-1} (C=C); nmr δ 3.68 (s, 3 H, OCH_3) and unresolved absorption in the region 2.5–1.7 (13 H); uv max (95% EtOH) 243 mμ (ε 14,500). A sample of this material was distilled, bp 119–122° (0.11 mm), for elemental analysis.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.29; H, 7.82.

Isomeric Mixture of 7-Carbomethoxy-10-methyl-1-decalones (12a–15a).—A mixture of 0.25 g (37.4 mmol) of lithium wire and 20 ml of dry ether was treated with 1.07 ml (2.45 g, 17 mmol) of methyl iodide. This mixture was refluxed for 1 hr and transferred to a second flask under anhydrous conditions. After 1.11 g (5.75 mmol) of cuprous iodide had been added and the mixture had been cooled to 0°, 1.06 g (5.05 mmol) of ketone **3** in 2.5 ml of anhydrous ether was added with stirring over a 10-min period. The mixture was stirred for 1.5 hr at 0° and treated with 33 ml of saturated ammonium chloride solution. The solid material was removed by filtration and the aqueous layer was separated and extracted with two 25-ml portions of ether. The combined ether layers were washed with saturated ammonium chloride solution, saturated sodium carbonate solution, and brine. The ethereal extract was dried and concentrated to afford 0.880 g (78%) of the crude isomeric keto esters: ir 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr δ 3.63 (s, OCH_3), 1.17 (s, CH_3), 0.95 (s, CH_3), and 0.82 (s, CH_3). Vpc analysis (6 ft × 0.25 in. 10% C6-DEGS on Chromosorb W, 195°) revealed the presence of four components later shown to be the four isomeric keto esters (see below) in relative proportions as follows: 26% **12a**, 43% **13a**, 11% **14a**, and 20% **15a**. Approximately 1% starting material was found to be present.

A sample (490 mg) of the crude mixture of isomeric keto esters was chromatographed on silica gel (Mallinckrodt, Silic AR, CC-7, 49 g) collecting 65-ml fractions. Fractions 18 and 19 (ether–hexane, 1:1) contained 64 mg of a mixture. Fraction 20 (ether–hexane, 1:1) contained 137 mg (28%) of keto ester **13a** having essentially the same spectral and physical properties as

(15) H. O. House and H. W. Thompson, *J. Org. Chem.*, **26**, 3729 (1961).
(16) H. O. House, H. Babad, R. B. Toothill, and A. W. Noltes, *ibid.*, **27**, 4141 (1962).
(17) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

those of a sample prepared below. Fractions 21–23 (ether–hexane, 1:1) contained 96 mg of a mixture. Fractions 25–27 (ether–hexane, 1:1, 65-ml fractions) contained 6 mg of unreacted keto ester 3.

Equilibration of Keto Esters.—A sample of a mixture of the keto esters (1.33 g, 5.9 mmol) was refluxed in 50 ml of 0.24 *M* sodium methoxide in methanol. Aliquots were withdrawn from the reaction mixture, worked up, and subjected to vpc analysis. Equilibrium was reached after 46 hr. The mixture was added to 300 ml of ether and washed with 25 ml of saturated sodium carbonate solution. The basic solution was acidified to pH 2 and extracted with ether. The combined ether fractions were washed with brine and dried. After the solvent was removed, 477 mg of a dark yellow viscous mass was obtained which cystallized on standing. This material was shown by nmr and tlc analysis to consist mainly of the corresponding isomeric keto acids. The original ethereal extracts were washed with brine, dried, and concentrated to afford 732 mg (55%) of the equilibrated mixture of the keto esters. Vpc analysis (6 ft × 0.25 in. 10% DEGS on 60–80 mesh Chromosorb W, 194°) showed the presence of four isomers in the relative ratio of 10% **12a**, 14% **13a**, 58% **14a**, and 18% **15a**.

Saponification of Keto Esters. A. Unequilibrated Mixture.—A sample of the unequilibrated mixture of the keto esters (871 mg, 3.88 mmol) was refluxed with 3.30 g (59 mmol) of potassium hydroxide and 21 ml of water in 43 ml of methanol for 3 hr. The mixture was diluted with 30 ml of water, saturated with sodium chloride, and extracted with 20 ml of ether. After acidification (pH 2) the mixture was extracted with four 50-ml portions of ether. The combined extracts wre dried and concentrated to afford 572 mg (70%) of the crude mixture of isomeric keto acids as a yellow solid mass. This material was recrystallized from ether–hexane to afford 209 mg of white needles, mp 150–157°, which was shown by nmr to consist mainly of keto acid **13b**. The mother liquor was concentrated and the residue (355 mg) was subjected to chromatography on silca gel (Mallinckrodt, Silic AR, CC-4, 18 g).

Fractions 24 and 25 (ether–hexane, 1:1) afforded 94 mg of crude keto acid **12b** which, after two recrystallizations from 5% acetronitrile in water, afforded 25 mg of pure **12b** as white needles: mp 130.5–132°; ir ($CHCl_3$) 3600–2250 (COOH) and 1710 cm^{-1} (ketone and acid C=O); nmr ($CDCl_3$) δ 9.3 (s, 1, COOH), 0.82 (s, 3, CH_3) and unresolved absorption in the region 2.4–1.2 (14 H). A sample for elemental analysis was prepared by sublimation, mp 131.5–132.5°.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.71; H, 8.57.

Fraction 26 (ether–hexane, 1:1) contained 67 mg which, after two recrystallizations from 5% acetonitrile–water, afforded 36 mg of keto acid **13b** as white needles: mp 159–160°; ir ($CHCl_3$) 3600–2300 (COOH) and 1710 cm^{-1} (acid and ketone C=O); nmr ($CDCl_3$) δ 8.9 (s, 1, COOH), 0.95 (s, 3, CH_3) and unresolved absorption in the region 2.5–1.1 (14 H). A sample for elemental analysis was prepared by sublimation, mp 159.5–160°.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.65; H, 8.55.

B. Equilibrated Mixture.—In the same manner, 732 mg (3.26 mmol) of the equilibrated mixture of the keto esters was saponified to afford 551 mg (80%) of a crude mixture of isomeric keto acids. This material was subjected to chromatography on silica gel (Mallinckrodt, Silic AR, CC-4, 50 g), whereby fractions 32–36 (ether–hexane, 1:1) afforded 235 mg (34%) of the keto acid **14b** in a high state of purity (tlc analysis). A sample of this material was recrystallized from 5% acetonitrile–water, which afforded a sample of **14b** as white needles: mp 123.8–125° (lit.[13] mp 124–125.8°); ir ($CHCl_3$) 3600–2300 (COOH) and 1710 cm^{-1} (acid and ketone C=O); nmr ($CDCl_3$) δ 9.3 (s, 1, COOH), 0.82 (s, 3, CH_3), and unresolved absorption in the region 2.5–1.2 (14 H). This material was identical with an authentic sample.[11]

Conversion of Keto Acids to Keto Esters.—Authentic samples[11] of keto acids **14b** and **15b** and keto acids **12b** and **13b**, isolated above, were treated with ethereal diazomethane and the corresponding four keto esters were obtained. Each ester was subjected to vpc analysis (6 ft × 0.25 in. 10% C6-DEGS on 60–80 mesh Chromosorb W, 193°) and correlated with the four isomeric keto esters obtained in the reaction mixture of 3 with lithium dimethylcopper(I).

Keto ester **12a** had bp 130–150° (pot temperature, 0.05 mm); ir (CCl_4) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.63 (s, 3, OCH_3), 0.82 (s, 3, CH_3), and unresolved absorption in the region 2.8–1.2 (14 H); $\Delta W_{1/2}$ = 0.64 ± 0.01 Hz.

Keto ester **13a** had bp 120–130° (pot temperature, 0.04 mm); ir (CCl_4) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.63 (s, 3, OCH_3) and 0.95 ppm (s, 3, CH_3), and unresolved absorption in the region 2.4–1.1 (14 H); $\Delta W_{1/2}$ = 0.47 ± 0.03 Hz.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.42; H, 9.20.

Keto ester **14a** had bp 130–150° (pot temperature, 0.05 mm); ir (CCl_4) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.63 (s, 3, OCH_3) and 0.82 ppm (s, 3, CH_3) and unresolved absorption in the region 2.4–1.1 (14 H); $\Delta W_{1/2}$ = 0.73 ± 0.01 Hz.

Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.45; H, 9.27.

Keto ester **15a** had bp 130–150° (pot temperature, 0.05 mm); ir (CCl_4) 1735 (ester C=O) and 1710 cm^{-1} (ketone C=O); nmr (CCl_4) δ 3.63 (s, 3, OCH_3), 1.17 (s, 3, CH_3), and unresolved absorption in the region 2.4–1.3 (14 H); $\Delta W_{1/2}$ = 0.46 ± 0.03 Hz.

Registry No.—**3**, 34407-92-6; **7**, 18631-96-4; **9**, 34407-94-8; **10**, 34407-95-9; **11**, 32178-64-6; **12a**, 34407-97-1; **12b**, 34407-98-2; **13a**, 34407-99-3; **13b**, 32298-30-9; **14a**, 2450-96-6; **14b**, 2450-97-7; **15a**, 34408-02-1.

Sulfur-Containing Polypeptides. XV. Synthetic Routes to the A_{6-13} Segment of Ovine Insulin[1-3]

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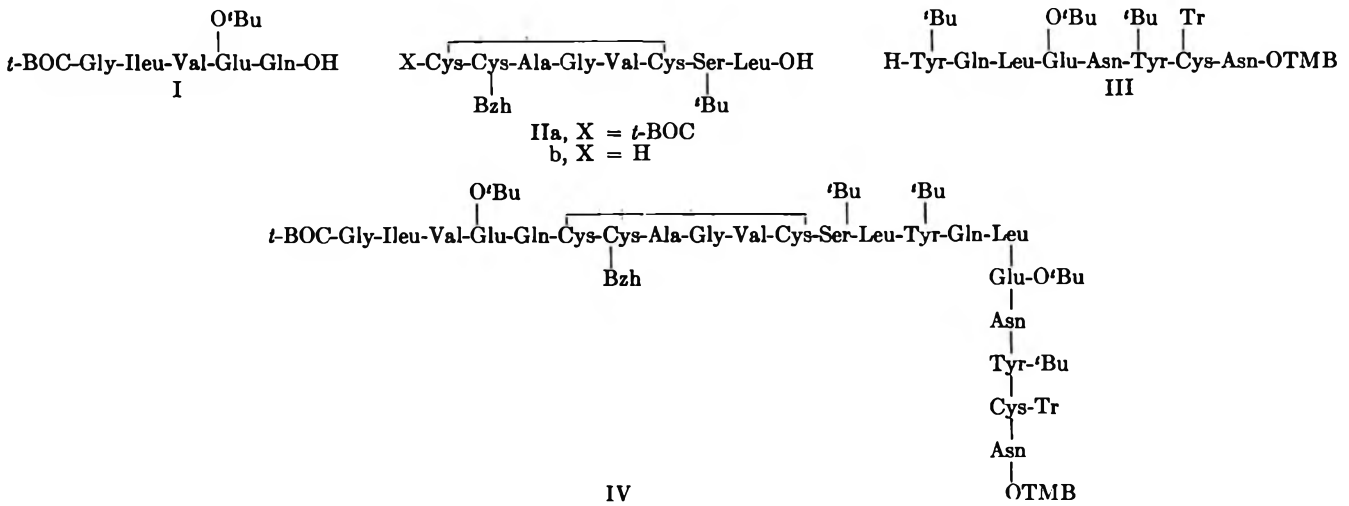
Received March 9, 1971

The synthesis of the protected A_{6-13} segment of ovine insulin (IIa) was accomplished by a route utilizing acid-labile protective groups and *N*-hydroxysuccinimide coupling procedures. The resulting octapeptide derivative, *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycyl-L-valyl-*S*-trityl-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine (XXV) was cyclized to IIa with thiocyanogen. The action of a trifluoroacetic acid–chloroform mixture on IIa selectively removed the *N*-*tert*-butyloxycarbonyl group and provided *S*,*S*-L-hemicystyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycyl-L-valyl-L-hemicystyl-*O*-*tert*-butyl-L-seryl-L-leucine (IIb).

In order to more fully evaluate the general accessibility of complex cystine-containing peptides *via* the sulfenylthiocyanate route[5] and also to develop a synthetic procedure adaptable to the unambiguous synthesis of structural variants of insulin, we have initiated studies directed toward the synthesis of ovine insulin.



The projected plan is similar to that developed from studies with a model system[6] and is designed to allow the stepwise introduction of the three sulfur–sulfur bonds in the molecule.

The most complex aspect of the synthesis, from a protective group point of view, is the preparation of the A-chain derivative IV. The projected route to this substance differs substantially from the elegant and successful syntheses previously described[7] in that (a) the proposed route provides S-protective groups of differing acid lability at cysteine residues A_7 and A_{21} (this should allow the A_{21}–B_{19} interchain disulfide bond to be selectively introduced); (b) the synthesis allows the formation of an A chain with a preformed A_{6-11} intrachain sulfur–sulfur bond; and (c) it involves the protection of all side-chain functional groups with acid-labile *tert*-butyl esters or ethers.

Although several alternative choices of A-chain fragments were available, those finally adopted were the A_{1-5} pentapeptide I, the A_{6-13} octapeptide II, and the A_{14-21} octapeptide III. While the synthesis of I is straightforward and essentially follows a known route, fragments II and III were more formidable because of the restrictions introduced by the synthetic features of the route a–c. The scheme that was adopted for the preparation of the A_{6-13} fragment is described in the present report; an accompanying paper describes the synthesis of III.

A peptide related to II was described by Zervas, *et al.*,[8] in an earlier investigation. Although the route

(1) The preceding paper of this series: R. G. Hiskey, L. M. Beacham, III, V. G. Matl, J. N. Smith, E. B. Williams, Jr., A. M. Thomas, and E. T. Wolters, *J. Org. Chem.*, **36**, 488 (1971).

(2) Supported by Grants A-3416 and GM-07966 from the Institute of Arthritis and Metabolic Diseases and the Institute of General Medical Science, National Institutes of Health, U. S. Public Health Service.

(3) The following abbreviations have been employed in the text: Z = carbobenzoxy; 'Bu = *tert*-butyl; *t*-BOC = *tert*-butyloxycarbonyl; Su = *N*-hydroxysuccinimide; *o*-NPS = *o*-nitrophenylsulfenyl; Tr = trityl; Bzh = benzyhydryl; DCC = *N*,*N'*-dicyclohexylcarbodiimide; WSC = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; TMB = 2,4,6-trimethylbenzyl.

(4) Abstracted in part from the dissertation of L. M. Beacham, III, and the thesis of V. G. Matl submitted to the University of North Carolina in partial fulfillment of the requirements for the Ph.D. and the M.S. degrees, respectively, Jan 1970 and Aug 1968.

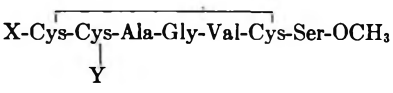
(5) R. G. Hiskey and B. F. Ward, Jr., *J. Org. Chem.*, **35**, 1118 (1970).

(6) R. G. Hiskey, A. M. Thomas, R. L. Smith, and W. C. Jones, Jr., *J. Amer. Chem. Soc.*, **91**, 7525 (1969).

(7) J. Meienhofer, E. Schnabel, H. Bremer, O. Brinkoff, R. Zabel, W. Sroka, H. Klostermeyer, D. Brandenburg, T. Okuda, and H. Zahn, *Z. Naturforsch.*, *B*, **18**, 1120 (1963); Y. Wang, J. Z. Hsu, W. C. Chang, L. L. Cheng, C. Y. Hsing, A. H. Chi, T. P. Loh, C. H. Li, P. T. Shi, and Y. H. Yieh, *Sci. Sinica (Peking)*, **13**, 2030 (1964); P. G. Katsoyannis, A. M. Tometsko, C. Zalut, and K. Fukuda, *J. Amer. Chem. Soc.*, **88**, 5625 (1966); A. Marglin and R. B. Merrifield, *ibid.*, **88**, 5051 (1966); H. Zahn, W. Kanho, H. Klostermeyer, H. G. Gattner, and J. Repin, *Z. Naturforsch.*, *B*, **24**, 1127 (1969).

(8) L. Zervas, I. Photaki, A. Cosmatos, and D. Borovas, *J. Amer. Chem. Soc.*, **87**, 4922 (1965).

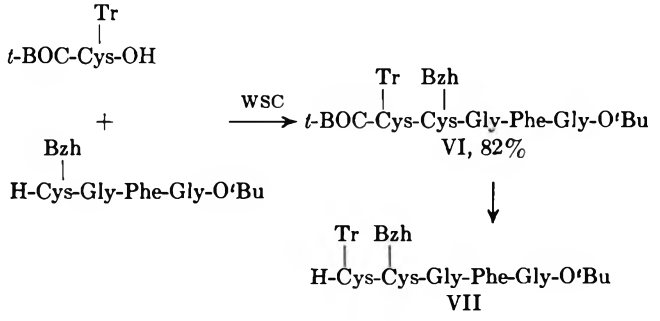
employed for the preparation of Va,b was remarkable in that many new protective groups were used in con-



Va, X = *t*-BOC; Y = Bzh
b, X = *o*-NPS; Y = Tr

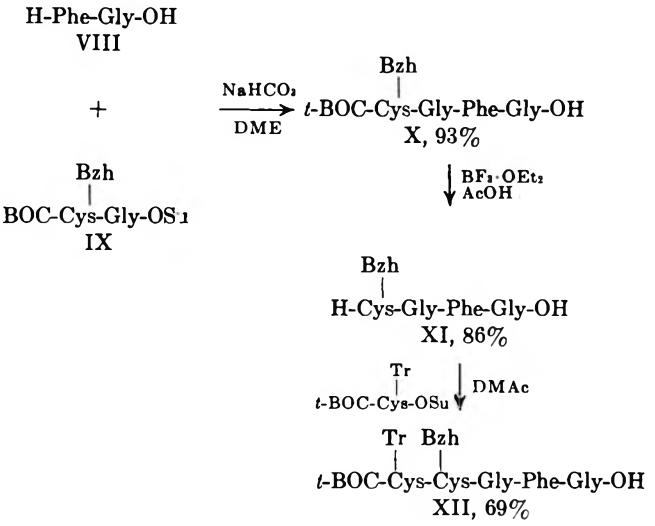
junction on a complicated synthetic problem, several features of the synthesis were relatively unattractive for the purposes of the present studies. For example, the presence of the methyl ester, while simplifying the overall synthesis, limited the choice of coupling methods to be employed for the condensation of A_{6-12} and A_{13-21} to the azide method, since the methyl ester could probably not be removed without serious side reactions elsewhere in the molecule. Furthermore, treatment of V with hydrazine to obtain the hydrazide, and subsequent oxidation to the azide, raised the possibility of side reactions involving the sulfur–sulfur bond. In addition, the presence of a free hydroxyl group on the A_{12} serine residue was to be avoided in order to reduce possible side reactions in the fragment condensations leading to fully protected A chain. Hence a route to II that (a) employed only acid-labile protective groups and (b) allowed the use of blocking groups on the N terminus (A_6) and C terminus (A_{13}) that could be removed without disturbing the A_{6-11} disulfide or protective groups at A_7 and A_{12} was the most attractive.

Initially the combination of the *N-tert*-butyloxycarbonyl group and a *tert*-butyl ester was tested as potential blocking groups for A_6 and A_{13}. Although these groups are quite similar, it appeared in principle that the former could be selectively removed in the presence of the latter. In order to test this possibility, a model peptide, *N-tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine *tert*-butyl ester (VI), was studied. Treatment of VI with hydrogen chloride in dioxane or trifluoroacetic acid invariably led to mixtures of the desired ester VII, unreacted VI, and *S*-trityl-L-cysteinyl-*S*-



benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine, the doubly deblocked substance. Boron trifluoride etherate in acetic acid at 25° produced the same mixture; at 0° only VI and VII resulted. Although VII could be obtained by this route, the separation of VI and VII was not practical on a large scale, and hence alternatives were considered.

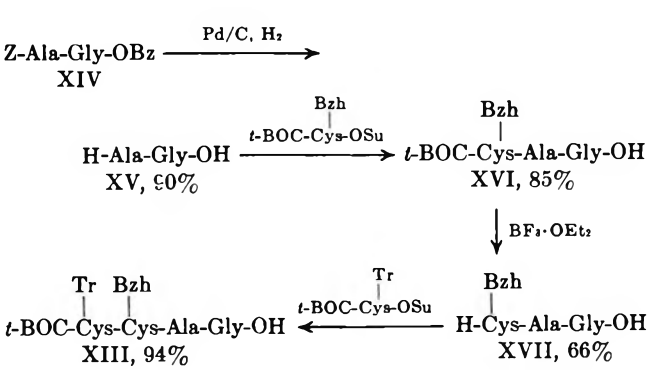
The most desirable solution would be to completely avoid the use of an ester protective group (or other protective groups for that matter). This approach was evaluated by the use of a model system. L-Phenylalanylglycine (VIII) was coupled, in a mixture of dimethoxyethane (DME) and aqueous bicarbonate, to the *N*-hydroxysuccinimide ester[9] of *tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycine (IX). The reaction proceeded smoothly and provided *N-tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine (X) in excellent yield. Treatment of X



with boron trifluoride etherate in acetic acid produced *S*-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine (XI) which was allowed to react with the *N*-hydroxysuccinimide ester of *N-tert*-butyloxycarbonyl-*S*-trityl-L-cysteine. When the coupling was performed in aqueous bicarbonate–DME–DMAc mixtures, low yields (40–50%) resulted because of the low solubility of XI. However, the use of *N*-methylmorpholine, as the base, in DMAc avoided the solubility problem and provided *N-tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine (XII) in reasonable yield and high purity.

These experiments demonstrated that the *t*-BOC group could be successfully employed without the necessity of an ester protective group, and thus attention was given to the actual synthesis of II. The synthetic plan for the octapeptide involved the preparation of two tetrapeptide fragments. The synthesis of the fully protected N-terminal portion, *N-tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinylalanylglycine (XIII), proceeded smoothly by the procedure utilized for the model compound XII (Scheme I).

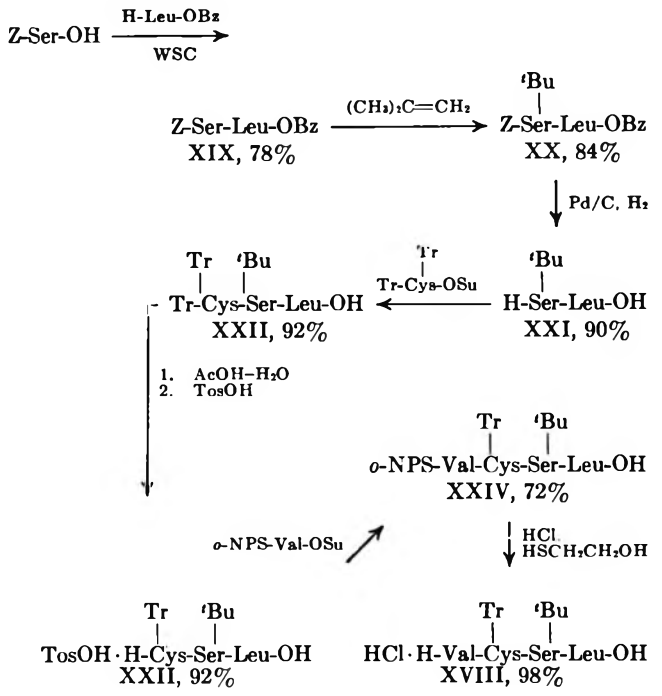
SCHEME I



(9) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *ibid.*, **86**, 1839 (1964); G. W. Anderson, F. M. Callahan, and J. E. Zimmerman, *ibid.*, **89**, 178 (1967).

The second tetrapeptide fragment, L-valyl-*S*-trityl-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine (XVIII), was prepared by the route outlined in Scheme II. Although

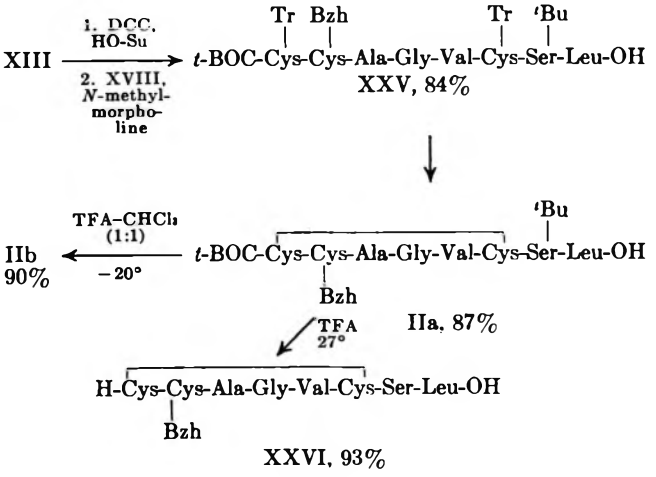
SCHEME II



benzyl *N*-carbobenzoxy-L-seryl-L-leucinate (XIX) could be obtained *via* the *N*-hydroxysuccinimide ester method (57% yield), an improved yield of XIX resulted by the use of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC); the use of the latter reagent allowed any *N*-acylurea formed to be removed by extraction with dilute acid. Introduction of the *O*-*tert*-butyl protective group followed by hydrogenolysis provided a good overall yield of *O*-*tert*-butyl-L-seryl-L-leucine (XXI). Since the *t*-BOC group had previously been shown to cleave at a rate only slightly greater than the *tert*-butyl ester, the more acid-labile *N*-trityl group was used as the amino protective group for the *S*-tritylcysteine residue, A_{11}. *N*,*S*-Ditrityl-L-cysteine *N*-hydroxysuccinimide ester was readily prepared and coupled with XXI in chloroform to provide *N*,*S*-ditrityl-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine (XXII). Selective removal of the *N*-trityl group in the presence of O and S ethers was accomplished by the action of 80% acetic acid on XXII; the ether-soluble free base was isolated as the salt XXIII. Formation of XXIV followed by selective removal of the *N*-*o*-nitrophenylsulfenyl group using hydrochloric acid provided L-valyl-*S*-trityl-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine as the hydrochloride salt (XVIII).

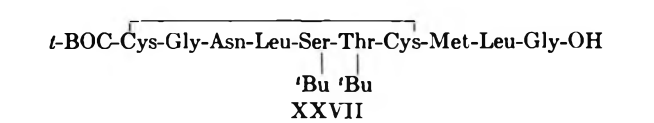
Coupling of the two fragments XIII and XVIII was accomplished *via* the *N*-hydroxysuccinimide ester method (Scheme III). The purification of the active ester of XIII was facilitated by the fact that both unreacted DCC and the urea by-product were reasonably soluble in isopropyl alcohol whereas the active ester was not. Treatment of XVIII with the *N*-hydroxysuccinimide derivative provided the octapeptide, *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycyl-L-valyl-*S*-trityl-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine (XXV) in 84% yield.

SCHEME III



Previous experience had shown that the cyclization of a di-*S*-trityl-L-cysteine peptide similar to XXV could be accomplished[10] by the action of thiocyanogen in acetic acid without prior liberation of the dithiol form. Although the low solubility of XXV in acetic acid or acetic acid–ethyl acetate mixtures did not permit these solvent systems to be employed, a chloroform–acetic acid system was satisfactory. In contrast to the previous experiments,[10] the cyclization proved to be quite slow but could be driven to completion by the use of excess thiocyanogen. The thiocyanogen polymer could be separated from the peptide by solution of the latter in hot methanol; *S*,*S*′,*N*-*tert*-butyloxycarbonyl-L-hemicystyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycyl-L-valyl-L-hemicystyl-*O*-*tert*-butyl-L-seryl-L-leucine (IIa) was obtained in 84% yield. The results of the combustion and amino acid analyses of a performic acid–oxidized acid hydrolysate of IIa were consistent with the expected structure. An osmometric molecular weight determination indicated the substance was the cyclic monomer as opposed to possible dimeric or polymeric forms.

At this point the selective cleavage of a *N*-*t*-BOC group in the presence of an *O*-*tert*-butyl ether was reinvestigated. Gray and Khoujah[11] reported the selective cleavage of the *N*-*tert*-butyloxycarbonyl group in the presence of a *tert*-butyl ester using an acidic ion-exchange resin. These conditions were not generally adaptable to IIa for solubility reasons, and an attempt to employ this method with a model system gave no reaction. In the elegant synthesis of thyrocalcitonin, Riniker, *et al.*,[12] noted that complete removal of the *O*-*tert*-butyl ethers from the intermediate, XXVII, with



90% trifluoroacetic acid required more than 2 hr although a few minutes appeared sufficient for the cleavage of the *N*-*tert*-butyloxycarbonyl group. They suggested that the proximity of the protonated free amine to the *O*-*tert*-butyl ethers retarded the cleavage of the latter groups. For reference purposes the doubly

(10) R. G. Hiskey and R. L. Smith, *J. Amer. Chem. Soc.*, **90**, 2677 (1968).
(11) C. J. Gray and A. M. Khoujah, *Tetrahedron Lett.*, **31**, 2647 (1969).
(12) B. Riniker, M. Brugger, B. Kamber, P. Sieber, and W. Rittel, *Helv. Chim. Acta*, **52**, 1058 (1969).

deblocked peptide XXVI was initially prepared from IIa. Treatment of IIa with boron trifluoride etherate in acetic acid or with neat trifluoroacetic acid at room temperature provided XXVI in good yield, and, using XXVI as a marker, a variety of conditions were investigated by tlc. At room temperature with excess boron trifluoride etherate a second ninhydrin positive spot of slightly greater mobility than XXVI appeared; longer reaction times (up to 12 hr) led to the disappearance of this spot and the enhancement of the spot due to XXVI. The rate of formation of the more mobile product, IIb, was dependent on the amount of acid used; at low temperature with boron trifluoride etherate the formation of IIb was too slow to observe. Hydrogen chloride in dioxane was less effective than the boron trifluoride reagent. Neat trifluoroacetic acid at 27° removed both of the N- and O-blocking groups; however, when the temperature was lowered to −20° the rate of *O-tert*-butyl cleavage was drastically reduced. Using a 1:1 (v/v) mixture of TFA–chloroform, the *O-tert*-butyl group was stable for at least 10 hr at −20°; treatment of IIa with this mixture provided only a trace of XXVI, and a good yield of *S,S'*-L-hemicystyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycyl-L-valyl-L-hemicystyl-*O-tert*-butyl-L-seryl-L-leucine (IIb) was obtained by recrystallization. The material exhibited a single ninhydrin positive spot on tlc and gave combustion and amino acid analyses that were consistent with IIb. Experiments leading to the preparation of the A_{1-13} fragment from the azide of the pentapeptide I and IIb are in progress.

Experimental Section[13]

***N-tert*-Butyloxycarbonyl-*S*-trityl-L-cysteine Dicyclohexylammonium Salt.**—The compound was prepared by the procedure of Schnabel.[14] *tert*-Butyloxycarbonylazide, (10.7 ml, 55 mmol, 10% excess) was added to a suspension of 18.2 g (50 mmol) of *S*-trityl-L-cysteine in 200 ml of dioxane–water (1:1). The pH of the reaction mixture was brought to 9.6 with 4 *N* sodium hydroxide using a pH meter. The stirred suspension was titrated with 4 *N* sodium hydroxide to maintain pH 9.6 (±0.2) for 14 hr. The solution was extracted with 300 ml of ether. The aqueous layer was acidified with citric acid to pH 4.5 and extracted twice with 250 ml of ether and twice with 200 ml of ethyl acetate. The combined organic extract was washed with ten 200-ml portions of water (final washing neutral to Congo Red) and 200 ml of saturated sodium chloride, dried, and evaporated to a foam. A solution of the foam in chloroform was absorbed on a silica gel column (250 g) and eluted with chloroform and 1–6% methanol in chloroform (v,v). The product was dissolved in 150 ml of ether and treated with 9.8 ml (50 mmol) of DCHA to yield an off-white precipitate which was washed with ether. The crude product was twice recrystallized from methanol–ether to afford the salt: 19.5 g (60.6%); mp 210–211° dec; $[\alpha]^{20}D$ +23.8° (*c* 1.0, methanol).

Anal. Calcd for $C_{39}H_{52}N_2O_4S$: C, 72.63; H, 8.13; N, 4.34; S, 4.971 Found: C, 71.96; H, 8.10; N, 4.19; S, 4.97.

***N-tert*-Butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine *tert*-Butyl Ester (VI).**—The oxalate salt of *S*-benzhydryl-L-cysteinylgycyl-L-phenylalanylglycine *tert*-butyl ester[15] (1.4 g, 2.03 mmol) was partitioned between 10 ml of 5% potassium carbonate and 15 ml of ether–ethyl acetate (2:1). The aqueous phase was extracted twice with 10 ml of ether and twice with 5 ml of ethyl acetate. The combined organic extract was washed with three 30-ml portions of water and a 25-ml portion of saturated sodium chloride, dried, and evaporated to 1.15 g (94%) of the free base as a white foam. A suspension of 1.35 g (2.9 mmol, 10% excess) of *N-tert*-butoxycarbonyl-*S*-trityl-L-cysteine dicyclohexylammonium salt in 25 ml of ethyl acetate was shaken with 15 ml of 0.5 *N* sulfuric acid until complete solution was achieved. The organic extract was washed five times with 25 ml of water (final washing was neutral to Congo Red), washed with 20 ml of saturated sodium chloride, dried, and evaporated to a colorless foam, 0.94 g (70%). WSC (0.372 g, 1.95 mmol) was added to a cold (−10°) solution of 0.884 g (1.95 mmol) of *N-tert*-butyloxycarbonyl-*S*-trityl-L-cysteine and 1.15 g (1.95 mmol) of *S*-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine *tert*-butyl ester in 7 ml of DMF–methylene chloride (2.5:1). The reaction mixture was stirred at −10° for 1 hr and at 20° for 24 hr. An additional 9 ml of methylene chloride was added to effect stirring. The reaction mixture was evaporated to a slurry and transferred to 40 ml of 1 *N* sulfuric acid–ice by means of 20 ml of methanol. The resulting white suspension was stirred for 15 min and filtered. The collected solid was washed with cold methanol–ether and dried. The crude pentapeptide was suspended first in hot methanol, and then in warm ether, and cooled to room temperature. The yield was 1.69 g (82.5%) (including 0.21 g and 0.06 g of the second and third crops), mp 220–221°, homogeneous by tlc (system A). The analytical sample was obtained by recrystallization from methanol–chloroform, mp 217–218°, $[\alpha]D$ −22.3° (*c* 1.0, DMF).

Anal. Calcd for $C_{60}H_{67}N_5O_8S_2$: C, 68.61; H, 6.43; N, 6.67; S, 6.10. Found: C, 68.65; H, 6.49; N, 6.63; S, 6.03.

***N-tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycine.**—A solution of *N-tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteine dicyclohexylammonium salt (13.05 g, 23 mmol) in 100 ml of ethyl acetate was washed with 2 *N* sulfuric acid (100 ml) and then with water until the wash was neutral to Congo Red, dried over magnesium sulfate, filtered, and concentrated to an oil. This oil was dissolved in 25 ml of DME, 2.9 g (25 mmol) of *N*-hydroxysuccinimide added, the solution cooled to 0°, and 5.0 g (24 mmol) of DCC added. The reaction was allowed to warm to room temperature overnight, the DCU was filtered and washed with 25 ml of DME, and the combined filtrate and washings were added to a stirred solution of glycine (1.73 g, 23 mmol) and potassium bicarbonate (4.6 g, 46 mmol) in 50 ml of water. This produced considerable gas evolution and a turbid solution which slowly cleared. After 2 hr the solution was cooled to 0° and slowly acidified with 2 *N* sulfuric acid, producing an oil, which was extracted into ether (two 50-ml portions). The ether solution was washed with water until the wash was neutral to Congo Red, dried over magnesium sulfate, and evaporated to a foam (8.75 g, 86%), which tlc (system B) revealed to be slightly contaminated with *N-tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteine. Several attempts at recrystallization or salt formation failed to remove this impurity, and so the product was used without further purification.

***N-tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycine *N*-Hydroxysuccinimide Ester (IX).**—To a cold (0°), stirred solution of *N-tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycine (3.4 g, 7.85 mmol) and *N*-hydroxysuccinimide (0.91 g, 7.91 mmol) in 10 ml of DME, DCC (1.62 g, 7.85 mmol) was added. After warming to room temperature overnight, the DCU was filtered and washed with ethyl acetate, and the combined filtrate and washings were concentrated to an oil, which was crystallized from 30 ml of 2-propanol to give a white solid (3.04 g, 72%), mp 154–156°, $[\alpha]^{22}D$ +6.34° (*c* 0.93, chloroform),

Anal. Calcd for $C_{27}H_{31}N_3O_7S$: C, 59.87; H, 5.77; N, 7.76; S, 5.92. Found: C, 59.89; H, 5.73; N, 8.27; S, 5.78.

***N-tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine (X).**—A solution of IX (7.62 g, 14.1 mmol) in 30 ml of DME was added to a stirred solution of VIII[16] (3.50

(13) Melting points are uncorrected. Combustion analyses were performed by Micro-Tech Laboratories, Skokie, Ill., and Galbraith Laboratories, Knoxville, Tenn. Molecular weights were determined on a Mechrolab Model 301A osmometer, using *o*-chlorophenol at 37°. Amino acid analyses were performed with a Beckman Model 116 amino acid analyzer on samples hydrolyzed for 24 hr in evacuated sealed tubes with 6 *N* hydrochloric acid. The results have not been corrected for cysteic acid or serine destruction. Thin layer chromatograms were run on 3-in. microscope slides or on 5 × 20 cm plates, coated with silica gel GF_{254}. Solvent systems employed were chloroform–methanol, 9:1 (system A); chloroform–acetone–acetic acid, 8:1:1 (system B); chloroform–methanol–17% ammonia, 6:6:1 (system C); chloroform–methanol–17% ammonia, 24:6:1 (system D). Unless otherwise stated, products were dried *in vacuo* over phosphorus pentoxide.

(14) E. Schnabel, *Justus Liebig's Ann. Chem.*, **702**, 188 (1967).

(15) R. G. Hiskey, J. T. Staples, and R. L. Smith, *J. Org. Chem.*, **32**, 2772 (1967).

(16) J. R. Vaughn, Jr., and J. A. Eichler, *J. Amer. Chem. Soc.*, **75**, 5556 (1953).

g, 14.5 mmol) and 2.9 g (29 mmol) of potassium bicarbonate in 30 ml of water, producing considerable evolution of gas. After 1 hr the reaction mixture was diluted with 200 ml of 1 *N* sulfuric acid, producing a gummy precipitate, which was extracted into ethyl acetate (two 100-ml portions). This extract was washed with water (three 200-ml portions) and saturated brine (two 100-ml portions), dried over magnesium sulfate, filtered, and concentrated to 30 ml. Dilution with ether produced a precipitate, which was collected and dried to yield 8.6 g (93%) of a white solid, mp 108–111°, $[\alpha]^{22}D$ +0.01° (*c* 0.89, $CHCl_3$), homogeneous (system B).

Anal. Calcd for $C_{34}H_{40}N_4O_7S$: C, 62.94; H, 6.22; N, 8.64; S, 4.94. Found: C, 62.96; H, 6.20; N, 8.48; S, 4.78.

***S*-Benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine (XI).**—Boron trifluoride etherate (3.3 ml, 25 mmol) was added to a stirred solution of X (6.5 g, 10 mmol) in 30 ml of acetic acid, producing a faint yellow color and considerable bubbling. After 30 min the solution was poured into 200 ml of 0.1 *N* potassium hydroxide, producing a fine white precipitate, which was collected, washed with water, dried, and recrystallized from DMAc to yield 4.7 g (86%), mp 191–193° dec. Drying at 100° raised the decomposition point to above 230°, $[\alpha]^{22}D$ −18.34° (*c* 1.03, DMF), homogeneous (system C).

Anal. Calcd for $C_{29}H_{32}N_4O_5S \cdot 1.15H_2O$: C, 60.50; H, 6.13; N, 9.73; S, 5.57. Found: C, 60.71; H, 5.91; N, 9.84; S, 5.46.

***N*-*tert*-Butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinylglycyl-L-phenylalanylglycine (XII).**—DCC (2.27 g, 11 mmol) was added to a stirred solution of *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteine (4.64 g, 10 mmol) and *N*-hydroxysuccinimide (1.27 g, 11 mmol) in 10 ml of DME at −10°. The reaction was allowed to warm to room temperature for 6 hr; the DC was filtered and washed with ethyl acetate (three 10-ml portions). The combined filtrate and washings were concentrated to a foam which was dissolved in 40 ml of DMAc. *N*-Methylmorpholine (1.1 ml, 10 mmol) and XI (5.0 g, 9.1 mmol) were added and the reaction mixture was stirred overnight. *p*-Toluenesulfonic acid (2 g, 10.4 mmol) was added to neutralize the base, and the solution was poured into 100 ml of ice water, producing an immediate fine white precipitate. This was collected and washed with water (three 30-ml portions), methanol (20 ml), and ethyl acetate (two 20-ml portions) and then dried to yield 6.83 g (69%) of a white solid, mp 217–220°, $[\alpha]^{22}D$ −18.8° (*c* 1.0, DMF), homogeneous (system B).

Anal. Calcd for $C_{56}H_{59}N_5O_8S$: C, 67.64; H, 5.98; N, 7.04; S, 6.45. Found: C, 67.69; H, 6.04; N, 7.05; S, 6.78.

***N*-Carbobenzoxy-L-alanylglycine Benzyl Ester (XIV).**—The compound was prepared in 97% yield by the method of Stelakatos,[17] mp 109–111° (lit.[17] mp 111–112°).

L-Alanylglycine (XV).—A solution of XIV (23 g, 0.062 mol) in 350 ml of ethanol and 6 ml of acetic acid was treated with 2.3 g of 10% palladium on charcoal; hydrogen was bubbled through this suspension for 4 hr. Water (150 ml) was added in 50-ml portions as the reaction proceeded to maintain solubility of the product. The catalyst was filtered on a Celite bed; the filtrate was concentrated to 300 ml and diluted with 3.5 l of acetone, producing a white precipitate, which was collected to yield 8.19 g (90%) of a white powder, mp 234–235°, $[\alpha]^{22}D$ +49.36° (*c* 2.04, H_2O) [lit.[18] mp 232–235°, $[\alpha]^{25}D$ +49.1° (*c* 2.0, H_2O)].

***N*-*tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteine Dicyclohexylammonium Salt.**—A stirred suspension of *S*-benzhydryl-L-cysteine[19] (17.5 g, 61 mmol) in dioxane–water, 1:1 (320 ml), was maintained at pH 10.2 by dropwise addition of 4 *N* sodium hydroxide. After 5 hr the clear solution was extracted with ether (50 ml), and the extract was discarded. The solution was acidified with 2 *N* sulfuric acid to pH 3.1 and extracted twice with ethyl acetate; the extracts were washed with water (three 200-ml portions), dried over magnesium sulfate, filtered, and evaporated to an oil. This was dissolved in ether and treated with dicyclohexylamine (15.6 ml, 80 mmol) producing an immediate white precipitate, which was collected and washed with ether. Recrystallization from chloroform–hexane gave 27.4 g (79%) of a white crystalline solid, mp 157–158°, $[\alpha]^{22}D$ +6.38° (*c* 0.93, chloroform).

Anal. Calcd for $C_{33}H_{48}N_2O_4S$: C, 69.68; H, 8.51; N, 4.93; S, 5.64. Found: C, 69.64; H, 8.62; N, 4.82; S, 5.31.

***N*-*tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteine *N*-Hydroxysuccinimde Ester.**—*tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteine was prepared as above, on a 0.1 *M* scale, and the free acid dissolved in 100 ml of DME. *N*-Hydroxysuccinimide (11.5 g, 0.1 mol) was added, the solution cooled to 0°, and DCC (20.6 g, 0.1 mol) added. After stirring 2 hr at 0° and 10 hr at 27°, the solution was filtered and evaporated. The resulting oil was dissolved in 200 ml of ethyl acetate, washed with 200 ml of cold 5% potassium bicarbonate, water (three 200-ml portions), and saturated brine (two 200-ml portions), dried over calcium sulfate, filtered, and evaporated. Crystallization was effected from ethyl acetate–hexane to give a white solid (38.9 g, 76%), which was used without further purification.

***N*-*tert*-Butyloxycarbonyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycine (XVI).**—A solution of the *N*-hydroxysuccinimide ester (0.653 g, 1.35 mmol) in 5 ml of DME was added to a stirred solution of XV (0.220 g, 1.50 mmol) and potassium bicarbonate (0.30 g, 3.0 mmol) in 5 ml of water. After 2.5 hr the mixture was poured into 50 ml of ice–2 *N* sulfuric acid. The resulting gum was dissolved in 20 ml of ethyl acetate, washed with water (two 20-ml portion) and saturated brine (20 ml), dried over calcium sulfate, filtered, and concentrated to 5 ml. Dilution with 80 ml of ether and cooling to 0° gave a crystalline precipitate, 0.59 g (85%), mp 124–125°, $[\alpha]^{24}D$ +71.06° (*c* 1.13, DMF), homogeneous (system B).

Anal. Calcd for $C_{26}H_{33}N_3O_6S$: C, 60.56; H, 6.45; N, 8.15; S, 6.22. Found: C, 60.96; H, 6.10; N, 8.17; S, 6.34.

***S*-Benzhydryl-L-cysteinyl-L-alanylglycine (XVII).**—Boron trifluoride etherate (2.6 ml, 18 mmol) was added to a stirred solution of XVI (3.17 g, 6.15 mmol) in 25 ml of dry acetic acid. After 30 min the solution was poured into 6% aqueous sodium acetate (150 ml), producing a fine precipitate. After cooling to 0° overnight the solid was collected and washed with water and then recrystallized from DMAc–ethyl acetate, yielding 1.70 g (66%) of a white solid, mp 178–180° dec, $[\alpha]^{24}D$ −5.18 (*c* 0.56, DMF), homogeneous (system C).

Anal. Calcd for $C_{21}H_{25}N_3O_4S \cdot 0.5H_2O$: C, 59.08; H, 5.98; N, 9.95; S, 7.49. Found: C, 59.41; H, 6.17; N, 9.90; S, 7.55.

***N*-*tert*-Butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycine (XIII).**—A stirred solution of *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteine (0.92 g, 2.0 mmol) and *N*-hydroxysuccinimide (0.25 g, 2.2 mmol) in 2 ml of DME was cooled to 0° and DCC (0.45 g, 2.2 mmol) added. After 2 hr at 0° and overnight at room temperature the reaction was filtered, the DCU was washed with DME (three 2-ml portions), and the combined filtrate and washings were added to a stirred solution of XVII (0.79 g, 1.9 mmol) and potassium carbonate (0.265 g, 1.9 mmol) in 5 ml of water. This solution was stirred for 6 hr and poured into ice–2 *N* sulfuric acid (60 ml), producing an immediate white precipitate, which was collected and washed with water (three 25-ml portions) and ether (four 25-ml portions) to yield 1.62 g (94%) of a white solid, mp 170–175° dec, $[\alpha]^{28}D$ −6.42° (*c* 1.03, DMF), homogeneous (system B).

Anal. Calcd for $C_{48}H_{52}N_4O_7S_2$: C, 66.95; H, 6.09; N, 6.51; S, 7.45. Found: C, 66.85; H, 6.04; N, 6.50; S, 7.34.

***N*-Carbobenzoxy-L-serine** was prepared in 89% yield by the procedure of Guttman and Boissonnas,[20] mp 115–116° (lit. mp 119.5°).

L-Leucine Benzyl Ester *p*-Toluenesulfonate.—The compound was prepared by the method of Zervas, *et al.*,[21] in 90% yield, mp 154–154.5° (lit. mp 158.5–160°).

***N*-Carbobenzoxy-L-seryl-L-leucine Benzyl Ester (XIX).**—To a stirred solution of *N*-carbobenzoxy-L-serine (35 g, 0.146 mol) in 300 ml of ethyl acetate and 20 ml of DMAc were added L-leucine benzyl ester *p*-toluenesulfonate (57.5 g, 0.146 mol) and *N*-methylmorpholine (16.2 ml, 0.146 mol). The resulting solution was cooled to 0° and WSC (31 g, 0.161 mol, 10% excess) was added. After stirring for 2 hr at 0° and overnight at room temperature, the solution was partitioned between ether (200 ml) and 2 *N* sulfuric acid (400 ml). The organic phase was washed with 2 *N* sulfuric acid (three 400-ml portions), 10% potassium bicarbonate (three 400-ml portions) and saturated brine (300 ml), dried over sodium sulfate, filtered, and evaporated to a clear oil. Crystallization from ethyl acetate–hexane and washing with ether gave a white solid (46.7 g, 73%), mp 81–83°, $[\alpha]^{20}D$ −22.6° (*c* 1.0, chloroform). A sample of the protected dipeptide pre-

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(18) J. L. Bailey, *J. Chem. Soc.*, 3461 (1950).
(19) R. G. Hiskey and J. B. Adams, Jr., *J. Org. Chem.*, **30**, 1340 (1965).
(20) S. Guttman and R. Boissonnas, *Helv. Chim. Acta*, **41**, 1852 (1958).
(21) L. Zervas, M. Winitz, and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).

pared *via* the *N*-hydroxysuccinimide ester method was obtained in 57% yield, mp 81–83°, $[\alpha]^{24}D$ −22.5° (*c* 1.0, chloroform) (lit.[22] mp 83–84°).

***N*-Carbobenzoxy-*O*-*tert*-butyl-L-seryl-L-leucine Benzyl Ester (XX).**—A solution of XIX (26 g, 0.059 mol) in 125 ml of chloroform in a 500-ml pressure flask was treated with 1.3 ml of concentrated sulfuric acid and 60 ml of isobutylene, capped, and stirred at 27° for 12 hr. The solution was washed with 5% potassium bicarbonate (300 ml) and saturated brine (three 200-ml portions) and evaporated to a clear oil, which was purified from traces of XIX by chromatography on 150 g of silica gel, eluting with chloroform. The resulting oil was crystallized from hexane to give a white solid (24.7 g, 84%), mp 69–70°, $[\alpha]^{25}D$ +4.20° (*c* 1.85, chloroform), homogeneous (system A).

Anal. Calcd for $C_{28}H_{38}N_2O_6$: C, 67.44; H, 7.68; N, 5.65. Found: C, 67.92; H, 7.72; N, 5.62.

***O*-*tert*-Butyl-L-seryl-L-leucine (XXI).**—A solution of XX (10 g, 20 mmol) in ethanol (70 ml) and water (30 ml) was treated with 2 g of 10% palladium on charcoal and hydrogen was bubbled through the solution for 2.3 hr. The catalyst was filtered on a Celite bed and the colorless filtrate evaporated to a white solid, which was collected and washed with ether to yield 5.17 g (90%), mp 96–98°, $[\alpha]^{28}D$ −14.37° (*c* 1.03, methanol), homogeneous (system C).

Anal. Calcd for $C_{13}H_{26}N_2O_4 \cdot 0.8H_2O$: C, 54.06; H, 9.63; N, 9.70. Found: C, 54.16; H, 9.55; N, 9.66.

Diketopiperazine of *O*-*tert*-Butyl-L-seryl-L-leucine.—A solution of XX (18 g 36 mmol) in acetic acid (200 ml) was treated with 2 g of 10% palladium on charcoal and hydrogen was bubbled through the solution for 2.5 hr. The catalyst was filtered on a Celite bed and the filtrate lyophilized. The material was revealed by tlc to be mostly XX, and was therefore hydrogenated again, this time in neat ethanol. A product (1.7 g, 18.5%) was isolated after filtration and removal of most of the solvent, which was insoluble in ethanol and ninhydrin negative. The nmr was very similar to that of XXI, which was obtained from the filtrate (6.2 g, 63%); the diketopiperazine had mp 267–270°, $[\alpha]^{22}D$ −5.73° (*c* 0.75, hexamethylphosphoramide), homogeneous (system A).

Anal. Calcd for $C_{13}H_{24}N_2O_3$: C, 60.91; H, 9.44; N, 10.93. Found: C, 60.88; H, 9.54; N, 10.89.

***N*,*S*-Dityril-L-cysteine *N*-Hydroxysuccinimide Ester.**—A solution of *N*,*S*-dityril-L-cysteine diethylammonium salt[23] (48 g, 0.071 mol) in ethyl acetate (400 ml) was partitioned with 400 ml of 0.5 *N* sulfuric acid. The organic phase was washed with water (two 400-ml portions), dried over sodium sulfate, and evaporated to a foam, which was dissolved in 70 ml of DME and treated with 9.2 g (0.080 mol) of *N*-hydroxysuccinimide. The solution was cooled to 0° and DCC (16.5 g, 0.080 mol) added. After stirring for 2 hr at 0° and 11 hr at room temperature, the solution was filtered and evaporated to an oil, which was crystallized from 2-propanol to yield a white powder (48.3 g, 97%), mp 109–113°, $[\alpha]^{28}D$ +70.0 (c 1.37, chloroform).

Anal. Calcd for $C_{45}H_{38}N_2O_4S$: C, 76.90; H, 5.45; N, 3.99; S, 4.56. Found: C, 76.46; H, 5.63; N, 3.81; S, 4.68.

***N*,*S*-Dityril-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine (XXII).**—A solution of XXI (4.65 g, 17 mmol) and the *N*-hydroxysuccinimide ester (10.5 g, 15 mmol) in 30 ml of chloroform was treated with *N*-methylmorpholine (4.0 ml, 37 mmol) and stirred at room temperature for 12 hr. After partitioning between ether (300 ml) and 2 *N* sulfuric acid (300 ml), the organic phase was washed with 2 *N* sulfuric acid (two 300-ml portions), water (three 300-ml portions), and saturated brine (300 ml), dried over sodium sulfate, and evaporated to a white foam (11.86 g, 92%). A 0.5-g sample was chromatographed on a 10-g silica gel column, eluting with chloroform, and crystallized from ether–hexane. The remainder was used without further purification, mp 110–114°, $[\alpha]^{28}D$ +40.52° (*c* 0.96, chloroform).

Anal. Calcd for $C_{54}H_{59}N_3O_5S \cdot 0.5H_2O$: C, 74.45; H, 6.94; N, 4.82; S, 3.68. Found: C, 74.79; H, 6.93; N, 4.75; S, 4.01.

***S*-Trityl-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine *p*-Toluenesulfonate Salt (XXIII).**—A solution of XXII (6.7 g, 7.8 mmol) in 15 ml of acetic acid and 3 ml of water was warmed for 10 min on the steam bath, cooled, and lyophilized to a white powder. The powder was dissolved in 100 ml of ether, filtered, and treated with a solution of *p*-toluenesulfonic acid (1.46 g, 7.8 mmol) in ether. The resulting white precipitate was stored at 0° overnight, collected, and washed with ether to yield a white solid (3.84 g, 62%), mp 146–147°, $[\alpha]^{28}D$ +25.09° (*c* 1.08, ethanol).

Anal. Calcd for $C_{42}H_{53}N_3O_8S_2$: C, 63.69; H, 6.75; N, 5.31; S, 8.10. Found: C, 63.59; H, 6.78; N, 5.30; S, 8.30.

***o*-Nitrophenylsulfenyl-L-valine *N*-Hydroxysuccinimide Ester.**—The compound was prepared in 77% yield by the method of Meienhofer,[24] mp 138–139° (lit.[24] mp 138–139°).

***o*-Nitrophenylsulfenyl-L-valyl-*S*-trityl-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine (XXIV).**—*N*-Methylmorpholine (0.63 ml, 5.8 mmol) was added to a solution of the *N*-hydroxysuccinimide ester (1.05 g, 2.9 mmol) and XXIII (2.29 g, 2.9 mmol) in 6 ml of DME. After stirring for 48 hr the orange solution was partitioned between ethyl acetate (100 ml) and 1 *N* sulfuric acid. The organic phase was washed with water (two 100-ml portions) and saturated brine (100 ml), dried over sodium sulfate, filtered, and stripped to a yellow foam, which was chromatographed on 60 g of silica gel, eluting with chloroform–acetone–acetic acid, 45:25:1. Crystallization from ether–hexane yielded 1.82 g (72%) of a bright yellow crystalline compound, mp 184–186°, $[\alpha]^{27}D$ −27.2° (*c* 0.99, DMF).

Anal. Calcd for $C_{46}H_{57}N_5O_8S_2$: C, 63.35; H, 6.59; N, 8.03; S, 7.35. Found: C, 63.16; H, 6.67; N, 7.97; S, 7.20.

L-Valyl-*S*-trityl-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine Hydrochloride (XVIII).—To a stirred solution of XXIV (1.59 g, 1.82 mmol) and 0.7 ml (10 mmol) 2-mercaptoethanol in 6 ml of chloroform was added 0.31 ml (2.0 mmol) of 6.5 *N* hydrogen chloride in dioxane, dissolved in 30 ml of ether. Precipitation began in a few seconds; after 5 min the precipitate was poured into 200 ml of ether, cooled to −10°, collected, and washed with ether to yield a white solid (1.35 g, 98%), mp 137–138°, $[\alpha]^{28}D$ +11.2° (*c* 1.09, ethanol).

Anal. Calcd for $C_{40}H_{55}O_6SCl \cdot 0.5H_2O$: C, 62.85; H, 7.38; N, 7.32; S, 4.19. Found: C, 62.56; H, 7.31; N, 7.39; S, 4.10.

***N*-*tert*-Butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycine *N*-Hydroxysuccinimide Ester.**—A solution of XIII (215 mg, 0.25 mmol), *N*-hydroxysuccinimide (58 mg, 0.50 mmol), and DCC (103 mg, 0.50 mmol) in 0.6 ml of DMAc was stirred at 27° for 24 hr and then poured into 20 ml of 2-propanol, producing an immediate precipitate. The suspension was warmed on the steam bath, cooled to 27°, collected, washed with 2-propanol (three 10-ml portions), and dried *in vacuo* to yield 235 mg (97.5%) of product. The compound was used without further purification.

***N*-*tert*-Butyloxycarbonyl-*S*-trityl-L-cysteinyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycyl-L-valyl-*S*-trityl-L-cysteinyl-*O*-*tert*-butyl-L-seryl-L-leucine (XXV).**—To a solution of the *N*-hydroxysuccinimide ester of XIII (235 mg, 0.246 mmol) and XVIII (196 mg, 0.26 mmol) in 0.6 ml of DMAc was added *N*-methylmorpholine (0.082 ml, 0.75 mmol). The solution gradually solidified as stirring was continued for 48 hr. The solid was transferred into 0.5 *N* sulfuric acid, stirred well, collected, washed with water, and dried. Tlc (system D) revealed traces of the active ester and XVIII; so the product was suspended in 20 ml of hot ethyl acetate, cooled to room temperature, collected, and washed with ethyl acetate, (three 10-ml portions), yielding 331 mg (84%), mp 222° dec, $[\alpha]^{29}D$ −12.75° (*c* 0.8, DMF), homogeneous (system D).

Amino acid analysis. Found: $CysSO_3H$, 2.5; Ser, 0.92; Gly, 1.0; Ala, 1.1; Val, 1.1; Leu, 0.84.

Anal. Calcd for $C_{88}H_{104}N_8O_{12}S_3$: C, 67.66; H, 6.71; N, 7.17; S, 6.16. Found: C, 67.50; H, 6.87; N, 7.27; S, 5.79.

***S*,*S*′,*N*-*tert*-Butyloxycarbonyl-L-hemicystyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycyl-L-valyl-L-hemicystyl-*O*-*tert*-butyl-L-seryl-L-leucine (IIa).**—Thiocyanogen was generated by the addition of bromine (100 mg, 0.625 mmol) in 15.0 ml of ethyl acetate to a rapidly stirred, dark suspension of lead thiocyanate (243 mg, 0.75 mmol) in 15.0 ml of ethyl acetate. All color had disappeared within 5 min and 10.6 ml (0.22 mmol) of this solution was added to a cold (0°), dark, rapidly stirred solution of XXV (312.4 mg, 0.2 mmol) in chloroform (100 ml) and acetic acid (20 ml). After 24 hr tlc (system D) showed a considerable amount of XXV had not reacted, so thiocyanogen was prepared as above and 0.1 mmol was added to the reaction mixture. After 48 hr the solution was filtered into 400 ml of ice water, and 21 ml of ammonium hydroxide was added to the rapidly stirred solution, producing a very heavy emulsion. After storing at 0° overnight the solution was filtered, and the resulting off-white solid washed with water and chloroform and recrystallized from methanol–water to yield

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(23) L. Zervas and I. Photaki, *J. Amer. Chem. Soc.*, **84**, 3887 (1962).

(24) J. Meienhofer, *Nature (London)*, 205 (1965).

186 mg (87%) of a white solid, mp 219–221°, $[\alpha]^{31}D$ −5.16° (*c* 0.62, DMF); homogeneous (system D).

Amino acid anal. Found: $CysSO_3H$, 2.4; Ser, 0.84; Gly, 1.00; Ala, 1.02; Val, 0.98; Leu, 0.95.

Anal. Calcd for $C_{59}H_{74}N_8S_3O_{12}$: C, 55.84; H, 6.94; N, 10.42; S, 8.94; mol wt, 1075.35. Found: C, 56.34; H, 7.05; N, 10.46; S, 8.88; mol wt, 1050 (osmometric, *o*-chlorophenol).

***S,S'*-L-Hemicystyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycyl-L-valyl-L-hemicystyl-*O*-*tert*-butyl-L-seryl-L-leucine (IIb).**—Solid IIa (100 mg, 0.093 mmol) was added to 2 ml of trifluoroacetic acid–chloroform, (1:1 v/v) at −20°, producing a bright yellow solution. After 10 hr at −20° the solution was poured into 100 ml of ether at −10° producing an immediate fine white precipitate (82 mg, 90%). After collecting and drying *in vacuo* at 83° overnight, the compound was recrystallized for analysis from DMAc–water, and washed with 2-propanol: mp 218–220°; $[\alpha]^{22}D$ −12.06° (*c* 0.92, DMF); homogeneous (system D); ninhydrin positive.

Amino acid anal. Found: $CysSO_3H$, 2.4; Ser, 0.88; Gly, 1.00; Ala, 1.04; Val, 1.00; Leu, 1.00.

Anal. Calcd for $C_{45}H_{66}N_8S_3O_{10}\cdot H_2O$: C, 54.41; H, 6.90; N, 11.28; S, 9.68. Found: C, 54.28; H, 6.60; N, 11.27; S, 9.67.

***S,S'*-L-Hemicystyl-*S*-benzhydryl-L-cysteinyl-L-alanylglycyl-L-valyl-L-hemicystyl-L-seryl-L-leucine (XXVI).**—A solution of IIa (50 mg, 0.046 mmol) in 1 ml of TFA was stirred for 50 min at room temperature and then poured into 100 ml of ether at −10°. The resulting fine precipitate was collected and dried to give 40 mg (93%) of a white solid, mp 219–221°, $[\alpha]^{22}D$ −13.33° (*c* 0.51, DMF), homogeneous (system D), ninhydrin positive. The product was recrystallized from DMAc–2-propanol–ether for analysis.

Amino acid anal. Found: $CysSO_3H$, 2.2; Ser, 0.81; Gly, 0.99; Ala, 1.02; Val, 1.00; Leu, 0.96.

Anal. Calcd for $C_{41}H_{58}N_8O_{10}S_3\cdot CF_3CO_2H\cdot DMAC$: C, 50.39; H, 6.12; N, 11.25; S, 8.59. Found: C, 50.64; H, 6.32; N, 11.68; S, 8.90.

Registry No.—IIa, 33578-92-6; IIb, 33515-71-8; VI, 27039-89-0; IX, 33515-73-0; X, 33515-74-1; XI, 33515-75-2; XII, 33515-76-3; XIII, 33511-31-8; XVI, 33511-32-9; XVII, 33511-33-0; XVIII, 33511-34-1; XX, 33511-35-2; XXI, 33511-36-3; XXI diketopiperazine, 33511-37-4; XXII, 33511-38-5; XXIII, 33511-39-6; XXIV, 33511-40-9; XXV, 33511-41-0; XXVI, 33649-61-5; *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteine dicyclohexylammonium salt, 26988-59-0; *N*-*tert*-butyloxycarbonyl-*S*-benzhydryl-L-cysteine dicyclohexylammonium salt, 26988-51-2; *N,S*-ditrityl-L-cysteine *N*-hydroxysuccinimide ester, 27560-18-5.

Sulfur-Containing Polypeptides. XVI. Synthesis of the A_{14-21} Fragment of Ovine Insulin[1-3]

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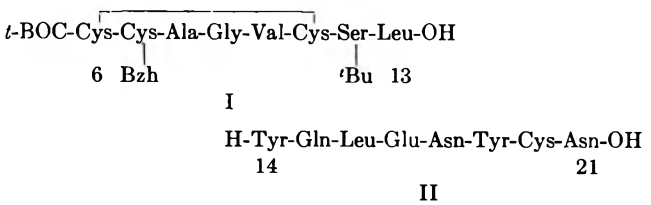
Received March 9, 1971

The protected octapeptide *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutaminyl-L-leucyly-γ-*tert*-butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester (III) has been synthesized. The route involves the use of the *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl (DpOC) group as the principle amino protective group and *N*-hydroxysuccinimide and azide coupling methods.

In the accompanying report[1] a synthetic route to a suitably blocked peptide containing the A_{6-13} sequence of ovine insulin (I) was described. The present report concerns the development of a synthesis leading to the A_{14-21} sequence (II) and describes our experience with the *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl protective group developed by Sieber and Iselin[5] for the elegant synthesis of thyrocalcitonin.[6]



The preparation of the A_{14-21} sequence was complicated by the presence of seven functional side chains in the octapeptide; four of these required protection. Since acid-labile protective groups were required and the presence of a cysteine residue ruled out the possibility of removal of groups by hydrogenolysis, it was clear that only protective groups of very specific acid lability could be utilized. The protective group of choice for the phenolic hydroxyl groups at $A_{14,19}$ was the *tert*-butyl ether; the *S*-trityl group was required for the A_{20} cysteine residue to permit selective formation of the two interchain disulfide bonds at A_7B_7 and $A_{20}B_{19}$. The *tert*-butyl ester seemed to be suitable for the A_{17} carboxyl group. The choice of the 2,4,6-trimethylbenzyl ester as the blocking group for the asparagine-21 residue was governed by the overall stability of this ester and the earlier use by Stewart[7] in a synthesis of a modified sequence of the C-terminal portion of the A chain. Given these choices of ether and ester protective groups, relatively few possibilities were available for amino protective groups. The *N*-*tert*-butyloxycarbonyl group could not be used since *O*-*tert*-butyl ethers and esters generally cleave at comparable rates[1] and the presence of the cysteine residue prevented removal of the *N*-carbobenzyloxy group by hydrogenolysis. Thus the choices of amino protective groups were essentially limited to the *N*-trityl (Tr), the *N*-*o*-

(1) The preceding paper of this series: R. G. Hiskey, L. M. Beacham, III, and V. G. Matl, *J. Org. Chem.*, **37**, 2472 (1972).

(2) Supported by Grant AM-03416 from the Institutes of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(3) The following abbreviations have been employed in the text: *t*-BOC = *tert*-butyloxycarbonyl; DpOC = 2-(*p*-diphenylyl)isopropyloxycarbonyl; *o*-NPS = *o*-nitrophenylsulfenyl; ^tBu = *tert*-butyl; TMB = 2,4,6-trimethylbenzyl; Tr = trityl; Bzl = benzyl, Su = *N*-hydroxysuccinimide; DCC = *N,N'*-dicyclohexylcarbodiimide; DME = 1,2-dimethoxyethane; NMM = *N*-methylmorpholine; DMF = *N,N*-dimethylformamide; DMAc = *N,N*-dimethylacetamide.

(4) Laboratory of Organic Chemistry, Roman Catholic University, Nymegen, The Netherlands.

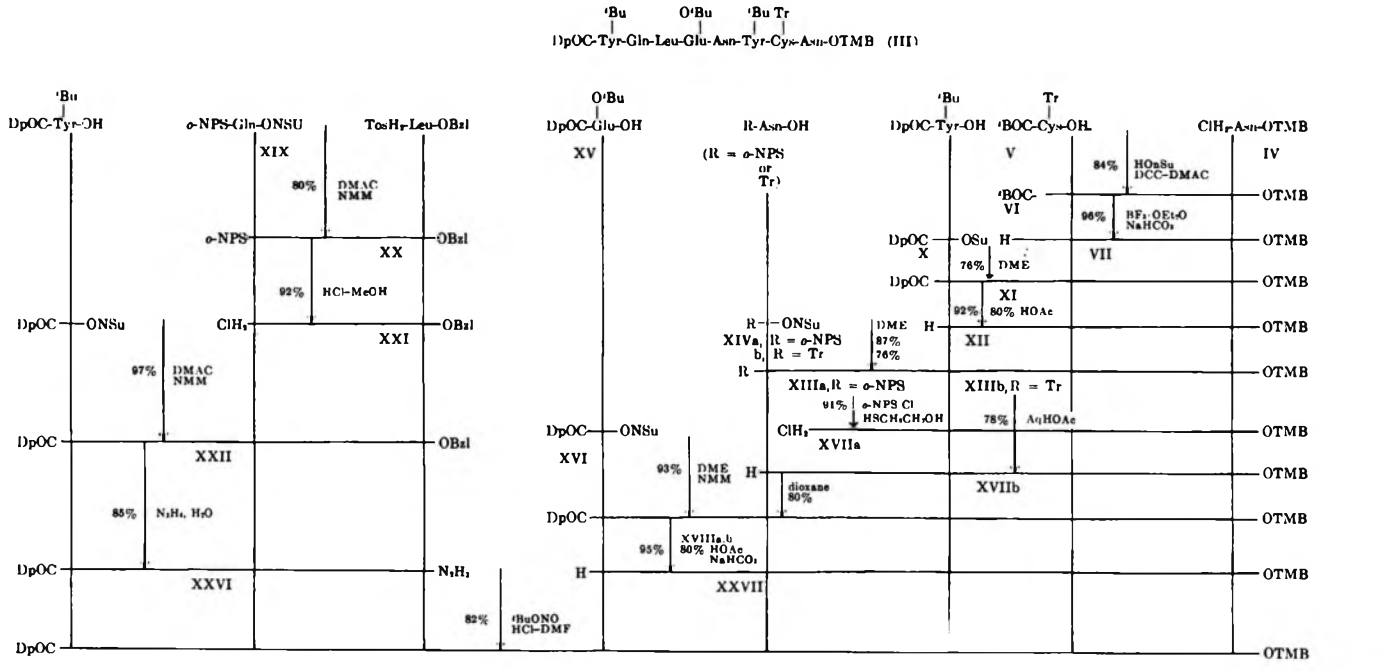
(5) P. Sieber and B. Iselin, *Helv. Chim. Acta*, **51**, 622 (1968).

(6) B. Riniker, M. Brugger, B. Kamber, P. Sieber, and W. Rittel, *ibid.*, **52**, 1058 (1969).

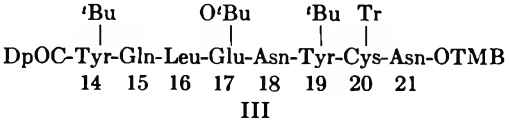
(7) F. H. C. Stewart, *Aust. J. Chem.*, **20**, 1991 (1967).

SCHEME I

SYNTHESIS OF THE PROTECTED A_{14-21} PEPTIDE DERIVATIVE



nitrophenylsulfenyl[8] (*o*-NPS), and the *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl[5,6] (DpOC) groups. The synthetic goal was then the fully protected octapeptide derivative III; the route finally adopted is shown in Scheme I.



L-Asparagine 2,4,6-trimethylbenzyl ester hydrochloride (IV) was coupled *via* the *N*-hydroxysuccinimide method to *tert*-butyloxycarbonyl-*S*-trityl-L-cysteine dicyclohexylamine salt (V). The *t*-BOC group of the dipeptide VI was subsequently removed by the action of boron trifluoride in acetic acid, and *S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester (VII) was obtained in 82% overall yield. The DpOC group was not employed at this point since a group of this lability was not required and since the preparation of this particular cysteine derivative has provided low-melting solids that are difficult to purify. In our early experiments VII was converted to the oxalate salt VIII for characterization purposes; subsequently VII was used directly in the following coupling step.

Since the acid-labile *tert*-butyl ether was required for the protection of the phenolic hydroxyl of Tyr_{19}, clearly either the *o*-NPS, the DpOC, or the Tr group was necessary for amino protection. Despite the fact that a number of separate steps are required for the preparation of *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosine dicyclohexylamine salt (IX), this group was preferable to the *o*-NPS group since *S*-trityl cleavage can sometimes occur when the *o*-NPS group of an *S*-trityl-L-cysteine peptide is removed from the amino terminus[9,10] or to the *N*-trityl group which is known to give lowered yields in the coupling steps because of steric hindrance. In the preparation of IX, *O*-*tert*-butyl-L-tyrosine was cleanly acylated by the action of [2-(*p*-diphenylyl)isopropyl]phenyl carbonate; IX was obtained in 61% yield and could readily be converted into the crystalline *N*-hydroxysuccinimide ester derivative (X) in 66% yield. The coupling reaction between X and the crude free base VII proceeded smoothly and afforded the tripeptide derivative, *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester (XI) in 76% yield. Alternatively, XI could be prepared from the crystalline oxalate salt VIII and the active ester X by using 2 equiv of *N*-methylmorpholine. Although both preparations exhibited identical behavior on tlc and essentially the same melting point, the product obtained from 2 equiv of base showed a slightly lower specific rotation and hence subsequent preparations were conducted using VII. Removal of the *N*-DpOC group was accomplished using the conditions described by Sieber and Iselin.[5] The free base XII was obtained as a ninhydrin-positive solid, homogeneous on tlc; cleavage over a 17-hr period gave better results than when shorter times were employed.

The choice of an amino protective group for asparagine-18 was complicated by the earlier observations of Sieber and Iselin concerning the DpOC derivative of L-asparagine. This derivative was obtained in rather low yield and exhibited low solubility in common solvents employed for coupling. Thus it appeared that *o*-nitrophenylsulfenyl-L-asparagine would provide better results despite the anticipated deblocking problems. *N*-*o*-Nitrophenyl-L-asparagine *N*-hydroxysuccinimide ester (XIVa) was prepared by the procedure of Walter, *et al.*;[11] the coupling reaction between XII and XIVa

(8) L. Zervas, D. Borovas, and E. Gazis, *J. Amer. Chem. Soc.*, **85**, 3660 (1963).

(9) W. C. Jones, Jr., Ph.D. Dissertation, University of North Carolina, June 1969.

(10) D. Brandenburg, *Tetrahedron Lett.*, 6201 (1966).

(11) C. Meyers, R. T. Havran, I. L. Schwartz, and R. Walter, *Chem. Ind. (London)*, 136 (1969).

proceeded readily in DME to provide *N*-*o*-nitrophenylsulfenyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester (XIIIa) in 88% yield.

Removal of the *o*-NPS group from XIIIa was studied rather carefully. Cleavage experiments in acetic acid, methanol–pyridine, or acetic acid–pyridine–DMF gave incomplete reaction. Treatment of XIIIa with thioglycolic acid in DMF gave no reaction; similar results were also obtained using *o*-nitrothiophenol.[10] Complete cleavage was finally observed using exactly 1 equiv of *o*-nitrophenylsulfenyl chloride in the presence of β-mercaptoethanol.[10] This reagent generated 1 equiv of hydrogen chloride and produced the hydrochloride salt of the tetrapeptide XVIIa, in 91% crude yield. The product was homogeneous on tlc, and colored impurities due to *S*-trityl cleavage[9,10] were not observed. The salt XVIIa was converted to the free base XVIIb and coupled with *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl-γ-*tert*-butyl-L-glutamic acid *N*-hydroxysuccinimide ester (XVI), obtained in 83% yield from the corresponding acid XV. When the reaction was carried out on a small scale, a good yield of the pentapeptide *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl-γ-*tert*-butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester (XVIII) was obtained. However, when the conversion of the *o*-NPS peptide XIIIa to the hydrochloride salt XVIIa was performed on a large scale, the resulting salt XVIIa was not homogeneous and mobile colored impurities were detected on tlc. Since purification of XVIIa from this preparation was difficult, the use of the *o*-NPS group was abandoned in favor of the *N*-trityl group. *N*-Trityl-L-asparagine *N*-hydroxysuccinimide ester (XIVb) was prepared in 52% yield and was allowed to react with XII in dioxane solution. The coupling reaction appeared to proceed smoothly and *N*-trityl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester (XIIIb) was obtained in 76% yield. Treatment of XIIIb with aqueous acetic acid at room temperature provided the free base XVIIb in 78% crude yield. The product was homogeneous on tlc and was coupled directly with XVI without further purification. The pentapeptide XVIII was obtained in reasonable yield (80%) and high purity as indicated by tlc, elemental, and amino acid analysis. Thus in subsequent experiments using larger quantities the route involving *N*-trityl-L-asparagine has been the method of choice.

At this point a second fragment corresponding to the A_{14-16} portion of III was prepared and coupled to the free base XXVII by the azide method. Initially *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutaminyl-L-leucine methyl ester (XXIII) was prepared from the *N*-hydroxysuccinimide ester (X) and *N*-*o*-nitrophenylsulfenyl-L-glutaminyl-L-leucine methyl ester (XXIV). Although the resulting tripeptide was obtained in fair yield and pure condition, the procedure was complicated by the hygroscopic nature of the dipeptide hydrochloride XXV resulting from the removal of the *o*-NPS group from XXIV with hydrogen chloride. Attempts to obtain a crystalline free base invariably led to diketopiperazine formation. More satisfactory results were obtained using the corresponding benzyl ester. Treatment of L-leucine benzyl ester *p*-toluenesulfonate salt with *N*-*o*-nitrophenylsulfenyl-L-glutamine *N*-hydroxysuccinimide ester[11] (XIX) provided *N*-*o*-nitrophenylsulfenyl-L-glutaminyl-L-leucine benzyl ester (XX) in 80% yield. Removal of the amino protective group proceeded smoothly and provided the crystalline hydrochloride of L-glutaminyl-L-leucine benzyl ester (XXI) in 92% yield. The dipeptide was then coupled with X to provide *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutaminyl-L-leucine benzyl ester (XXII) in 97% yield. Treatment of either the methyl ester XXIII or the benzyl ester XXII with hydrazine provided the same hydrazide derivative, *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl-*O*-*tert*-L-tyrosyl-L-glutaminyl-L-leucine hydrazide (XXVI). The substance was obtained as a gel which could be solidified by crystallization from alcohol and was homogeneous on tlc.

Formation of the azide from the hydrazide XXVI was now considered. In order to avoid any cleavage of the DpOC group, our initial diazotization experiments utilized 1 equiv of hydrogen chloride in DMF. Treatment of the azide, generated by this method, with the free base of the pentapeptide XXVII, obtained by acetic acid cleavage of the DpOC group XVIIIa, gave low yields of the desired octapeptide derivative, *N*-2-(*p*-diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl L-glutaminyl-L-leucyl-γ-*tert*-butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-trimethylbenzyl ester (III). However, subsequent control experiments with XXVI established that the DpOC group was stable to excess hydrogen chloride in THF–DMF mixtures at low temperatures (−20 to −40°). The coupling between the azide, prepared by the Rudinger method,[12] and the free base XXVII proceeded smoothly and provided good yields (75–85%) of the desired octapeptide III. The product was homogeneous on tlc and gave the expected elemental and amino acid analyses. Future experiments will deal with the formation of the fully blocked A chain and the combination of this material with an appropriate B chain.

Experimental Section[13]

N-*o*-Nitrophenylsulfenyl-L-asparagine.—L-Asparagine (79.2 g, 0.6 mol) was dissolved in 750 ml of dioxane, cooled to 5°, and treated with 300 ml of 2 *N* sodium hydroxide solution. The clear solution was treated simultaneously with 126 g (10% excess) of nitrophenylsulfenyl chloride and 360 ml of cold 2 *N* sodium hydroxide. The pH of the solution was maintained at 9–10. Vigorous stirring was continued for 2 hr at room temperature and 600 ml of water was added, and the reaction mixture filtered. The filtrate was acidified with cold 2 *N* sulfuric acid and the product washed with water to yield 154 g (92%) of yellow solid, mp 161–162°, homogeneous (system B) (lit.[8] mp 165–166°).

N-*o*-Nitrophenylsulfenyl-L-asparagine 2,4,6-Trimethylbenzyl Ester.—A solution of 46 g (0.16 mol) of *N*-*o*-nitrophenylsulfenyl-L-asparagine in 80 ml of DMF was treated with 22.5 ml of tri-

(12) J. Honzl and J. Rudinger, *Collect. Czech. Chem. Commun.*, **26**, 2333 (1961).

(13) Melting points are uncorrected. Combustion analyses were performed by Micro-Tech Laboratories, Skokie, Ill. Amino acid analyses were determined on a Beckman Model 116 amino acid analyzer and have not been corrected for destruction during hydrolysis. Thin layer chromatography (tlc) was conducted on silica gel GF_{254} with the following solvent systems: (A) chloroform–methanol (9:1); (B) chloroform–methanol–acetic acid (8:1:1); (C) 1-butanol–acetic acid–water (10:1:3); (D) *n*-heptane–*tert*-butyl alcohol–acetic acid–water–pyridine (25:70:6:24:20); (E) *sec*-butyl alcohol–3% ammonium hydroxide (7:3); (F) 1-butanol–acetic acid–water–pyridine (60:6:24:20). Unless otherwise stated products were dried *in vacuo* over phosphorus pentoxide and sodium hydroxide pellets.

ethylamine and 27.6 g (0.16 mol) of molten 2,4,6-trimethylbenzyl chloride. The clear solution was stirred 4 days at room temperature and diluted with cold 10% sodium bicarbonate solution. The crude product was filtered and washed with water; recrystallization from a cyclohexane–chloroform mixture provided 45.2 g (67.6%) of yellow solid, homogeneous (system D), mp 173–174° (lit.[14] mp 173–174°).

L-Asparagine 2,4,6-trimethylbenzyl ester hydrochloride (IV) was prepared by the procedure of Stewart in 69% yield, homogeneous (system B), mp 198–199° (lit.[14] mp 194.5–195.5°).

***N*-*tert*-Butyloxycarbonyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester (VI).**—A suspension of 12.86 g (0.02 mol) of *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteine dicyclohexylamine salt (V) and 6.02 g (0.02 mol) of L-asparagine 2,4,6-trimethylbenzyl ester hydrochloride (IV) in 140 ml of DMAc was cooled to −10° and treated with 2.3 g (0.02 mol) of *N*-hydroxysuccinimide and 4.2 g (0.02 mol) of DCC. The stirred suspension was allowed to warm to room temperature overnight and was stirred an additional 10 hr. The suspension was filtered into a cold brine solution and the filtrate extracted with ethyl acetate. The organic layer was washed with cold brine, cold 10% citric acid solution, cold 1 *M* sodium bicarbonate solution, and cold brine. The dried solid (13.6 g) was recrystallized from a petroleum ether–ether mixture to yield 12.0 g (84.6%) of white solid, mp 179–180°, $[\alpha]^{26}D$ +20.6° (*c* 1.4, methanol).

Anal. Calcd for $C_{41}H_{47}N_3O_6S$: C, 69.36; H, 6.67; N, 5.92; S, 4.51. Found: C, 69.18; H, 6.71; N, 6.01; S, 4.32.

***S*-Trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester (VII).**—The protected dipeptide VI was dissolved in 100 ml of glacial acetic acid and treated dropwise with 13 ml (0.1 mol) of boron trifluoride diethyl etherate at room temperature. After 2 hr the solution was diluted with cold water, treated with 34 g (0.3 mol) of sodium acetate, and precipitated by saturating the solution with sodium chloride. The resulting precipitate was filtered, washed with brine, partitioned between ethyl acetate and 10% sodium bicarbonate solution, and washed with water and brine. Removal of the solvent provided 14.6 g (85.2%) of white solid, homogeneous (system A). The material was used directly in the subsequent coupling reaction.

***S*-Trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester Oxalate Salt (VIII).**—An oxalate salt of VII was prepared in the following manner. A 10.79-g (0.0179 mol) sample of VII was dissolved in 10 ml of methanol and treated with 1.6 g (0.0177 mol) of anhydrous oxalic acid. The salt was precipitated with ether and recrystallized from methanol–ether to yield 7.8 g (56%) of white solid, $[\alpha]^{27}D$ +48.9° (*c* 1.65, methanol).

Anal. Calcd for $C_{38}H_{41}N_3O_8S$: C, 65.22; H, 5.91; N, 6.00; S, 4.58. Found: C, 64.68; H, 5.97; N, 6.06; S, 4.78.

***N*-2-(*p*-Diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosine Dicyclohexylamine Salt (IX).**—A solution containing 4.7 g (0.02 mol) of *O*-*tert*-butyl-L-tyrosine in 9.1 ml of Triton B (40% in methanol) was maintained at 50° and the methanol was evaporated. The remaining oil was carefully dried *in vacuo*, dissolved in 15 ml of DMF, and treated with 6.6 g (0.02 mol) of [2-(*p*-diphenylyl)isopropyl] phenyl carbonate.[5] The solution was stirred for 3 hr at 50° and then partitioned between water and ether. The aqueous layer was acidified at 0° with 10% citric acid solution and extracted with ether. The ether extract was washed, dried, and evaporated to an oil which was dissolved in ether and treated with 4 ml of dicyclohexylamine. The salt was recrystallized from isopropyl alcohol to yield 8.0 g (61.5%) of salt, mp 160–161°, $[\alpha]^{21}D$ +42.5° (*c* 1.2, methanol).

Anal. Calcd for $C_{41}H_{56}O_5N_2$: C, 74.96; H, 8.59; N, 4.26. Found: C, 74.74; H, 8.71; N, 4.22.

***N*-2-(*p*-Diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosine *N*-Hydroxysuccinimide Ester (X).**—A 18.38-g (0.028 mol) sample of the dicyclohexylamine salt IX was dissolved in ethyl acetate and extracted with 15% citric acid solution. The citric acid layer was reextracted with ethyl acetate, and the combined organic extracts were washed with citric acid solution, water, and brine. The dried organic layer was evaporated to an oil which was dissolved in 40 ml of 1,2-dimethoxyethane, cooled to 0°, and treated with 3.22 g (0.028 mol) of *N*-hydroxysuccinimide and 5.80 g (0.028 mol) of DCC. The reaction mixture was stirred for 3 hr at 0° and allowed to stand at 0° overnight. Evaporation of the filtrate provided a solid which was crystallized twice from isopropyl alcohol to yield 10.51 g (66%) of the active ester, mp 136–138°, $[\alpha]^{27}D$ −18.6° (*c* 1.7, methanol).

Anal. Calcd for $C_{33}H_{36}O_7N_2$: C, 69.21; H, 6.34; N, 4.89. Found: C, 69.09; H, 6.30; N, 4.82.

***N*-2-(*p*-Diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester (XI).**—A solution containing 4.52 g (0.0074 mol) of the *S*-trityl dipeptide in 30 ml of 1,2-dimethoxyethane was treated with 4.26 g (0.0074 mol) of the *N*-hydroxysuccinimide ester. Stirring was continued for 3 hr at room temperature. The solution was poured into ice water and filtered. The solid was washed with 10% sodium bicarbonate solution and water. Recrystallization from a methanol–water mixture provided 6.0 g (76.0%) of the protected tripeptide, mp 189–190° homogeneous (system A), $[\alpha]^{27}D$ −2.08 (*c* 1.25, DMF).

Anal. Calcd for $C_{65}H_{70}O_8N_4S$: C, 73.07; H, 6.69; N, 5.24; S, 3.00. Found: C, 72.93; H, 6.52; N, 5.24; S, 3.00.

The tripeptide XI could also be obtained from the oxalate salt VIII. To a solution of 6.99 g (0.01 mol) of VIII in 20 ml of DME at 0° was added 1.1 ml (0.02 mol) of *N*-methylmorpholine and 5.72 g (0.01 mol) of X. After 3 hr of stirring at 20° the oxalate salt of *N*-methylmorpholine was precipitated with water and the aqueous layer was extracted with chloroform. Evaporation of the solvent provided an oil which could be crystallized from a methanol–water–2-propanol mixture to yield 7.7 g (73%) of XI, mp 187–188°, $[\alpha]^{29}D$ −1.53 (*c* 1.25, DMF), homogeneous (system A).

Anal. Calcd for $C_{65}H_{70}N_4O_8S$: C, 73.07; H, 6.69; N, 5.24; S, 3.00. Found: C, 73.01; H, 6.74; N, 5.19; S, 2.86.

***O*-*tert*-Butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester (XII).**—A suspension of 3.6 g (3.34 mmol) of the fully blocked tripeptide in 75 ml of 80% acetic acid was vigorously stirred at room temperature for 17 hr. The solution was poured into 200 ml of cold brine and the product partitioned between 100 ml of ethyl acetate and 10% sodium bicarbonate, washed with water and brine, and dried. Removal of the solvent and recrystallization from isopropyl alcohol provided 2.69 g (97.9%) of white solid, mp 182–183°, homogeneous (system A), $[\alpha]^{26}D$ +6.9° (*c* 1.1, methanol).

Anal. Calcd for $C_{49}H_{56}O_6N_4S$: C, 70.90; H, 6.92; N, 6.75; Sk 3.86. Found: C, 70.99; H, 6.92; N, 6.84; S, 3.71.

***N*-*o*-Nitrophenylsulfenyl-L-asparagine *N*-Hydroxysuccinimide Ester (XIVa).**—A solution of 11.41 g (0.04 mol) of *N*-*o*-nitrophenylsulfenyl-L-asparagine in 40 ml of DMAc was cooled to 0° and treated with 4.61 g (0.04 mol) of *N*-hydroxysuccinimide and 8.7 g (0.04 mol) of DCC. The solution was stirred for 2 hr at 0° and stored in the cold overnight. The solution was filtered and washed with 2 ml of DMAc; the filtrate was poured into 600 ml of cold isopropyl alcohol. The yellow solid was filtered, washed with cold isopropyl alcohol, and dried to yield 8.9 g (59%) of the active ester, mp 150–151°, $[\alpha]^{26}D$ −51.1° (*c* 1, dioxane) [lit. mp 150–151°, $[\alpha]^{23}D$ −52.7° (*c* 1, dioxane)].

Anal. Calcd for $C_{14}H_{14}O_7N_4S$: C, 43.97; H, 3.69; N, 14.65; S, 8.38. Found: C, 43.88; H, 3.77; N, 14.49; S, 8.27.

***N*-*o*-Nitrophenylsulfenyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester (XIIIa).**—A solution containing 5.13 g (0.0062 mol) of the free base XII in 60 ml of 1,2-dimethoxyethane was treated, at room temperature, with 2.46 g (0.0062 mol) of the *N*-hydroxysuccinimide ester XIVa. The slurry was stirred overnight and filtered and the product washed with cold chloroform. Recrystallization from a chloroform–methanol solvent provided 6.0 g (88.5%) of tetrapeptide, mp 204–206°, homogeneous (system A), $[\alpha]^{27}D$ −22.8° (c 0.90 DMF).

Anal. Calcd for $C_{59}H_{65}O_{10}N_7S_2$: C, 64.57; H, 6.06; N, 8.93; S, 5.84. Found: C, 64.31; H, 5.86; N, 8.98; S, 5.92.

***N*-2-(*p*-Diphenylyl)isopropyloxycarbonyl-γ-*tert*-butyl-L-glutamic Acid Dicyclohexylamine Salt (XV).**—A solution containing 6 g (0.03 mol) of γ-*tert*-butyl-L-glutamic acid[15] in 13.6 ml of Triton B (40% in methanol) was maintained at 50° and the methanol was evaporated. The remaining oil was carefully dried *in vacuo*, dissolved in 20 ml of DMAc, and treated with 9.99 g (0.03 mol) of [2-(*p*-diphenylyl)isopropyl]phenyl carbonate. The solution was stirred for 3 hr at 50° and then partitioned between water and ether. The aqueous layer was acidified at 0° with 10% citric acid solution and extracted with ether. The ether extract was washed, dried, and evaporated to an oil which was dissolved in ethyl acetate and treated with 6 ml of dicyclohexylamine. The salt was recrystallized from an isopropyl alcohol–ether–petroleum

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(15) E. Schrocer and E. Klieger, *Justus Liebigs Ann. Chem.*, **673**, 196 (1964).

ether mixture to yield 12.0 g (65%) of the salt, mp 136–138°, $[\alpha]^{30}D$ +12.9° (c 1.7, methanol).

Anal. Calcd for $C_{37}H_{34}O_6N_2$: C, 71.35; H, 8.74; N, 4.50. Found: C, 71.17; H, 8.51; N, 4.37.

N-2-(p-Diphenylyl)isopropyloxycarbonyl-γ-*tert*-butyl-L-glutamic Acid N-Hydroxysuccinimide Ester (XVI).—A 6.22-g (0.01 mol) sample of the salt XV was partitioned between a 10% aqueous citric acid solution and ethyl acetate at 0°. The layers were separated and the aqueous phase extracted again with ethyl acetate. The organic layers were washed with 10% citric acid solution, water, and brine. The dried extract was concentrated to a clear oil which was dissolved in 20 ml of 1,2-dimethoxyethane and treated with 1.30 g (0.012 mol) of *N*-hydroxysuccinimide and 2.5 g (0.012 mol) of DCC at 0°. The mixture was stirred for 12 hr in an ice bath and stored overnight at 0°. Filtration and evaporation of the filtrate yielded an oil which crystallized on trituration with isopropyl alcohol to yield 4.5 g (83%) of the active ester, mp 117–118°, $[\alpha]^{30}D$ −24.9° (c 1.55, dioxane).

Anal. Calcd for $C_{29}H_{34}O_8N_2$: C, 64.67; H, 6.36; N, 5.20. Found: C, 64.75; H, 6.28; N, 5.12.

N-Trityl-L-asparagine N-Hydroxysuccinimide Ester (XIVb).—A solution of *N*-tritylasparagine[16] (2.6 g, 0.007 mol) in 30 ml of dioxane was cooled to 10° and treated with 0.88 g (0.0077 mol) of *N*-hydroxysuccinimide and 1.6 g (0.0077 mol) of DCC. The solution was stirred for 4 hr at 10° and was allowed to stand at 4° overnight. The dicyclohexylurea was filtered and washed with cold dioxane. The filtrate was concentrated *in vacuo* and the solid on crystallization from ethyl acetate–*n*-hexane provided 1.7 g (52%) of the active ester, mp 152–153°, $[\alpha]^{26}D$ −73.1° (c 1, dioxane).

Anal. Calcd for $C_{27}H_{25}O_5N_3$: C, 68.78; H, 5.30; N, 8.91. Found: C, 68.90; H, 5.47; N, 9.07.

N-Trityl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester (XIIIb).—A solution containing 2.49 g (0.003 mol) of the free base XII in 25 ml of dioxane was treated at room temperature with 1.9 g (0.004 mol) of the *N*-hydroxysuccinimide ester XIVb and stirred overnight. The dioxane was evaporated and the residue dissolved in chloroform, washed with 1 *N* sodium bicarbonate and water, and dried over sodium sulfate. Evaporation of the chloroform, trituration of the residue with ether, and crystallization from ethyl acetate–*n*-hexane provided 2.7 g (76%) of the tetrapeptide, mp 202–205°, homogeneous (system A), $[\alpha]^{26}D$ −13.3° (c 2, dioxane).

Anal. Calcd for $C_{72}H_{76}O_8N_6S$: C, 72.91; H, 6.47; N, 7.08; S, 2.76. Found: C, 72.87; H, 6.76; N, 7.04; S, 3.15.

L-Asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparaginyl 2,4,6-Trimethylbenzyl Ester (XVIIb).—A suspension of 1.0 g of the protected tetrapeptide XIIIb in a mixture of 10 ml of acetic acid and 2 ml of water was stirred at room temperature for 6 hr. The reaction mixture was diluted with brine and triturated (three 10-ml portions), and the resulting gum was partitioned between ethyl acetate and 1 *N* sodium bicarbonate. The ethyl acetate solution was washed with water, dried over sodium sulfate, and evaporated. The residue was triturated with ether to provide 0.62 g (78%) of the crude product, homogeneous (system B). The crude solid was used directly in the next step.

N-2-(p-Diphenylyl)isopropyloxycarbonyl-γ-*tert*-butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester (XVIIIb).—A solution of 0.471 g (0.0005 mol) of the crude tetrapeptide XVIIb and 0.54 g (0.001 mol) of the *N*-hydroxysuccinimide ester in dioxane was stirred for 24 hr at room temperature. The mixture was diluted with ice and 1 *N* sodium bicarbonate solution, followed by brine. The solid was filtered, washed with water, and triturated with ether to yield, after recrystallization from chloroform–hexane, 0.55 g (80%) of the product, mp 160–161°, homogeneous (system A), $[\alpha]^{24}D$ −8.6° (c 1, methanol).

Anal. Calcd for $C_{78}H_{91}O_{13}N_7S$: C, 68.54; H, 6.71; N, 7.17; S, 2.34. Found: C, 68.53; H, 6.66; N, 7.08; S, 2.40.

Amino acid analysis after performic acid oxidation and acid hydrolysis showed $Asp_{1.9}CySO_3H_{0.9}Glu_{1.0}$. Amino acid analysis of an acid hydrolysate in the presence of phenol showed $Asp_{2.0}$-$Glu_{1.0}Tyr_{1.0}$.

L-Asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester Hydrochloride Salt (XVIIa).—A suspension of 2.2 g (2.0 mmol) of the protected tetrapeptide in 80 ml of chloroform, containing 1 ml of β-mercaptoethanol, was stirred vigorously and treated with 0.568 g (3 mmol) of *o*-nitrophenylsulfenyl chloride in 40 ml of chloroform, containing 0.5 ml of β-mercaptoethanol. The suspension was stirred 30 min at room temperature, filtered, and evaporated. The residue was triturated with ether and the resulting hydrochloride salt (1.8 g), homogeneous in system A, was used directly in the following coupling reaction.

N-2-(p-Diphenylyl)isopropyloxycarbonyl-γ-*tert*-butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester (XVIIIa).—A solution of 1.77 g (1.8 mmol) of the crude tetrapeptide hydrochloride salt XVIIa and 1.08 g (2.0 mmol) of the *N*-hydroxysuccinimide ester was dissolved in 20 ml of 1,2-dimethoxyethane and at 0° treated with 0.25 ml of *N*-methylmorpholine. The mixture was stirred 24 hr at room temperature and diluted with water and the product filtered. The solid was washed with water and then triturated with ether to yield a gelatinous solid, 2.5 g (93%), mp 160° (recrystallized from chloroform–*n*-hexane), homogeneous (system A), $[\alpha]^{30}D$ −7.3° (c 1, methanol).

Anal. Calcd for $C_{78}H_{91}O_{13}N_7S$: C, 68.54; H, 6.71; N, 7.17; S, 2.34. Found: C, 68.64; H, 6.92; N, 7.05; S, 2.09.

Amino acid analysis after performic acid oxidation and acid hydrolysis showed $Asp_{1.9}CySO_3H_{1.0}Glu_{1.0}$. Amino acid analysis of an acid hydrolysate in the presence of phenol showed $Asp_{2.0}$-$Glu_{1.2}Tyr_{1.0}$.

γ-*tert*-Butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparaginyl 2,4,6-Trimethylbenzyl Ester (XXVII).—The blocked pentapeptide XVIIIa (2.3 g, 1.68 mmol) was dissolved in 20 ml of glacial acetic acid and after 24 hr diluted with 3 ml of water. The reaction mixture was stirred 36 hr at room temperature, and diluted with 200 ml of brine; the resulting semisolid was isolated by decantation. The product was dissolved in chloroform, washed with 2 *N* sodium bicarbonate and water, and dried. Evaporation and trituration of the solid with ether provided 1.8 g (95%) of the crude deblocked pentapeptide. The crude solid was used directly in the subsequent coupling reaction with the azide generated from XXVI.

N-*o*-Nitrophenylsulfenyl-L-glutamine N-Hydroxysuccinimide Ester (XIX).—A solution of 2.99 g (0.01 mol) of *N*-*o*-nitrophenylsulfenyl-L-glutamine in 20 ml of DMAc was treated at 0° with 1.15 g (0.01 mol) of *N*-hydroxysuccinimide and 2.06 g (0.01 mol) of DCC. After stirring 3 hr at 0° the reaction was stored at 0° overnight, filtered and diluted with 200 ml of isopropyl alcohol. Recrystallization of the solid from isopropyl alcohol provided 3.2 g (79%) of the active ester, mp 146–148°, $[\alpha]^{25}D$ −55.6° (c 2.0, DMF) (lit.[10] mp 142–146°).

N-*o*-Nitrophenylsulfenyl-L-glutaminyl-L-leucine Benzyl Ester (XX).—A solution containing 7.92 g (0.02 mol) of the active ester and 7.86 g (0.02 mol) of L-leucine benzyl ester *p*-toluenesulfonate salt in 120 ml of 1,2-dimethoxyethane was cooled to 0° and treated with 2.2 ml of *N*-methylmorpholine. The reaction mixture was stored overnight at room temperature, the solvent removed, and the residue dissolved in ethyl acetate. The solution was washed with water, 10% sodium bicarbonate, and water. Removal of the solvent and trituration of the residue with cold ether provided 8.1 g (80.5%) of product, mp 116–120°, $[\alpha]^{21}D$ −54.6° (c 1, methanol).

Anal. Calcd for $C_{24}H_{30}O_6N_4S$: C, 57.82; H, 6.01; N, 11.16; S, 6.38. Found: C, 57.82; H, 6.07; N, 10.78; S, 6.34.

L-Glutaminyl-L-leucine Benzyl Ester Hydrochloride Salt (XXI).—A solution of 5.5 g (0.011 mol) of the dipeptide derivative in 15 ml of methanol was treated with 5 ml of 4 *N* hydrogen chloride in methanol solution. The reaction mixture was stirred for 5 min and evaporated; the resulting oil was triturated with ether. The solid was recrystallized from a chloroform–ether mixture to yield 3.9 g (92%) of product, mp 151–152°, $[\alpha]^{23}D$ −10.6° (c 1, methanol).

Anal. Calcd for $C_{18}H_{28}ClO_4N_3$: C, 55.93; H, 7.04; N, 10.92. Found: C, 55.90; H, 7.25; N, 11.01.

N-2-(p-Diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutaminyl-L-leucine Benzyl Ester (XXII).—A solution of the hydrochloride (3.1 g, 8 mmol) was dissolved in 15 ml of DMAc and cooled to 0°. The cold solution was treated with 4.6 g (8 mmol) of the active ester and 0.9 ml of *N*-methylmorpholine and allowed to stir overnight at room temperature. The reaction mixture was diluted with cold water and filtered and the product washed with water. The product appeared as 6.3 g (97%) of white solid, mp 150–151°, $[\alpha]^{23}D$ −15.4° (c 1, methanol), homogeneous (system A).

(16) L. Zervas and D. M. Theodoropoulos, *J. Amer. Chem. Soc.*, **78**, 1359 (1956).

Anal. Calcd for $C_{47}H_{58}O_8N_4$: C, 69.90; H, 7.24; N, 6.94. Found: C, 70.17; H, 7.26; N, 7.03.

***N*-o-Nitrophenylsulfenyl-L-glutaminyl-L-leucine Methyl Ester (XXIV).**—A mixture containing 3.2 g (0.008 mol) of XIX and 1.5 g (0.008 mol) of leucine methyl ester hydrochloride salt in 25 ml of DME was cooled to 0°, treated with 1.2 ml (0.008 mol) of triethylamine, and stirred for 2 hr at room temperature. The reaction mixture was diluted with water and the product was extracted with chloroform and washed with 10% $NaHCO_3$, 0.2 *N* sulfuric acid, and H_2O. Evaporation of the solvent gave a crude product which on recrystallization from methanol–ether yielded 2.5 g (73%) of product, mp 124–125°, $[\alpha]^{25}D$ +6.35 (c 2, DMF), homogeneous (system A).

Anal. Calcd for $C_{18}H_{26}O_6N_4S$: C, 50.70; H, 6.10; N, 13.14; S, 7.51. Found: C, 51.24; H, 6.26; N, 13.30; S, 7.47.

Diketopiperazine of XXIV.—A solution of 2.13 g (0.005 mol) of XXIV in 5 ml of MeOH was treated with 2.5 ml of 4 *N* HCl in absolute methanol. The reaction mixture was stirred for 3 min and diluted with ether. The clear solution was decanted, and the remaining oil on trituration with ether provided a white hygroscopic solid. The semisolid was dissolved in 5 ml of H_2O, neutralized with saturated $NaHCO_3$ solution, and extracted with chloroform. The chloroform was removed and the bicarbonate solution cooled to yield the diketopiperazine derivative, 0.73 g (44%), mp 239–240° (recrystallized from methanol–chloroform).

Anal. Calcd for $C_{11}H_{19}O_3N_3$: C, 54.77; H, 7.88; N, 17.49. Found: C, 54.43; H, 7.87; N, 17.45.

***N*-2-(*p*-Diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutaminyl-L-leucine Hydrazide (XXVI).**—The tripeptide benzyl ester XXII (0.8 g, 1.0 mmol) was dissolved in 10 ml of dry methanol and treated with 1.3 ml of hydrazine monohydrate (90%). The solution was stirred for 5 days at room temperature and diluted with ether and the resulting solid collected. The product was washed with ether and recrystallized from a methanol–ether mixture to yield 0.62 g (85%) of solid, mp 183–184°, homogeneous (system A), $[\alpha]^{25}D$ −11° (*c* 1.05, MeOH).

Anal. Calcd for $C_{40}H_{54}O_7N_6$: C, 65.73; H, 7.45; N, 11.50. Found: C, 65.27; H, 7.39; N, 11.31.

***N*-2-(*p*-Diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutaminyl-L-leucyl-γ-*tert*-butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine 2,4,6-Trimethylbenzyl Ester (III).**—A solution of the hydrazide (0.6 g, 0.81 mmol) in 30 ml of DMF was cooled to −20° and treated with 2.2 ml of 3 *N* hydrogen chloride in tetrahydrofuran solution. The temperature was lowered to −40° and 0.11 ml of *n*-butyl nitrite was added dropwise. The reaction mixture was stirred at −20 to −25° for 40 min, cooled to −60°, and treated with 0.8 ml of *N*-methylmorpholine. The solution of the azide at −40° was treated with a precooled (−40°) solution of the pentapeptide (0.9 g, 0.8 mmol) in 10 ml of DMF. The stirring was continued for 1 hr at −30 to −20° and in an ice bath (0–2°) for 3.5 days.

The reaction mixture was diluted with ice water and saturated with sodium chloride. The separated product was washed with water, dried, and triturated with ether. A chloroform solution of the octapeptide derivative was applied to a silica gel column and eluted with chloroform–methanol (98:2). The product was collected and recrystallized from chloroform–petroleum ether to yield 1.2 g (82%) of white solid, $[\alpha]^{28}D$ −13.2° (*c* 0.5, DMF).

Anal. Calcd for $C_{102}H_{128}O_{18}N_{11}S \cdot 2H_2O$: C, 65.71; H, 7.13; N, 8.26; S, 1.72. Found: C, 65.80; H, 7.05; N, 7.98; S, 1.85.

The amino acid analysis of a performic acid oxidized, acid hydrolysate was $Asp_{2.1}CysSO_3H_{1.1}Glu_{2.2}Leu_{1.0}$. The amino acid analysis of an acid hydrolysate in the presence of phenol was $Asp_{2.0}Glu_{2.0}Leu_{1.0}Tyr_{2.0}$.

***N*-2-(*p*-Diphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutaminyl-L-leucine Methyl Ester (XXIII).**—A solution of the crude hydrochloride XXV (2.07 g, 6.7 mmol) in 40 ml of DME and 4.13 g (6.7 mmol) of the active ester X was treated at 0° with 0.75 ml (6.7 mmol) of *N*-methylmorpholine, stirred overnight at room temperature, and diluted with water. The product was extracted with chloroform and washed with cold 1 *N* sodium hydroxide solution, water, 0.2 *N* sulfuric acid, and water. Evaporation of the chloroform and crystallization from a mixture of methanol–ethyl acetate gave 1.6 g (33.2%) of the tripeptide, mp 161–163°, $[\alpha]^{30}D$ −7.33° (*c* 1.65, DMF).

Anal. Calcd for $C_{41}H_{54}O_5N_4$: C, 67.37; H, 7.45; N, 7.67. Found: C, 67.33; H, 7.30; N, 7.58.

***N*-2-(*p*-Diphenylyl)isopropyloxycarbonyl-*o*-*tert*-butyl-L-tyrosyl-L-glutaminyl-L-leucine Hydrazide (XXVI).**—A solution of the methyl ester XXII (0.82 g 1.12 mmol) in 20 ml of methanol was stirred with 1.3 ml of hydrazine monohydrate at 50° for 1 hr and an additional 2 hr at 30°. Dilution with ether afforded 0.67 g (87%) of the product which on recrystallization frm ethanol melted at 180–182°.

Registry No.—III, 33608-46-7; VI, 30806-18-9; VIII, 30806-19-0; IX, 33532-10-4; X, 33527-03-6; XI, 33527-04-7; XII, 33527-05-8; XIIIa, 33608-48-9; XIIIb, 33527-06-9; XIVa, 21753-83-3; XIVb, 33527-08-1; XV, 25461-15-8; XVI, 33527-10-5; XVIII, 33527-11-6; XX, 33527-12-7; XXI, 33527-13-8; XXII, 33527-14-9; XXIII, 33527-15-0; XXIV, 33527-16-1; XXIV diketopiperazine, 33527-17-2; XXVI, 33527-18-3.

Electroreduction of Diphenyliodonium, Dibenziodolium, and 4,5-Phenanthryleneiodonium Ions[1]

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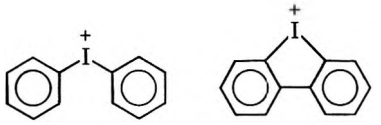
Received November 19, 1971

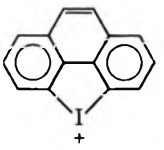
The electroreduction of diphenyliodonium (1), dibenziodolium (2), and 4,5-phenanthryleneiodonium (3) ions has been investigated by both polarography at the dropping mercury electrode and by coulometry at controlled potential. Ions 1 and 2 appear to undergo three reduction processes corresponding to the total uptake of one, two, and four electrons, respectively. The polarographic behavior of ion 1 was affected by its concentration and by the nature and concentration of the supporting electrolyte and the maximum suppressor. For all three species controlled-potential electrolysis on wave I gave mercury-containing products. Ion 3 appears to undergo only two electroreduction processes, corresponding to the uptake of two and of three electrons. An attempt is made to explain this result in terms of the structure and behavior of free-radical intermediates.

The electrochemical reduction of iodonium salts has been investigated by three different groups over the past 20 years,[2,3] and at least four different schemes have been proposed to account for the processes occurring at the dropping mercury electrode in the course of the reduction.[2-4] Further, some question has recently arisen[3] concerning the products of the electrochemical reduction of the diphenyliodonium ion.

The aim of the present work was to clarify and compare the processes occurring during the electroreduction of the diphenyliodonium ion (species 1), the dibenziodolium ion (species 2), and the 4,5-phenanthryleneiodonium ion (species 3) at the mercury cathode. To accomplish this, we have employed reduction at the dropping mercury electrode as well as coulometry at controlled potential.



1 2



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Results

Diphenyliodonium Ion (1). Polarography.—The polarogram of 1 was sensitive to its concentration and to the nature and concentration of the supporting electrolyte and of the maximum suppressor. A previous report[2b] stated that in a tetraethylammonium phosphate (TEAP) buffer of pH 7.45 (less than 1×10^{-3} *M* in 1) the polarogram consisted of three waves whose heights were in the ratio 1:1:2. Up to concentrations of 8×10^{-3} *M* in 1 the polarogram did not change significantly except for slight shifts in half-wave potentials. The polarogram was reported to be unaffected by changes in the supporting electrolyte. That work was carried out by using 0.02% gelatin as a maximum suppressor. In the present work 0.002% Triton x-100 (a polyethylene glycol ether of monoisooctyphenol) was employed, but all other conditions were identical. These results are reported in Table I.

In the TEAP buffer at concentrations of 1 below 1×10^{-3} *M* the polarogram consisted of only two waves (waves IA and II/III) whose half-wave potentials were −0.13 and −1.36 V (*vs.* Ag/AgCl), respectively. The wave heights were in the ratio 1:3. In the citrate buffer[5] at similar concentrations of 1 the polarogram showed three waves, IA, II, and III, whose heights were in the ratio 1:1:2 and whose half-wave potentials were −0.13, −1.17, and −1.53 V, respectively. As the concentration of 1 was increased beyond 1×10^{-3} *M*, another wave (IB) appeared at −0.53 V. Above this concentration the height of wave IA remained virtually constant while wave IB increased in height. The combined height of waves IA and IB increased proportionally with the concentration of 1. This effect was observed in both the TEAP and citrate buffers. In TEAP at a 4×10^{-3} *M* concentration of 1 wave II/III divided into two waves of equal height (waves II and III) whose half-wave potentials were −1.03 and −1.53 V, respectively. The $E_{1/2}$ of wave 1A was shifted to less negative potentials with increasing concentration of 1. At a 5×10^{-4} *M* concentration of 1 in TEAP the slope of wave IA was 91.02 mV.

Measurements correlating the heights of waves IA and IB with mercury column height are reported in Table II. These results indicate that when only wave 1A appears, its height varies as does $(h_{corr})^{1/2}$. When both IA and IB appear, the height of IA varies more closely as does h_{corr}. The height of waves IA and IB combined varies approximately as does $(h_{corr})^{1/2}$.

In order to compare our present results with those previously reported,[2b] we recorded the polarogram of 1 in both buffer systems employing 0.02% gelatin as a suppressor (Table I). Wave IB was completely suppressed by the gelatin even at concentrations of 1 as high as 0.010 *M*. At a concentration of 1 of 5×10^{-4} *M* in TEAP only two waves (IA and II/III) were observed when no suppressor whatever was present.

Diphenyliodonium Ion (1). Electrolysis at Controlled Potential.—Electrolyses were carried out at a potential on the plateau between waves IA and IB

(1) Taken from the dissertation of S. Messing in partial fulfillment of the degree of Doctor of Philosophy (Chemistry), 1972.

(2) (a) E. L. Colichman and H. P. Maffei, *J. Amer. Chem. Soc.*, **73**, 2744 (1951); (b) H. E. Bachofner, F. M. Beringer, and L. Meites, *ibid.*, **80**, 4269 (1958).

(3) J. A. Azoo, F. G. Coll, and J. Grimshaw, *J. Chem. Soc. C*, 2521 (1969).

(4) S. Wawzonek, *Anal. Chem.*, **26**, 65 (1954).

(5) P. J. Elving, J. M. Markowitz, and I. Rosenthal, *ibid.*, **28**, 1179 (1956).

TABLE I

HALF-WAVE POTENTIALS ($E_{1/2}$) OF IODONIUM SALTS

Ion	[Ion][a]	pH	Electrolyte	IA	IB	II	II/III[b]	III	Ratio[c] of I:II:III
1	4×10^{-4}	7.45	0.1 *M* TEAP	−0.13			−1.36		1:3
1	1×10^{-3}	7.45	0.1 *M* TEAP	−0.13			−1.35		1:3
1	2×10^{-3}	7.45	0.1 TEAP	−0.08	−0.53		−1.35		1:3
1	4×10^{-3}	7.45	0.1 *M* TEAP	−0.06	−0.53	−1.03		−1.44	1:1:2
1	1×10^{-3}	8.0	0.003 *M* Citrate	−0.13		−1.17		−1.53	1:1:2
1	2×10^{-3}	8.0	0.003 *M* Citrate	−0.10	−0.53	−1.22		−1.53	1:1:2
1	3×10^{-3}	8.0	0.003 *M* Citrate	−0.09	−0.53	−1.22		−1.53	1:1:2
1[d]	5×10^{-4}	7.45	0.1 *M* TEAP	−0.20			−1.25		1:3
1[e]	5×10^{-4}	7.45	0.1 *M* TEAP	−0.15		−1.03		−1.43	1:1:2
1[e]	1×10^{-3}	7.45	0.009 *M* Citrate	−0.14		−1.00		−1.47	1:1:2
2	$4.0\text{–}8.0 \times 10^{-4}$	7.45	0.1 *M* TEAP		−0.60		−1.20		1:3
2	4×10^{-4}	7.45	0.009 *M* Citrate		−0.62	−1.17		−1.42	1:1:2
2	8×10^{-4}	8.0	0.003 *M* Citrate		−0.65	−1.17		−1.46	1:1:2
3[d]	$\sim 1 \times 10^{-4}$	8.0	0.05 *M* Potassium phosphate		+0.016	−0.78			1:1

[a] In mol/l. [b] Actually a composite of waves II and III. [c] When both waves IA and IB are present, the combined height is used. [d] Without suppressor. [e] With 0.02% gelatin as maximum suppressor.

TABLE II

INFLUENCE OF MERCURY PRESSURE ON WAVE HEIGHT POLAROGRAM OF DIPHENYLIODONIUM ION

Wave	Potential, V	$[Ph_2I^+]$, m*M*	h_{corr}, cm	Time, sec	Diffusion current, μA	100 (id/h)	100 ($id/h^{1/2}$)
IA	−0.13	2	62.8	5.07	1.005	1.60	1.27
			82.8	3.90	1.275	1.54	1.40
			92.8	3.48	1.420	1.53	1.48
			102.8	3.15	1.575	1.53	1.55
IA	−0.35	0.5	62.8	5.07	0.0776	0.1235	0.9810
			82.8	3.90	0.0864	0.1043	0.950
			92.8	3.48	0.0928	0.1000	0.965
			102.8	3.15	0.0992	0.0965	0.978
IA + IB	−0.75	2	62.8	5.13	5.10	8.12	64.5
			82.8	3.90	5.70	6.88	62.6
			92.8	3.48	6.21	6.69	64.6
			102.8	3.15	6.57	6.39	64.8

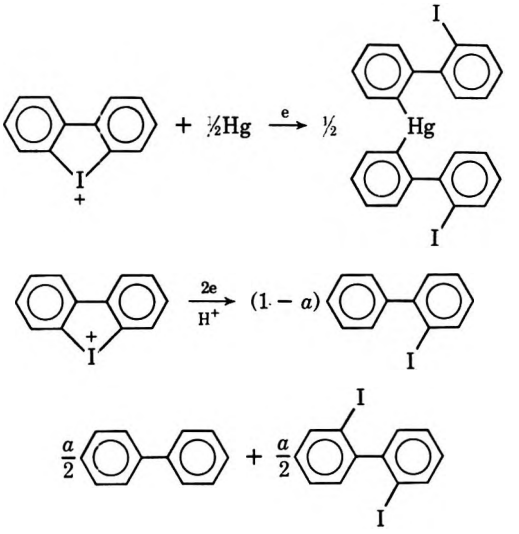
(−0.20 to −0.40 V). A value of 0.92 mfaraday/mmol was observed. A determination carried out at a potential between waves IB and II (−0.40 to −0.60 V) gave a value of 0.98 mfaraday/mmol. In both cases the only products found were iodobenzene (vpc) and diphenylmercury. The amounts of these products accounted for virtually all of **1**. Determinations carried out on the plateau between waves II and III (−1.20 to −1.30 V) gave a value of 1.92 mfaraday/mmol. The only products obtained were iodobenzene and benzene.

$$\text{Wave I:}\quad Ph_2I^+ + {}^1/_2Hg \xrightarrow{e} {}^1/_2Ph_2Hg + PhI$$

$$\text{Wave II:}\quad Ph_2I^+ + H^+ \xrightarrow{2e} PhH + PhI$$

Dibenziodolium Ion (2).—The results of the polarographic measurements made on this species are reported in Table I. Low solubility of **2** prevented measurements at concentrations higher than 1.6×10^{-3} *M*. There was no wave IA observed for **2** (*i.e.*, no wave with $E_{1/2} \sim -0.13$ V). The first wave is therefore designated as IB. As with species **1** only one wave appears between −1.0 and −2.0 V in the TEAP buffer, while two waves are observed in this region in the citrate buffer.

Electrolyses at controlled potential on the plateau between waves IB and II (−0.6 to −0.8 V) gave a value of 1.06 mfaraday/mmol and afforded biphenyl, 2-iodobiphenyl, and 2,2′-diiodobiphenyl as minor products.



Evidence strongly suggests that the second electron needed for the formation of these products is acquired through reduction by mercury. A white solid containing both iodine and mercury obtained as the major product (*ca.* 70%) is tentatively identified as impure bis-2-

(2′-iodobiphenylyl)mercury (see Experimental Section). Electrolysis on the plateau between waves II and III (−1.20 to −1.30 V) gave a value of 1.98 mfaraday/mmol. The products obtained after such electrolyses were biphenyl, 2,2′-diiodobiphenyl (*ca.* 95% combined) and, as a minor component, biphenylene.

4,5-Phenanthryleneiodonium Ion (3).—Because of the low solubility of the iodonium bisulfate **3** in the phosphate buffer, polarograms were obtained only at concentrations of about 1×10^{-4} *M*. In a potassium phosphate buffer of pH 8.0 the polarogram consisted of two waves of equal height, whose half-wave potentials were at 0.16 and −0.78 V, respectively.

Electrolysis at controlled potential on the plateau of wave I (−0.6 to −0.8 V, 1.97 mfaraday/mmol) afforded phenanthrene (vpc analysis) as well as a brown solid with a decomposition temperature of about 300°. The properties and behavior of this mercury-containing material are presented and discussed in the Experimental Section. Electrolysis on the plateau of wave II (−1.20 to −1.30 V) gave a value of 3.13 mfaraday/mmol. The only organic products obtained were phenanthrene and a trace amount of the brown solid.

Discussion

Diphenyliodonium Cation.—There are two principal differences between the polarograms reported here and those previously reported:[2b] (1) the appearance of wave IB at −0.53 V at concentrations of **1** as low as 1×10^{-3} *M*, and (2) the appearance of only one wave between −1.0 and −2.0 V in TEAP at low concentrations of **1**. Both differences may be attributed to the different nature and concentration of the maximum suppressors. This is evidenced by the fact that we were able to duplicate the previous results when 0.02% gelatin was substituted for 0.002% Triton x-100. It appears that a concentration of 0.02% gelatin was sufficiently high to distort the polarogram of **1**. A concentration of 0.005% is presently recommended[6a] as being adequate. A concentration of 0.01% is considered by some[6b] to be maximal. It is well known that too high a concentration of suppressor may completely obscure the appearance of a wave or in some other way distort the polarogram.[6b] Polarograms of **1** obtained in the absence of any suppressor (Table I) were like those obtained using 0.002% Triton x-100, including wave IB and the region from −1.0 to −2.0 V. We are reasonably certain, then, that the 0.002% Triton is not distorting the polarogram or obscuring any waves.

Of particular interest is the behavior of waves IA and IB. Both the concentration dependence and the data in Table II (see previous section) would indicate that wave IA is an adsorption wave whereas wave IB is the "true" or "normal" wave corresponding to the formation of products in solution.[6c]

The formation of diphenylmercury during the electrolysis at controlled potential indicates the presence of a mercury intermediate. The presence of such intermediates has been subjected to debate for some time.[2-4] We propose the following processes to account for waves IA and IB.

$$\text{Wave IA:}\quad Ph_2I^+ \text{ (adsorbed)} + e \xrightarrow{Hg} Ph_2\dot{I} \text{ (adsorbed)}$$

$$\text{Wave IB:}\quad Ph_2I^+ \text{ (dissolved)} + e \longrightarrow Ph_2\dot{I} \text{ (dissolved)}$$

Wave IB is observed when the surface of the mercury has become "saturated" with the adsorbed product. The decomposition of the adsorbed diphenyliodine results mainly in the formation of phenylmercury radicals and iodobenzene. The formation of (dissolved) diphenyliodine results mainly in the formation of iodobenzene and phenyl radicals.

$$Ph_2\dot{I} \text{ (adsorbed} \longrightarrow PhHg\cdot + PhI$$

$$Ph_2\dot{I} \text{ (dissolved)} \longrightarrow Ph\cdot + PhI$$

Formation of diphenylmercury can then result from either disproportionation of the phenylmercury radical or by its reaction with phenyl free radicals.

$$2PhHg\cdot \longrightarrow Ph_2Hg + Hg$$

$$PhHg\cdot + Ph\cdot \longrightarrow Ph_2Hg$$

The occurrence of adsorption has already been indicated in cyclic voltammetric measurements on solutions of **1**.[7] The involvement of mercury in wave IA is further indicated by the absence of the latter when platinum[8] or graphite is substituted for mercury.

The slope of wave IA as well as its shift in position with increasing concentration would indicate that it is not reversible.

The overall reaction taking place at wave II may be written as

$$\text{Wave II:}\quad Ph_2I^+ + 2e + H^+ \longrightarrow PhH + PhI$$

We may also consider wave II to be due to the reduction of the phenylmercury radical formed upon reduction of **1** at wave I.

$$PhHg\cdot + e + H^+ \longrightarrow PhH + Hg$$

A previous study of the electroreduction of phenylmercuric compounds[9] has shown that these compounds do exhibit a second cathodic wave in the region of wave II. This wave supposedly corresponds to the reduction of PhHg·. A polarogram of a solution containing equal concentrations (6×10^{-4} *M*) of phenylmercuric chloride and diphenyliodonium chloride showed only one wave in this region with an $E_{1/2}$ of −1.22 V. The presence of phenylmercuric radicals after electrolysis on wave I as well as the known reducibility of such radicals at the potential of wave II would indicate that the reduction of PhHg· is responsible for the second wave. The products obtained after electrolysis on the plateau of this wave as well as the results of coulometry confirm this.

The overall process at wave II may be written as

$$\text{Wave III:}\quad Ph_2I^+ + 4e + 2H^+ \longrightarrow 2PhH + I^-$$

This is consistent with the previous report[2] and with our present wave height and coulometry measure-

(6) (a) L. Meites, "Polarographic Techniques," Wiley, New York, N. Y., 1965, p 322; (b) p 325; (c) p 187.

(7) W. C. Danen and D. G. Saunders, *J. Amer. Chem. Soc.*, **91**, 5924 (1969).

(8) O. A. Pitsyna, S. I. Orlov, and B. A. Reutov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1947 (1966); *Chem. Abstr.*, **66**, 74533 (1967).

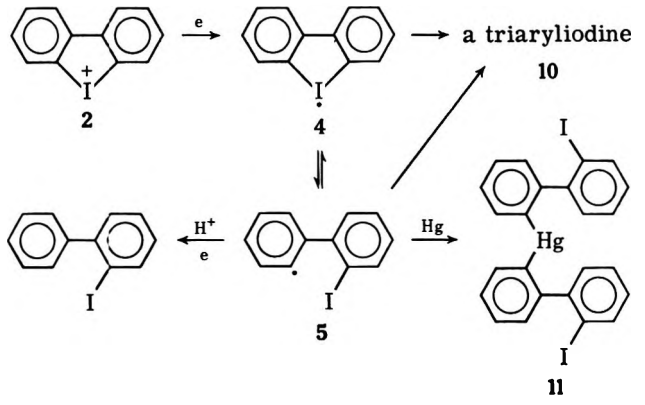
(9) R. Benesch and R. E. Benesch, *J. Amer. Chem. Soc.*, **73**, 3391 (1951).

ments. The third wave (III) may also be considered to be due to the reduction of iodobenzene.

$$PhI + 2e + H^+ \longrightarrow PhH + I^-$$

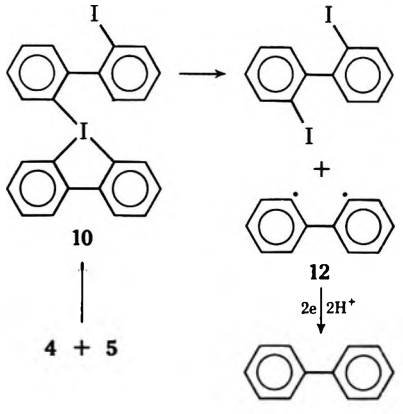
It has been shown[2b,10] that iodobenzene is reduced at this potential and that two electrons per molecule are involved. Iodobenzene is stable at the potentials of both waves I and II, as indicated by its presence after electrolysis at wave II.

Dibenziodolium Ion (2).—The polarogram of this species did not show a IA wave. However, a wave appeared in the same general region as did the IB wave for **1**. It is likely, then, that similar processes are occurring in both cases, namely the formation and further reaction of a diaryliodine radical. The main product (*ca.* 70%) is a diarylmercury, **11**, arising from



the reaction of radical **5** with mercury. This compound is accompanied by smaller amounts of related diarylmercury compounds with one or no iodines (*m/e* 634 and 508, respectively). A minor product, 2-iodobiphenyl, is apparently formed by the further reduction of radical **5**.

In addition there are products whose formation involves iodine transfer: biphenyl and 2,2′-diiodobiphenyl. It is suggested that these are formed by the coupling of **4** and **5** to give a triaryliodine, **10**, whose subsequent homolysis may result in overall iodine transfer.



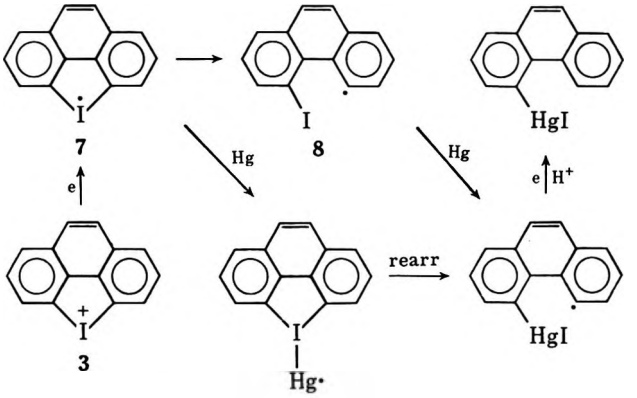
The formation of iodobiphenyl and biphenyl at this potential requires a source of electrons other than the electrode. The mass spectroscopic observation of mercuric iodide (*m/e* 456 and 329) in the solid product strongly supports the involvement of mercury as a reducing agent. Since species **2** does not itself react with mercury, this reduction must occur after the initial electrode reduction.

Wave II may result from the reduction of the biphenylene diradical **12**. Here again, some reduction by mercury may occur.

The third wave of the polarogram of **2** may correspond to the reduction of 2-iodobiphenyl to biphenyl.

4,5-Phenanthryleneiodonium Ion (3).—The polarogram of this species was different from those of **1** and **2** in that under no circumstances did it show three waves. In the phosphate buffer two waves were observed whose wave heights were in the ratio 1:1. Coulometry showed these waves to correspond to the uptake of two and of three electrons, respectively, through the circuit. The products of the electrolysis were also different in that no aryl iodide was obtained.

The mass spectroscopic data obtained from the brown solid (see following section) as well as those obtained from its thermal and chemical degradation products suggest a mixture of phenanthrene derivatives containing mercury, specifically, 4-phenanthrylmercuric iodide and di-4-phenanthrylmercury. From the weights of material obtained and the elemental analysis it is calculated that this mixture accounts for *ca.* 75% of the starting quantity of **3**. The absence of any products in which both mercury and iodine were bound to the 4 and 5 positions of phenanthrene is understandable in view of the steric requirements of the two large atoms. For wave I we may then write



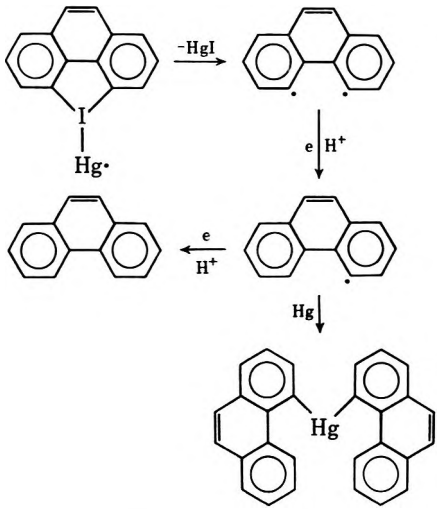
Homolysis of **7** would yield a 5-iodo-4-phenanthryl free radical, **8**, whose reaction with mercury (perhaps involving several steps) and subsequent reduction would give 4-phenanthrylmercuric iodide.

The cyclic iodine **7** may also react with mercury to give a trisubstituted iodine, whose rearrangement and further reduction may also give 4-phenanthrylmercuric iodide.

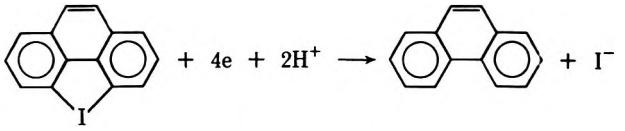
Still unexplained, however, is the formation of phenanthrene and the apparent intermediacy of the 4-phenanthryl free radical under the conditions of wave I (uptake of two electrons from the electrode). A partial answer may lie in the oxidation of mercury to mercuric iodide, followed by reduction of the 4,5-phenanthrylene diradical.

The formation of phenanthrene from the scheme below requires the uptake of three electrons. At the potential of wave I only two of these may come from the electrode. In analogy with the pathway suggested for species **2**, a reduction by mercury after the initial electrode reduction is proposed, although specific intermediates are not offered at this time.

(10) A. Gergely and T. Iredale, *J. Chem. Soc.*, 13 (1951).



We may also note that, while the ratio of wave heights in the polarogram of **3** is 1:1, the coulometry measurements indicate that two electrons are consumed on the first wave while only one additional (a total of three) electron is consumed on wave II. This discrepancy arises from the different natures of the polarographic and large-scale reduction experiments. The reduction of **3** to phenanthrene and iodide ion requires four electrons.



3

In the polarographic reduction this is apparently accomplished in two two-electron steps (waves I and II). In the large-scale electrolysis, however, where mercury is acting as a reducing agent as well, only about three quarters of the needed electrons are coming from the electrode, the rest being supplied by mercury. Since the coulometer only records the passage of electrons through the circuit, this latter reduction is unrecorded.

Experimental Section

Materials.—Iodonium salts were prepared by well-known routes and converted to the tosylate and fluoroborate by metathesis.[11-13] The 4,5-phenanthryleneiodonium salt was prepared by a recently published synthesis.[14]

Tetraethylammonium hydroxide was of Eastman White Label grade. Inorganic chemicals were CP, reagent, or NF grade. Water was distilled in all-glass equipment. Mercury was triple distilled. Triton x-100 (Rohm and Haas Co.) was diluted to make a 0.1% stock solution. Gelatin was highest purity grade supplied by Fisher Scientific Co. Prepurified nitrogen was bubbled through solutions of chromous chloride in order to remove any traces of oxygen.

Supporting Electrolytes.—Tetraethylammonium phosphate (TEAP) (0.1 *M*) was prepared by neutralizing the base to pH 7.45 with phosphoric acid. Dilution with an equal volume of water did not change the pH. Citrate buffers were prepared as outlined in ref 5. The potassium phosphate buffers used for electrolysis of species 1 and 2 were made as follows: 400 ml of 0.1 *M* KH_2PO_4, 370 ml of 0.1 *M* NaOH, total volume, 1 l., pH 8.0; for species 1 the buffer was also 1 *M* in KCl; for species 2, the buffer was made 0.5 *M* in K_2SO_4. The polarograms in both cases were identical with those in the citrate medium. Electrolyes of **3** were carried out in a phosphate buffer, pH 8.0, containing no additional salt.

Equipment and Procedures.—Polarograms were recorded on a Sargeant Model XXI automatically recording polarograph. A conventional H cell with a Ag/AgCl anode was employed in all measurements. Samples were thoroughly deaerated and blanketed with nitrogen prior to measurement. No corrections were made for *iR* drop. Measurements were made at 25–28°.

Gas chromatography was carried out on 6-ft columns packed with 50% OV-1 on Chromosorb W with an Aerograph 1520 gas chromatograph: for iodobenzene, column temperature 90°, injector temperature 190°, detector temperature 300°; for phenanthrene and halophenanthrenes, column temperature 215°, injector temperature 250°, detector temperature 300°; for biphenyl and iodobiphenyls, column temperature 175°, injector temperature 250°, detector temperature 300°. Melting points were taken in capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 521 grating infrared spectrophotometer. Mass spectra, taken on a Hitachi Perkin-Elmer RMU-6E instrument, were calibrated using perfluorokerosene as an internal standard. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., or Chemalytics Inc., Tempe, Ariz.

Measurements of pH were made with a Leeds and Northrup glass electrode pH meter.

Controlled-potential electrolyses were carried out in a double-diaphragm cell with the aid of an Analytical Instruments, Inc. (Bristol, Conn.) potentiostat and current integrator, using the previously described procedure.[2]

Electrolysis of Diphenyliodonium Tosylate (1). Wave I.—Solutions of diphenyliodonium tosylate (0.5–2.0 m*M*) were electrolyzed between −0.6 and −0.8 V. Electrolysis was complete in less than 30 min. A value of 0.98 mfaraday/mmol was obtained (six determinations). The two-phase system (aqueous solution–mercury) was separated into its components. Each phase was extracted several times with ether. The ether extracts were combined, dried ($MgSO_4$), and then concentrated. A white solid could be obtained from the cooled concentrate. The solid, when recrystallized from 95% ethanol, melted at 122–123°. Authentic diphenylmercury had mp 123–124°. Infrared and mass spectra were identical with those of authentic diphenylmercury. Vpc analysis of the concentrated ether extracts showed the presence of iodobenzene. In many cases it was possible to remove the solid before extraction.

Electrolysis of Diphenyliodonium Tosylate (1). Wave II.—Electrolyses were carried out on the plateau of wave II (−1.20 to −1.30 V). Electrolyzed solutions were worked up in the manner described above. No solid residues were found. A value of 1.92 mfaraday/mmol was obtained (six determinations). Vpc analysis of the ether extracts showed iodobenzene and benzene to be the only products.

Electrolysis of Dibenziodolium Tetrafluoroborate (2). Wave I.—Solutions (1.0 m*M*) of the dibenziodolium tetrafluoroborate in the phosphate buffer were electrolyzed in the same manner as for species 1 (−0.6 to −0.8 V). An average value of 1.06 mfaraday/mmol was obtained (12 determinations). The electrolyzed solutions were extracted with several equal volumes of ether. The combined ether extracts were dried ($MgSO_4$) and then concentrated. As in the case of compound 1, a white solid precipitated from the cooled, concentrated solution. This solid exhibited the following properties: mp 159–160°; ir (KBr) 3040, 1570, 1550, 1465, 1420, 1410, 1270, 1240, 1150, 1110, 1070, 1045, 1010, 995, 770, 755, 750, 735, 640, 615, 540, and 460 cm^{-1}; mass spectrum (50 eV) *m/e* 760,* 634,* 558,* 508,* 456,* 329,* and 279 (starred signals showed characteristic isotopic cluster of mercury; values reported are for ^{202}Hg).

Anal. Calcd for bis-2-(2′-iodobiphenylyl)mercury ($C_{24}H_{16}HgI_2$): C, 37.99; H, 2.13; Hg, 26.44; I, 33.45. Found: C, 37.69; H, 2.16; Hg, 27.40; I, 31.60.

Recrystallization of this material from a variety of solvents did not significantly change the analytical results.

The ether extracts were shown by vpc to contain biphenyl, 2-iodobiphenyl, and 2,2′-diiodobiphenyl (confirmed by mixed injection with authentic samples).

Electrolysis of Dibenziodolium Tetrafluoroborate (2). Wave II.—Electrolyses were carried out at −1.20 to −1.30 V and were

(11) J. Nachtigal, Ph.D. Thesis, Polytechnic Institute of Brooklyn, 1967.
(12) M. Yudis, Ph.D. Thesis, Polytechnic Institute of Brooklyn, 1970.
(13) L. Chang, Ph.D. Thesis, Polytechnic Institute of Brooklyn, 1971.
(14) F. M. Beringer, L. L. Chang, A. N. Fenster, and R. R. Rossi, *Tetrahedron*, **25**, 4339 (1969).

worked up in the usual manner. A value of 1.98 mfaraday/mmol was obtained (six determinations). Vpc analysis of the ether extracts showed them to contain 2,2′-diiodobiphenyl, biphenyl (in substantially larger amounts than after electrolysis on wave I), and a trace amount of a third component that was trapped at the exit port of the gas chromatograph. The retention time of this material as well as a mass spectroscopic comparison with authentic material showed it to be biphenylene. Trace amounts of the white solid (mp 160–162°) were also sometimes present after electrolysis, especially in those runs where n was less than 2.0.

Electrolysis of 4,5-Phenanthryleneiodonium Bisulfate (3). Wave I.—Electrolyses were carried out on 0.150 mM solutions in the usual manner at −0.4 to −0.6 V. A value of 1.97 mfaraday/mmol was obtained (six determinations). Work-up in the usual manner afforded a brown solid from the ether extracts as well as phenanthrene (vpc). The brown solid was washed with ether and dried under vacuum. It exhibited the following properties: mp ~366° dec; ir (KBr) 3040 (w), 1440 (w), 1395 (w), 1290 (w), 1180 (vw), 1140 (vw), 990 (vw), 820 (s), 730 and 710 cm^{-1}; mass spectrum (50 ev) m/e 556,* 506,* 456,* and 329.*

Anal. Found: C, 42.98; H, 2.37; Hg, 45.02; I, 9.36.

The chemical (see below) as well as the spectroscopic evidence accumulated strongly suggest a mixture of di-4-phenanthrylmercury and 4-phenanthrylmercuric iodide as the chemical composition of this material.

When decomposition of this solid was effected in a capillary tube, the lower portion of which was immersed in an oil bath, a yellow solid was deposited on the upper (cooler) portion of the tube. A mass spectrum (80 eV) of this material (90°) was identical with that of phenanthrene except for a characteristic mercury cluster between m/e 198 and 204. At 160° the spectrum became more complicated with the highest m/e observed being at 456 (mercury containing). A comparison of this spectrum with that of authentic mercuric iodide (above m/e 202) showed them to be virtually identical.

Electrolysis of 4,5-Phenanthryleneiodonium Bisulfate (3). Wave II.—Electrolysis of the bisulfate was carried out in the usual manner between −1.20 and −1.30 V. Work-up afforded phenanthrene as the major product. Only trace amounts of the brown mercury-containing solid were obtained. A value of 3.13 mfaraday/mmol was obtained (five determinations) by coulometry.

Reactions of the Electrolysis Product of 3 at Wave I. Reaction with Hydrochloric Acid.—The brown solid was suspended in about 1 ml of THF. To this suspension was added approximately an equal volume of concentrated HCl. An immediate exothermic reaction occurred along with a color change from clear to yellow. Extraction of the mixture with ether followed by drying ($MgSO_4$) afforded phenanthrene (vpc) as the organic product.

Reaction with Aqueous Halide/Halogen.—The brown solid was suspended in about 1 ml of an aqueous potassium bromide (or iodide) solution. Addition of several drops (milligrams) of bromine (or iodine) was followed by heating on a steam bath for about 1 hr. Extraction with ether, drying ($MgSO_4$), and vpc analysis subsequently revealed the 4-halophenanthrene as the product (determined by mixed injection with 4-iodo- and 4-bromophenanthrenes).

Reaction with Glacial Acetic Acid/THF.—The brown solid was suspended in about 3 ml of THF. To the suspension was added approximately 6 ml of glacial acetic acid. The suspension was heated for 3 hr on a steam bath. At the end of this period some of the solid remained undissolved while some appeared to have gone into solution. After the solution had cooled, the undissolved material was filtered and was washed with water and ether. After drying (under vacuum) the solid melted at ~240°. This material is apparently not a pure compound.

Anal. Calcd for 4-phenanthrylmercuric iodide ($C_{14}H_9HgI$): C, 33.38; H, 1.60; I, 25.19. Found: C, 28.62; H, 1.54; I, 27.58.

A second solid was obtained from the solution by addition of water to the solution. After similar treatment this material melted at 210°.

Anal. Calcd for 4-phenanthrylmercuric acetate ($C_{16}H_{12}HgO_2$): C, 43.99; H, 2.77. Found: C, 40.95; H, 2.36; I, 4.20.

This solid also showed a strong carbonyl stretching band at 1580 cm^{-1} identical with that shown by phenylmercuric acetate.

Neutralization of the acidic solution with sodium carbonate, followed by extraction with ether and drying, afforded phenanthrene (vpc).

Although treatment of the electrolysis product with acetic acid apparently did result in the formation of 4-phenanthrylmercuric acetate while leaving the 4-phenanthrylmercuric iodide unreacted, separation of these materials into analytically pure samples was not accomplished.

Registry No.—**1**, 10182-84-0; **1** tosylate, 6293-66-9; **2**, 244-54-2; **2** tetrafluoroborate, 18116-06-8; **3**, 25504-50-1; **3** bisulfate, 34737-75-2; bis-2-(2′-iodobiphenylyl)mercury, 34737-76-3; di-4-phenanthrylmercury, 34737-77-4; 4-phenanthrylmercuric iodide, 34737-78-5; 4-phenanthrylmercuric acetate, 34737-79-6.

Substituent Effects upon the Reductive Fission of Aryl Alcohols

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Received March 31, 1971

Reductive fission of substituted 1-phenyl-1-ethanols by potassium metal in *tert*-butyl alcohol occurs most readily when strongly electron-withdrawing substituents are present. In competitive reductions, the relative reactivity increases for electron-withdrawing substituents (−I), but decreases for several +I substituents as the amount of added potassium is increased. The former behavior is believed to be associated with the importance of a dianion pathway and the latter, a radical-anion pathway. Halide substituents (except *p*-F) are anomalous, with the initial reaction being the loss of halogen. Reactivity is diminished by increasing side chain substitution.

Reductive cleavages of allyl and benzyl alcohols to propene and toluene were first studied by Chablay over 60 years ago.[1] Similar cleavages of alkyl–aryl ethers with sodium and liquid ammonia were investigated by Freudenberg and coworkers,[2] and later also investigated by Birch, who determined the order of activating influence of aromatic substituent: *o*-OCH_3 > *m*-OCH_3 > H > *o*-CH_3 > *m*-CH_3 > *p*-CH_3 > *p*-OCH_3.[3] Sowa and coworkers found similar substituent effects upon the mode of cleavage of certain diaryl ethers.[4] Two mechanisms have been advanced for these active metal reductions, a radical-anion pathway and a dianion

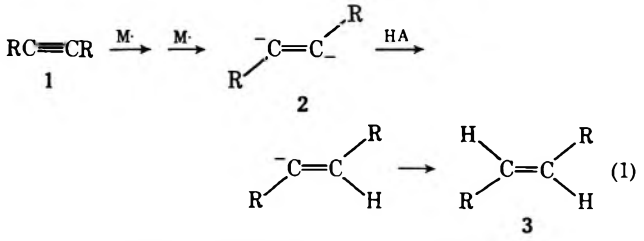
(1) (a) E. Chablay, *C. R. Acad. Sci.*, **140**, 1343 (1905); (b) *ibid.*, **143**, 829 (1906); (c) *ibid.*, **143**, 173 (1906); (d) see also L. Bouveault and G. Blanc, *ibid.*, **136**, 1676 (1903).

(2) (a) K. Freudenberg, K. Engler, F. Klink, E. Flickinger, and A. Sobek, *Chem. Ber.*, **71**, 1810 (1938); (b) K. Freudenberg, F. Klink, E. Flickinger, and A. Sobek, *ibid.*, **72**, 217 (1939).

(3) (a) A. J. Birch, *J. Chem. Soc.*, 102 (1947); (b) A. J. Birch, A. Fogiel, and G. J. Harvey, *Aust. J. Chem.*, **7**, 261 (1954).

(4) F. C. Weber and F. J. Sowa, *J. Amer. Chem. Soc.*, **60**, 94 (1938).

pathway.[5,6] Older work was generally interpreted in terms of the dianion pathway, *e.g.*, the reduction of alkynes to trans alkenes (eq 1).[7,8] More recently, Dauben and Wolf postulated a dianion intermediate for the reductive cleavage of certain cyclopropyl ketones.[9]



(1)

The advent of electron spin resonance[10,11] has permitted the observation of a plethora of radical anions. Radical anions were shown to be present in the sodium and liquid ammonia solutions of aromatics.[5] In recent years radical-anion reduction mechanisms have gained popularity, and indeed Krapcho and Bothner-By found kinetic evidence for these intermediates in the reduction of aromatics.[12] More recently the MIT group of workers presented strong evidence for a radical-anion pathway in the reduction of alkyl-substituted unsaturated ketones.[13]

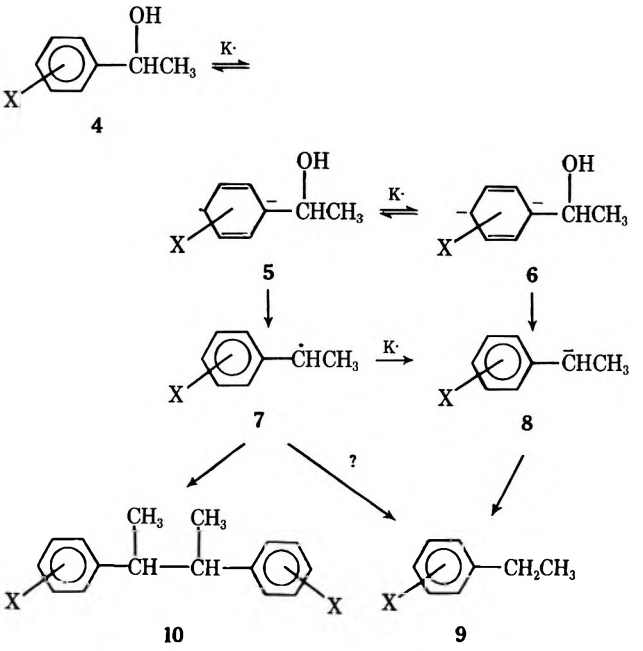
Notable among the radical-anion mechanisms was Zimmermann's interpretation[14] of Birch's observation[15] that *o*- and *m*-methoxybenzyl alcohols were reduced to methoxytoluenes, whereas *p*-methoxybenzyl alcohol suffered ring reduction. LCAO–MO calculations were used to show that the ring position of the radical anion adjacent to the $-CH_2OH$ function was comparatively electron rich in the ortho and meta isomers. It was suggested that this factor promoted facile expulsion of the hydroxyl function.

In contrast to the case with radical anions, a relatively small number of dianions are known in which both charges reside in the same π system.[16,17] Usually these dianions are derived from polynuclear hydrocarbons in which resonance structures can be drawn with the charges well separated. Other dianions are stabilized by quantum mechanical factors associated with the Huckel $4n + 2$ rule.[18]

Although organic dianions are rare and obviously destabilized by charge repulsion, dianions may serve as transient intermediates in some of the reductions cited above. The most attractive mechanism to us was that advanced by Birch, which considered the possibility of both radical-anion and dianion pathways. Recent work upon the solvent effect on the reduction of certain indoles was interpreted in terms of a duality of mechanism.[19,20] Recently Levin and Szwarc have shown that, although the radical anions of methyl phenyl acetylene are the most common species resulting from electron transfer, the disproportionation reaction of methyl phenyl acetylene takes place through a dianion intermediate.[21] In other cases, preservation of some optical activity in the reductive fission of aryl carbinols seems best explained in terms of proton capture by a short-lived carbanion intermediate, although some sort of surface reaction cannot be excluded.[22]

The present study is concerned with the competitive reduction of substituted 1-aryl-1-ethanols with potassium in *tert*-butyl alcohol. As a working hypothesis, an adaptation of Birch's mechanism[5] will be used (Scheme I).

SCHEME I



The importance of unsaturation in the compound to be reduced was appreciated by the early workers[1] and this observation is corroborated here. The saturated analog of **4**, 1-cyclohexyl-1-ethanol (**11**), was unreactive

(5) Several reviews have appeared: (a) H. Smith, "Chemistry in Nonaqueous Ionizing Solvents," Vol. 1, Interscience, New York, N. Y., 1963, p 212; (b) A. J. Birch, *Quart. Rev., Chem. Soc.*, **4**, 69 (1950); (c) A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958); (d) M. Schlosser, *Angew. Chem.*, **76**, 124 (1964); (e) N. L. Holy and J. D. Marcum, *ibid.*, **10**, 115 (1971).

(6) (a) K. N. Campbell and L. T. Eby, *J. Amer. Chem. Soc.*, **63**, 216 (1941); (b) *ibid.*, **63**, 2683 (1941); (c) K. W. Greenlee and W. C. Fernelius, *ibid.*, **64**, 2505 (1942); (d) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 71, presents a more modern mechanism.

(7) D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954).

(8) (a) G. Stork and J. Tsuji, *J. Amer. Chem. Soc.*, **83**, 2783 (1961); (b) G. Stork and S. D. Darling, *ibid.*, **82**, 1512 (1960); (c) *ibid.*, **86**, 1761 (1964).

(9) W. G. Dauben and R. F. Wolf, *J. Org. Chem.*, **35**, 374 (1970).

(10) L. A. Blynmenfel'd, V. V. Voerodskii, and S. P. Solodornik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 158 (1964).

(11) D. Paul, D. Lipkin, and S. I. Weissman, *J. Amer. Chem. Soc.*, **78**, 116 (1956), in later papers.

(12) (a) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959); see also J. F. Eastham and D. R. Larkin, *ibid.*, **81**, 3652 (1959); (c) J. F. Eastham, C. W. Keenan, and H. V. Secor, *ibid.*, **81**, 6523 (1959); (d) A. P. Krapcho and A. A. Bothner-By, *ibid.*, **82**, 751 (1960).

(13) (a) K. W. Bowers, R. Giese, J. Grinshaw, H. O. House, N. Kolodny, K. Kronberger, and D. Roe, *ibid.*, **92**, 2783 (1970); (b) H. O. House, R. Giese, K. Kronberger, J. Kaplan, and J. F. Simeine, *ibid.*, **92**, 2800 (1970).

(14) H. E. Zimmerman, *Tetrahedron*, **16**, 169 (1961).

(15) A. J. Birch, *J. Chem. Soc.*, 809 (1945).

(16) (a) C. Mao, C. R. Hauser, and M. L. Miles, *J. Amer. Chem. Soc.*, **89**, 5303 (1967); (b) R. L. Gay and C. R. Hauser, *ibid.*, **89**, 1647 (1967); (c) F. E. Henoch, K. Hampton, and C. R. Hauser, *ibid.*, **89**, 463 (1967).

(17) (a) T. L. Chu and S. C. Yu, *ibid.*, **76**, 3367 (1967), and references cited therein; (b) G. J. Hoijtink and P. H. van der Meij, *Z. Phys. Chem. (Leipzig)*, **20**, 1 (1959); (c) P. Balk, G. J. Hoijtink, and J. Schreurs, *Recl. Trav. Chim. Pays-Bas*, **76**, 813 (1957); (d) E. de Boer and S. I. Weissman, *ibid.*, **76**, 813 (1957); (e) A. Czerhegyi, J. Jagur-Grodzinski, and M. Szwarc, *J. Amer. Chem. Soc.*, **91**, 1892 (1969), found the equilibrium between two radical anions and a dianion plus a neutral molecule to be markedly solvent sensitive.

(18) (a) T. J. Katz and J. Schulman, *J. Amer. Chem. Soc.*, **86**, 3169 (1964); (b) T. J. Katz, M. Rosenberger, and R. K. O'Hara, *ibid.*, **86**, 249 (1964); (c) T. J. Katz, *ibid.*, **82**, 3784 (1960); (d) D. R. Dimmel and S. B. Gharpure, *ibid.*, **93**, 3991 (1971).

(19) (a) W. A. Remers, G. Gibs, C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **89**, 5513 (1967).

(20) H. Walborsky, F. P. Johnson, and J. Pierce, *ibid.*, **90**, 5222 (1968).

(21) G. Levin and M. Szwarc, *Chem. Commun.*, 1029 (1971).

(22) D. J. Cram, C. A. Kingsbury, and A. Langemann, *ibid.*, **81**, 5785 (1959); (b) R. Wepster, *Recl. Trav. Chim. Pays-Bas*, **83**, 1149 (1964).

under the conditions that the aromatic alcohol reacted smoothly. From this and other work,[1-4] the initial step involving the addition of electrons to the π system seems very probable. The unsaturated center need not be adjacent to the leaving group, as shown by the reduction of β-aryl mesylates.[23]

Although the radical intermediate **7** could dimerize to form **10**, comparison of the vpc traces of several of the reaction products with the vpc traces of authentic *meso*- and *dl*-**10** showed these products to be less than *ca.* 1% of theoretical yield.

The reductions with potassium in *tert*-butyl alcohol were, of course, surface reactions. The reaction of potassium and solvent also formed hydrogen gas and potassium *tert*-butoxide. In these reductions the "nascent hydrogen" mechanism of von Baeyer[24] cannot be specifically excluded, although it was considered unlikely in the liquid ammonia work.[12] The reduction of **4** to form **9** by potassium remarkably efficient compared to the reaction of potassium with solvent.

Although the metal–solvent system used in this study was heterogeneous and otherwise quite different from the liquid ammonia work cited above, the reduction seem quite similar in certain cases. For example, the reduction of 1-(4-anisyl)-1-ethanol gave a complex mixture of products which have resisted separation. However, it is quite clear from the nmr spectra that ring reduction has extensively occurred. The ortho and meta isomers underwent simple hydroxide displacement.

Table I lists the results for competitive reduction of

TABLE I

RELATIVE REACTIVITY FOR COMPETITIVE REDUCTION[c] OF X-SUBSTITUTED 1-PHENYL-1-ETHANOLS *vs.* THE STANDARD COMPOUND (X = H)

		Rel reactivity		
Compd	X	0.3 g K[b]	0.6 g K[b]	1.2 g K[b]
4a	*o*-CH_3	0.85	0.89	0.93
4b[d]	*m*-CH_3	0.71	0.72	0.76
4c	*p*-CH_3	1.04	0.90	0.77
4d	2,4-di-CH_3[a]	0.44	0.44	0.39
4e	2,4,6-tri-CH_3	0.15	0.16	0.16
4f	*p*-*t*-C_4H_9	0.22	0.18	0.17
4g	*o*-OCH_3[a]	1.13	1.17	1.30
4h	*m*-OCH_3		1.37	1.40
4i	*m*-CF_3[a]	1.14		1.47
4j	*p*-CF_3[a]	1.08	1.36	2.61
4k	*p*-F[a]	0.78	0.81	0.86
4l	*m*-Cl[a]	0.62	0.76	0.82
4m	*p*-Cl[a]	0.92	0.78	0.78
4n	H	(1.00)	(1.00)	(1.00)

[a] To avoid superposition of vpc peaks, the *m*-methyl compound **4b** was used as standard, and the data were corrected to represent the reactivity *vs.* X = H. [b] These reactions used a standard quantity of solvent, 35 ± 2 ml. [c] Reproducibility was checked in seven cases and found to be within 5% of the quoted value. [d] With **4b**, 20, 48, and 71% of starting material was consumed using 0.3, 0.6, and 0.9 g of potassium, respectively.

13 substituted 1-aryl-1-ethanols relative to the unsubstituted compound taken as standard. The ethylbenzene reduction products (**9**) were observed in the vpc analyses in approximately the correct ratios with respect to the amounts of reactants destroyed. However, owing to the necessity for an evaporative work-up, the ratios of these fairly volatile products are not considered reliable. Following the treatment of Krapcho and Bothner-By, the reaction mixtures were analyzed for unreacted starting materials, and the data were converted to relative rate constants as shown in eq 2,

$$\frac{d(S_X)/dt}{d(S_H)/dt} = \frac{k_X S_X K}{k_H S_H K}$$
$$\frac{k_X}{k_H} = \frac{\ln (S_X/S_X^0)}{\ln (S_H/S_H^0)} \qquad (2)$$

where S_X = final substrate concentration, S_X^0 = initial substrate concentration, S_H^0 = initial standard concentration, and K = effective surface area of potassium metal. This treatment was considered to give true relative rate constants, k_X/k_H only *if the order of reaction was the same for the substituted compounds and the standard.*[12] As the data in Table I show, substantial variations in $\ln (S_X/S_X^0)/\ln (S_H/S_H^0)$ were observed as the amount of potassium metal was varied (keeping solvent volume constant). This variation is taken as indicative of the incursion of a higher order term in the effective surface area of potassium for certain compounds. The expression $\ln (S_X/S_X^0)/\ln (S_H/S_H^0)$ will be termed "relative reactivity" hereafter.

Compounds with strongly electron withdrawing groups, *i.e.*, **4i** and **4j** (X = CF_3), were observed to be much more reactive than the standard. These compounds also show increasing relative reactivity with increasing levels of potassium. If either **5** → **6** or **6** → **8** were rate determining, the reaction would be second order in the effective surface of the potassium metal for that part of the reaction which proceeded by the **4** → **5** → **6** → **8** pathway. The strong sensitivity of **4i** and **4j** to the amount of added metal is suggestive that the dianion route, **4** → **5** → **6** → **8**, is more important for these substrates than for the standard. The **5** → **8** conversion may be more or less concerted. The extensive charge repulsion in **6** would then be diminished by the partial separation of the hydroxide anion. The high reactivity of **4i** and **4j** occurs despite the fact that *tert*-butoxide, which develops as the reaction progresses, converts the free alcohols in part to their less reactive alkoxide forms.

As Table I shows, compounds with alkyl substituents are generally less reactive than the standard. The order of reactivity is H > *p*-CH_3 > *o*-CH_3 > *m*-CH_3 > 2,4-di-CH_3 > *p*-*t*-C_4H_9 > 2,4,6-tri-CH_3 (using 0.6 g of potassium). The steric effect of large groups is apparent upon comparing the *p*-CH_3 and *p*-*t*-C_4H_9 compounds (**4c** and **4f**). Large para substituents impede approach of the aromatic ring to the metal surface, but these substituents are remote from the leaving group. This steric effect adds emphasis to the fact that electrons are added to the ring from the metal and the benzylic carbon becomes involved at a later stage of the reaction. In other work, steric hindrance to solvation of the intermediate(s) was considered to be important.[12] The electron-donating character of these alkyl groups would also hinder electron addition to the ring.

Certain of the alkyl-substituted compounds show slightly increasing relative reactivities, whereas others show diminishing values with increasing levels of potassium. It is noteworthy that all compounds which show diminishing values have para substituents. The radical-anion pathway, **4** → **5** → **7** → **8**, may be some-

(23) D. J. Cram and C. Dalton, *J. Amer. Chem. Soc.*, **85**, 1268 (1963).
(24) A. von Baeyer, *Justus Liebigs Ann. Chem.*, **269**, 145 (1892).

what more important for these compounds than for the standard.[25]

The possibility of medium effects upon the relative reactivities was briefly investigated (Table II). In

TABLE II
EFFECT OF 0.5 *M* POTASSIUM *tert*-BUTOXIDE ON RELATIVE REACTIVITY[a]

Compd	X	Rel reactivity 0.3 g K	0.6 g K	1.2 g K
4a	*o*-CH_3	0.87	0.89	0.91
4b	*m*-CH_3	0.75	0.78	0.78
4k	*p*-F	0.76	0.80	0.86
4b OCH_3[c]	*m*-CH_3	0.88	0.88	0.90
		(0.90)[b]	(0.90)[b]	(0.93)[b]

[a] These data are the average of duplicate runs. Reproducibility is ±5%. [b] The data in parentheses refer to reactions run in the absence of added 0.5 *M* potassium *tert*-butoxides prior to addition of potassium. [c] Methyl ether of alcohol **4b**. The standard used was the methyl ether of **4n**.

runs using 1.2 g of potassium, the metal reacts mainly with solvent, forming *ca.* 0.5 *M* potassium *tert*-butoxide. This reaction becomes markedly slower as the level of *tert*-butoxide increases. Table II shows the effect on relative reactivities of an initial added quantity of *tert*-butoxide. Within experimental error, added *tert*-butoxide has no effect on the magnitude or the trends of the reactivities.

Table II also shows the effect of changing to the leaving group to methoxide. The relative reactivity of the methyl ether of **4b** was significantly different from that of the alcohol and this relative reactivity was not affected by *tert*-butoxide (Table II). The methyl ether of **4b** (*m*-CH_3) was 8% *more* reactive than **4b** itself. However, the methyl ether of **4c** (*p*-CH_3) was ~60% *less* reactive than **4c** itself. The steps of the reaction that directly involve the leaving group are **5** → **7** and **6** → **8**. The fact that a leaving group effect is noted suggests that these step(s) may be kinetically and energetically significant. However, the complexity of the leaving group effect also suggests that Scheme I may be an oversimplification.

The halogen-containing compounds were surprisingly unreactive. Inspection of the reaction products revealed that the halogen had been lost in the course of the reduction for the chloro and bromo, but not lost for the fluoro compound.[26] When the reaction was carried out to a small conversion to product (Table III), 1-phenyl-1-ethanol (**4n**) and ethylbenzene (**9n**) were observed, but *p*-chloroethylbenzene was not observed. The reaction course very likely involves initial reduc-

(25) The reason for the greater importance of the radical-anion route for para substituents which are electron donating may be related to the fact that the node of the antibonding orbital passes through the para groups: T. R. Tuttle, Jr., and S. Weissman, *J. Amer. Chem. Soc.*, **80**, 5342 (1958). In a dianion route, a second electron would probably be added to this orbital which ineffectively leads to loss of hydroxide since charge density is not increased at the ring carbon bearing the leaving group function (see ref 14). For −I substituents, the nodes of the antibonding orbital are quite different: S. K. Bowers, "Radical-Anions," E. T. Kaiser and L. Kevan, Ed., Wiley, New York, N. Y., 1960, p 211.

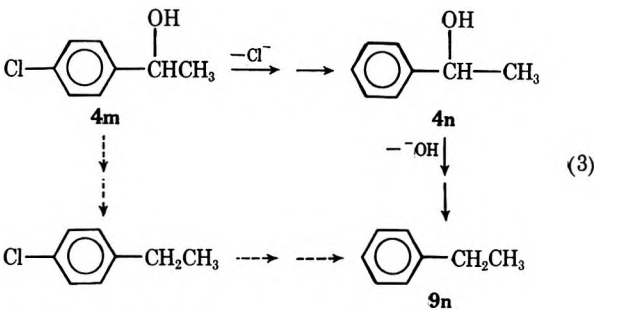
(26) (a) J. J. van Daalen, A. Kraak, and J. Arens, *Recl. Trav. Chim. Pays-Bas*, **80**, 810 (1961); (b) P. Bruck, *Tetrahedron Lett.*, 449 (1962); (c) P. Bruck, D. Thompson, and S. Winstein, *Chem. Ind. (London)*, 405 (1960); (d) see, however, G. D. Sargent, *J. Amer. Chem. Soc.*, **93**, 5269 (1971); (e) J. F. Garst and J. T. Barbas, *ibid.*, **91**, 3385 (1969).

TABLE III
REDUCTIVE FISSION OF 1-(4-CHLOROPHENYL)-1-ETHANOL (**4m**) AND 1-(4-BROMOPHENYL)-1-ETHANOL (**4o**) WITH POTASSIUM IN *tert*-BUTYL ALCOHOL[a]

Compd	*p*-Cl (**4m**), %	*p*-Br (**4o**), %
Unreacted carbinol	90.6	88.5
1-Phenyl-1-ethanol (**4n**)	2.6	4.0
Ethylbenzene (**9n**)	6.8	7.5

[a] The standard, **4n**, was omitted.

tive cleavage of the halogen–ring bond, then cleavage of the side chain hydroxyl bond (eq 3). It is conceiv-



(3)

able that the addition of an electron occurs to the d orbitals of chloride or bromide. However, this does not account for the lack of reactivity of the *p*-F compound toward hydroxide displacement.

In other experiments, the effect of side chain substitution was investigated. The relative order of reactivity (Scheme II) parallels the order of carbanion (**8**)

SCHEME II

	$PhCH_2$	Ph_2CH	$PhCHCH_3$	$PhCCH_3$	$PhCC_2H_5$
				CH_3	C_2H_5
	12	**13**	**4n**	**14**	**15**
rel reactivity (0.4 g K)	1.59	1.14	(1.00)	0.55	0.27

stability and not the order of radical (**7**) stability (with the possible exception of **13**). However, steric hindrance is again important, as shown by the relative reactivities of **14** and **15**. Since steps **5** → **7** and/or **6** → **8** are kinetically significant, the substituent stabilization of the developing carbanion or radical should also affect the energetics of the reaction. The parallel to the order of carbanion stability (with a reservation because of steric effects) reinforces the earlier judgment that a carbanion route does exist. With increasing amounts of potassium, **12** showed a strong increase in relative reactivity: 1.59 (using 0.4 g of K), 2.34 (0.8), and 2.4 (1.2). Surprisingly, **14** also showed increasing relative reactivities: 0.55 (0.4 g of K), 0.82 (0.8), and 0.83 (1.2). The one heterocycle tested, 1-(2-thienyl)-1-ethanol, proved to be the most reactive compound of all, relative reactivity 1.89 (0.4 g of K).

Experimental Section

Preparation of 1-Phenyl-1-ethanol (4n).—This material was prepared essentially by the method of Vogel,[27] by adding phenylmagnesium bromide (0.35 mol) to acetaldehyde (13.2 g, 0.3 mol). The crude product was vacuum distilled. The fraction boiling at 60° (0.5 mm) was collected (25 g, 72%): 60 mHz nmr δ 1.30 (d, 3, CH_3CH), 3.76 (s, 1, OH), 4.65 (q, 1, CH_3CH), and 7.2 (s, 5, C_6H_5).

Preparation of 1-(2-Methylphenyl)-1-ethanol (4a).—The same procedure as for the preparation of **4n** was used. From 54.5 g (0.319 mol) of *o*-bromotoluene, 7.76 g (0.319 g-atom) of magnesium, and 14.1 g (0.36 mol) of acetaldehyde, product **4a** (27.7 g, 63.8%) was obtained: bp 70° (0.7 mm); nmr δ 1.30 (d, 3, CH_3CH), 2.28 (s, 3, CH_3Ar), 3.85 (s, 1, OH), 5.03 (q, 1, CH_3CH), and 7.50 (m, 4, C_6H_4).

Preparation of 1-(3-Methylphenyl)-1-ethanol (4b).—This material was prepared by lithium aluminum hydride (12) (3.8 g, 0.10 mol) reduction of 1-acetyl-3-methylbenzene (25.0 g, 0.186 mol) by the procedure of Vogel. The crude product was distilled under vacuum, with the fraction boiling at 61° (0.7 mm) being collected (18 g, 71%): nmr δ 1.28 (d, 3, CH_3CH), 2.28 (s, 3, CH_3Ar), 3.73 (s, 1, OH), 4.57 (q, 1, $CHCH_3$), and 7.0 (s, 4, C_6H_4).

Preparation of 1-(4-Methylphenyl)-1-ethanol (4c).—The procedure for the preparation of **4n** was used. Vacuum distillation of the crude product afforded 13 g (60%): bp 68° (0.55 mm); nmr δ 1.30 (d, 3, CH_3CH), 2.30 (s, 3, CH_3Ar), 3.75 (s, 1, OH), 4.65 (q, 1, CH_3CH), and 7.10 (s, 4, C_6H_4).

Preparation of 1-(2,4-Dimethylphenyl)-1-ethanol (4d).—From 34.6 (0.26 mol) of aluminum chloride, 26.5 g (0.25 mol) of *m*-xylene, and 21.2 g (0.27 mol) of acetyl chloride, 2,4-dimethylacetophenone (30 g, 80%) was prepared following the procedure of Vogel: bp 70–72° (0.5 mm); nmr δ 2.30 (s, 3, CH_3CO), 2.45 [s, 6, $(CH_3)_2Ar$], 7.25 (m, 3, C_6H_3). Upon reduction of 14.8 g (0.1 mol) of this ketone by **17** (1.9 g, 0.05 mol) by the procedure used for **4b**, the product **4d** (11 g, 76%) was obtained: bp 75–78° (1 mm); nmr δ 1.23 (d, 3, CH_3CH), 2.14 (s, 3, CH_3Ar), 2.21 (s, 3, CH_3Ar), 3.56 (s, 1, OH), 4.77 (q, 1, CH_3CH), 7.01 (m, 3, C_6H_3).

Preparation of 1-(2,4,6-Trimethylphenyl)-1-ethanol (4e).—The Grignard preparation, as with **4n**, was successful, using 25.0 g (0.125 mol) of bromomesitylene, 3.04 g (0.125 g-atom) of magnesium, and 5.5 g (0.125 mol) of acetaldehyde. Very careful acidification during work was necessary. Ammonium chloride solution was added dropwise until the reaction mixture became clear, pH *ca.* 7. The organic layer was separated and dried ($MgSO_4$). The ether was evaporated and hexane was added. The chilled solution crystallized, mp 68–70°, yielding 8.3 g (45%) of **4e**: nmr δ 1.33 (d, 3, CH_3CH), 2.20 (s, 3, *p*-CH_3Ar), 2.31 [s, 6, *o*-$(CH_3)_2Ar$], 2.71 (s, 1, OH), 5.21 (q, 1, CH_3CH), 6.77 (s, 2, C_6H_2).

Preparation of 1-[4-(1,1-Dimethylethyl)phenyl]-1-ethanol (4f).—Reduction of *p-tert*-butylacetophenone (17.6 g, 0.1 mol) with **17** (1.9 g, 0.05 mol) formed **4f**, which crystallized from ether (16.0 g, 90%): mp 58–60°; nmr δ 1.30 (s, 9, *t*-C_4H_9), 1.30 (s, 3, CH_3CH), 3.47 (s, 1, OH), 4.60 (q, 1, CH_3CH), and 7.18 (s, 4, C_6H_4).

Preparation of 1-(2-Methoxyphenyl)-1-ethanol (4g).—The Grignard preparation was used. Beginning with 43.5 g (0.32 mol) of freshly distilled *o*-methoxybenzaldehyde, 8.5 g (0.35 g-atom) of magnesium, and 49.9 g (0.35 mol) of methyl iodide, the product **4g** was obtained by vacuum distillation: bp 97° (1.8 mm) (38.6 g, 79.3%); nmr δ 51.36 (d, 3, CH_3CH), 2.69 (s, 1, OH), 3.80 (s, 3, CH_3O), 5.04 (q, 1, CH_3CH), and 7.06 (m, 4, C_6H_4).

Preparation of 1-(3-Methoxyphenyl)-1-ethanol (4h).—The Grignard preparation was used. From *m*-bromoanisole (12.5 g, 0.067 mol), magnesium (1.63 g, 0.067 g-atom), and acetaldehyde (3.1 g, 0.07 mol), the product **4h** was obtained (5.0 g, 49%): bp 120° (8 mm); nmr δ 1.30 (d, 3, CH_3CH), 3.61 (s, 3, CH_3O), 3.71 (s, 1, OH), 4.56 (q, 1, CH_3CH), and 6.80 (m, 4, C_6H_4).

Preparation of 1-(3-Trifluoromethylphenyl)-1-ethanol (4i).—From *m*-bromotrifluoromethylbenzene (32.5 g, 0.144 mol), magnesium (3.5 g, 0.144 g-atom), and acetaldehyde (5.3 g, 0.12 mol), the product **4i** was obtained (15.4 g, 56%): bp 100–102° (17 mm); nmr δ 1.30 (d, 3, CH_3CH), 4.13 (s, 1, OH), 4.64 (q, 1, CH_3CH), and 7.34 (m, 4, C_6H_4).

Preparation of 1-(4-Trifluoromethylphenyl)-1-ethanol (4j).—From *p*-bromotrifluoromethylbenzene (11.3 g, 0.05 mol), magnesium (1.22 g, 0.05 g-atom), and acetaldehyde (2.64 g, 0.06 mol), the product **4j** was obtained (5.0 g, 53%): mp 64° (0.05 mm); nmr δ 1.33 (d, 3, CH_3CH), 4.00 (s, 1, OH), 4.70 (9, 1, CH_3CH), and 7.3[illegible] (m, 4, C_6H_4).

Preparation of 1-(4-Fluorophenyl)-1-ethanol (4k).—The hydride reduction was used. From *p*-fluoroacetophenone (13.8 g, 0.10 mol) and **17** (19 g, 0.05 mol), the product **4k** (12.5 g, 89.5%) was obtained: bp 49.5° (0.4 mm); nmr δ 1.25 (d, 3, CH_3CH), 3.90 (s, 1, OH), 4.53 (q, 1, CH_3CH), and 6.90 (m, 4, C_6H_4).

Preparation of 1-(3-Chlorophenyl)-1-ethanol (4l).—From *m*-chlorobromobenzene (24.0 g, 0.125 mol), magnesium (3.04 g, 0.125 g-atom), and acetaldehyde (6.2 g, 0.14 mol), the product **4l** (14.0 g, 71%) was obtained: bp 98–100° (4 mm); nmr δ 1.33 (d, 3, CH_3CH), 4.03 (s, 1, OH, 4.68 (q, 1, CH_3CH), and 7.25 (m, 4, C_6H_4).

Preparation of 1-(4-Chlorophenyl)-1-ethanol (4m).—From methyl iodide (49 9 g, 0.35 mol), magnesium (8.5 g, 0.35 g-atom), and *p*-chlorobenzaldehyde (42.15 g, 0.3 mol), the product **4m** (30.0 g, 65%) was obtained: bp 80° (0.5 mm); nmr δ 1.30 (d, 3, CH_3CH), 4.17 (s, 1, OH), 4.60 (q, 1, CH_3CH), and 7.15 (s, 4, C_6H_4).

Preparation of 1-(4-Bromophenyl)-1-ethanol (4o).—From *p*-bromoacetophenone (39.8 g, 0.2 mol) and **17** (3.8 g, 0.1 mol), the product **4o** was obtained: bp 76° (0.4 mm); nmr δ 1.25 (d, 3, CH_3CH), 3.81 (s, 1, OH), 4.43 (q, 1, CH_3CH), and 6.97 (m, 4, C_6H_4).

Preparation of 1-Cyclohexyl-1-ethanol (11).—From bromocyclohexane (24.8 g, 0.15 mol), magnesium (3.9 g, 0.16 g-atom), and acetaldehyde (6.1 g, 0.15 mol), the above product was obtained (15 g, 64%): bp 43° (0.4 mm); nmr δ 1.04 (d, 3, CH_3CH) *ca.* 1.42 (m, 11, C_6H_{11}), 3.28 (q, 1, CH_3CH), and 3.40 (s, 1, OH).

Preparation of 2-Phenyl-2-propanol (14).—From methyl iodide (49.9 g, 0.35 mol), magnesium (8.5 g, 0.35 g-atom), and acetophenone (36.0 g, 0.30 mol), the product **14** (25.0 g, 62.5%) was obtained: bp 62–64° (2 mm); nmr δ 1.43 [s, 6, $(CH_3)_2$], 3.54 (s, 1, OH), and 7.30 (m, 5, C_6H_5).

Preparation of 3-Phenyl-3-pentanol (15).—From bromobenzene (15.79 g, 0.10 mol), magnesium (2.4 g, 0.10 g-atom), and 3-pentanone (8.6 g, 0.1 mol), the product **15** (12.0 g, 73%) was obtained: bp 80° (2 mm); nmr δ 0.8 (t, 6, CH_3CH_2), and 7.23 (m, 5, C_6H_5).

Preparation of 1-Thienyl-1-ethanol (16).—From 2-bromothiophene (25.0 g, 0.143 mol), magnesium (3.72 g, 0.153 g-atom), and acetaldehyde (6.6 g, 0.15 mol), the product **16** (13.0 g, 67%) was obtained: bp 72° (3 mm); nmr δ 1.44 (d, 3, CH_3CHO), 3.89 (s, 1, OH), 4.90 (q, 1, CH_3CH), and *ca.* 6.97 (m, C_4H_3S).

Procedure for the Reductive Cleavages.—To a 500-ml, three-necked flask, fitted with condenser, stirrer, and addition funnel, which had been dried and placed under nitrogen, 35.0 ml of *tert*-butyl alcohol (previously distilled from sodium) was added. About 4 mmol of accurately weighed samples of the two alcohols (1:1 molar ratio) was added, using *tert*-butyl alcohol to wash the sample into the flask. Freshly cut potassium was added and the flask was stirred until all the potassium had disappeared (30–50 min). Necessarily the weight of the potassium was rather rough (±0.1 g) since quickness was necessary. Isopropyl alcohol was added to the final reaction mixture to react with any remaining bits of potassium. After stirring for 5 min, 200 ml of H_2O was added (*careful–fire danger*). The resulting solution was extracted twice with two 100-ml portions of pentane–ether (1:1). The combined organic layer was extracted with three 100-ml portions of water, dried ($MgSO_4$), and evaporated through a 25-cm Vigreux column until 3–5 ml of solution remained. This solution was analyzed by vapor phase chromatography on a Varian Aerograph A90-P-3 instrument using a 5-ft 3% SE-30 column (on Var-A-Fort 30 support). The result from at least three vpc traces were averaged. In most cases **4n** was used as the standard substrate, but owing to superposition of vpc peaks, the *m*-methyl compound **4b** was necessary in some cases. The relative reactivity of **4n** and **4b** was carefully determined at a range of potassium levels. The vpc molar response ratios of the various substrates were determined by running vpc traces of accurately measured quantities of substrate in question *vs.* **4b** or **4n**. Again at least three integrations were averaged.

(27) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1956, pp 812, 885.

Registry No.—**4a**, 7287-82-3; **4b**, 7287-81-2; **4b** methyl ether, 34386-38-4; **4c**, 536-50-5; **4d**, 5379-19-1; **4e**, 31108-34-6; **4f**, 34386-42-0; **4g**, 13513-82-1; **4h**, 23308-82-9; **4i**, 454-91-1; **4j**, 1737-26-4; **4k**, 403-41-8; **4l**, 6939-95-3; **4m**, 3391-10-4; **4n**, 98-85-1; **4n** methyl ether, 4013-34-7; **4o**, 5391-88-8; **11**, 1193-81-3; **14**, 617-94-7; **15**, 1565-71-5; **16**, 2309-47-9; potassium *tert*-butoxide, 865-47-4.

Acknowledgment.—Support by PRF Grant 4254-AC4 is gratefully acknowledged.

Semipinacolic Deamination of 2-Amino-1-(2-methoxyphenyl)-1-phenylethanol[1]

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Received November 16, 1971

To elucidate the behavior of the *o*-methoxyphenyl group in cationic rearrangements, 2-amino-1-(2-methoxyphenyl)-1-phenylethanol (**1**) has been deaminated with sodium nitrite in 50% aqueous acetic acid. This reaction produced 2-methoxydeoxybenzoin (**2**), 2′-methoxydeoxybenzoin (**3**), and 3-phenylbenzofuran (**4**), respectively, in proportions 47:12:27 at 0° and 43:13:19 at 30°. Ketones **2** and **3** were not produced in equal proportions as has previously been reported. Production of **4** demonstrates for the first time methoxy oxygen (*o*-MeO-5) involvement in deaminative rearrangements and shows that use of the ratio of **3** to **2** to determine "migratory aptitude" of *o*-methoxyphenyl is improper. A methanism is presented to account for the observed products.

Considerable attention has been given to migratory abilities of various aryl groups in pinacol and related rearrangements. Bachmann and coworkers,[2] in their studies of rearrangements of symmetrical tetraaryl glycols, assigned migratory aptitudes to a series of substituted aryl groups relative to phenyl; a few examples are *p*-methoxyphenyl (500), *p*-tolyl (15.7), phenyl (1.0), and *o*-methoxyphenyl (0.3).[3] With the exception of ortho-substituted phenyl groups, these relative migratory aptitudes follow the order expected from consideration of relative rates of electrophilic aromatic substitution. The low migratory abilities for the ortho-substituted phenyl groups have been ascribed to steric hindrance[4] or "ortho effect."[5] Matsumoto and coworkers[5b,6,7] reinvestigated the pinacolic rearrangement of the symmetrical di-*o*-methoxyphenyldiphenyl glycol, as suggested by Pocker.[3a] Their results, though varying with the diastereomer investigated, demonstrated a migratory aptitude of *o*-methoxyphenyl roughly in agreement with the above value. Matsumoto[7] concluded that Pocker's suggestion[3a] of *o*-anisyl oxygen involvement[8] with the developing carbonium ion was not in accord with his thermodynamic data.

A number of deaminations of substituted aminoethanols (semipinacols) of the type ArPhC(OH)CH(NH_2)R are known in which the predicted (on the basis of relative migratory aptitudes) aryl group does not migrate to provide the majority of rearranged product.[9] Curtin, *et al.*,[9] explained these results by means of a transition-state "cis effect," whereas Collins, *et al.*,[10] ascribe such behavior to ground-state conformational control. In cases in which the migration terminus is primary, the migratory aptitudes of aryl groups during deamination follow the expected order, but the values are much reduced compared to the symmetrical tetraaryl glycol cases. For example, in 2-amino-1-aryl-1-phenylethanols the migratory aptitudes (phenyl = 1.0) are *p*-methoxyphenyl (1.5), *p*-tolyl (1.3), and *p*-chlorophenyl (0.9).[9f] Rather similar results are obtained in systems lacking the hydroxyl group.[11]

Our desire to elucidate the behavior of the *o*-methoxyphenyl group in cationic rearrangements led us to inquire into the semipinacolic deamination of 2-amino-1-(2-methoxyphenyl)-1-phenylethanol (**1**), a case in which steric hindrance in the transition state should not play an important role. Here the apparently anomalous migratory aptitude of the *o*-methoxyphenyl group, as in the symmetrical tetraaryl glycol rearrangement, should not obtain if that behavior arises from steric effects in the transition state. Indeed, Kharasch, *et al.*,[12] demonstrated that treatment of *o*-anisyldiphenylcarbinol with *tert*-butyl hydroperoxide and perchloric acid in glacial acetic acid yields mostly guaiacol and benzophenone, which arise from predominant *o*-anisyl (rather than phenyl) migration to oxygen in the ion resulting from heterolytic scission of the first-formed peroxide. Further, there should be a likely possibility of *o*-anisyl oxygen involvement with the developing ionic center (the so-called *o*-MeO-5 participation[8]) during deamination of **1**, with the resulting

(1) Taken in part from the M.S. Thesis of C. E. S., San Fernando Valley State College, 1972.

(2) W. E. Bachmann and J. W. Ferguson, *J. Amer. Chem. Soc.*, **56**, 2081 (1934); W. E. Bachmann and H. R. Sternberger, *ibid.*, **56**, 170 (1934); W. E. Bachmann, *ibid.*, **54**, 2112 (1932); W. E. Bachmann and F. H Mosher, *ibid.*, **54**, 1124 (1932).

(3) For compilations of these and other results, see (a) Y. Pocker in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 1; (b) C. J. Collins, *Quart. Rev. Chem. Soc.*, **14**, 357 (1960).

(4) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 478.

(5) (a) C. H. Beale and H. H. Hatt, *J. Amer. Chem. Soc.*, **54**, 2405 (1932); (b) K. Matsumoto, R. Goto, A Sera, and T. Asano, *Nippon Kagaku Zasshi*, **87**, 1076 (1967).

(6) R. Goto, K. Matsumoto, and A. Sera, *ibid.*, **87**, 93 (1966).

(7) K. Matsumoto, *Bull. Chem. Soc. Jap.*, **41**, 1356 (1966).

(8) (a) S. Winstein, *Experientia, Suppl. 2*, 153 (1955); see also (b) R. Heck, J. Corse, E. Grunwald, and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 3278 (1957).

(9) (a) P. I. Pollack and D. Y. Curtin, *ibid.*, **72**, 961 (1950); (b) D. Y. Curtin and P. I. Pollack, *ibid.*, **73**, 992 (1951); (c) D. Y. Curtin, E. E. Harris, and P. I. Pollack, *ibid.*, **73**, 3453 (1951); (d) D. Y. Curtin and E. K. Meislich, *ibid.*, **74**, 5898 (1952); (e) *ibid.*, 5905 (1952); (f) D. Y. Curtin and M C. Crew, *ibid.*, **76**, 3719 (1954); (g) *ibid.*, **77**, 354 (1955).

(10) B. M. Benjamin, P. Wilder, Jr., and C. J. Collins, *ibid.*, **83**, 3654 (1961).

(11) L. S. Ciereszko and J. G. Burr, Jr., *ibid.*, **74**, 5431 (1952); P. S. Bailey and J. G. Burr, Jr., *ibid.*, **75**, 2951 (1953); B. M. Benjamin and C. J. Collins, *ibid.*, **78**, 4952 (1956). See also V. F. Raaen and C. J. Collins, *ibid.*, **80**, 1409 (1958), for comparison of solvolytic rearrangement of glycols and aldehydes with deamination of primary amines.

(12) M. S. Kharasch, A. Fono, W. Nudenbêrg, and A. C. Poshkus, *J. Org. Chem.*, **15**, 775 (1950).

appearance of a reaction pathway unlike those in the reactions mentioned above. Tiffeneau, *et al.*,[13] made brief mention of deamination of **1** along with several other related semipinacols. The results of these experiments seemed to be internally inconsistent, and no mention was made of any products which might have arisen from *o*-methoxy oxygen participation. In light of these facts we felt that deamination of **1** merited reinvestigation.

Results

Deamination of 2-amino-1-(2-methoxyphenyl)-1-phenylethanol (**1**) was effected with sodium nitrite in 50% aqueous acetic acid at 0 and 30°, yielding the deoxybenzoins **2**[14] and **3**[15] and 3-phenylbenzofuran (**4**)[16] (eq 1). The product compositions are recorded in

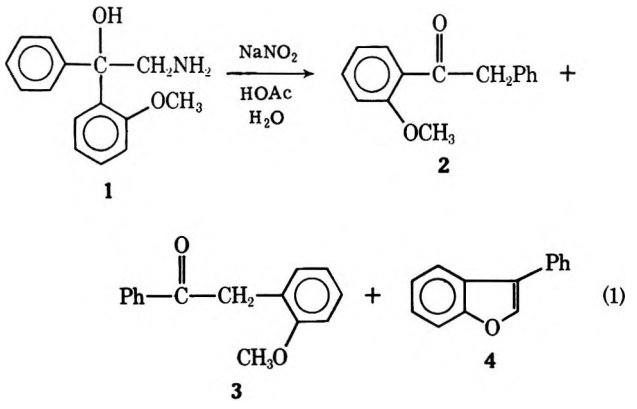


Table I. Determination of product composition was accomplished by glpc analysis of the total neutral

TABLE I
PRODUCT COMPOSITION IN DEAMINATION OF SEMIPINACOL 1

	Yield, %	
Product	0°	30°
2	47.1	42.5
3	11.6	12.6
4	26.7	18.8

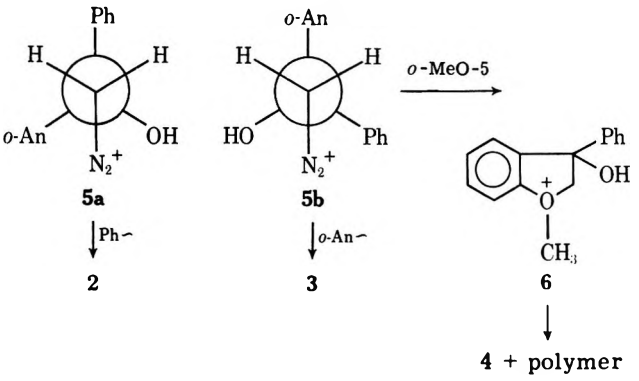
product (freed of polymer by filtration through alumina) to determine the ratio of **4** to the mixture of **2** and **3**, followed by nmr spectral analysis to determine the ratio of **2** to **3** (see Experimental Section). Compounds **2**, **3**, and **4** were synthesized independently and known mixtures were prepared to standardize the analyses.

Since a mechanism can be drawn for further reaction *via* *o*-methoxy oxygen attack on the protonated keto group, control experiments were performed to demonstrate that **3** was in fact stable to the deamination conditions. Ketones similar to **2** are known[9] to be stable to these conditions. The furan **4** would not be expected to decompose under these conditions, although vigorous conditions (polyphosphoric acid at 132° for 2 hr) cause a clean isomerization to 2-phenylbenzofuran (80%);[16] furthermore, **4** is largely insoluble in the reaction medium, as are **2** and **3**.

Discussion

Examination of the data in Table I shows that the *apparent* migratory aptitude of *o*-methoxyphenyl relative to phenyl (the ratio **3**/**2**) is 0.25 at 0° and 0.30 at 30°. This would appear to be in agreement with the results obtained from the rearrangement of the symmetrical di-*o*-anisyldiphenyl glycol.[2,5b,6,7] However, the presence of **4** in the product mixture demonstrates that *o*-MeO-5 involvement[8] is important and must arise from the rotamer which should otherwise lead to *o*-methoxyphenyl migration (see Scheme I). Thus it is

SCHEME I



o-An = *o*-$CH_3OC_6H_4$

apparent that the term "migratory aptitude" should not be applied in cases of this sort, since it does not reflect a proper comparison of total product formation. This is the first case in which *o*-MeO-5 involvement has been demonstrated in deaminative rearrangement.[17] Further, the relative proportions of **2** and **3** are considerably different from those previously reported (1:1).[13]

Scheme I portrays what we believe to be the best explanation of the observed results of deamination of semipinacol **1**. We represent the reactive intermediates as diazonium ions in which aryl migration and/or methoxy oxygen involvement take place in an anti relationship with the leaving group. Such a mechanism is generally accepted in reactions of this type, particularly in primary amines.[9,18-22] In an elegant stereo- and radiochemical study, Benjamin, Schaeffer, and Collins[23] showed that the deamination of optically active and radiolabeled 2-amino-1,1-diphenyl-1-propanol proceeded with 12% *retention* of configuration at the migration terminus. This result was interpreted in terms of classical carbonium ions as the active intermediates, with phenyl migration occurring in accord

(13) M. Tiffeneau, A. Oryékhoff, and M. Roger, *Bull. Soc. Chim. Fr.*, **49**, 1757 (1931). It should be noted that *Chem. Abstr.*, **26**, 2423 (1932), contains errors in the translation of this article, substituting twice *m*- for *o*-$MeOC_6H_4$ and once *p*- for *m*-$MeOC_6H_4$ at critical points.

(14) M. O. Farooq, W. Rahman, M. Ilyas, and S. Jehan, *Chem. Ber.*, **94**, 1996 (1961).

(15) Å. Spetz, *Acta Chem. Scand.*, **10**, 1422 (1956).

(16) W. Davies and S. Middleton, *J. Chem. Soc.*, 822 (1958).

(17) Oxygen involvement of a different type is known, as, for example, carbonyl participation in deamination of glutamine: A. T. Austin and J. Howard, *Chem. Ind. (London)*, 1413 (1959).

(18) D. J. Cram and J. E. McCarty, *J. Amer. Chem. Soc.*, **79**, 2866 (1957).

(19) A. Streitwieser, Jr., *J. Org. Chem.*, **22**, 861 (1957), and references cited therein.

(20) D. V. Banthorpe in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, London, 1968, Chapter 10.

(21) R. D. Guthrie, *J. Amer. Chem. Soc.*, **89**, 6718 (1967).

(22) M. C. Whiting, *Chem. Brit.*, **2**, 482 (1966).

(23) B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *J. Amer. Chem. Soc.*, **79**, 6160 (1957).

with the "cis effect;"[3b,9,23] a later interpretation was based on ground-state conformational control.[10] Nevertheless, in the present case a primary carbonium ion would be necessary in order to parallel the mechanism of Collins and coworkers,[23] and we believe that Scheme I is a better choice here.

Two comments on the details of Scheme I are in order. First, the high proportion of the apparently less sterically favorable ion **5a** (see Table I) might be influenced by a high population of the ground-state conformation leading to **5a** because of more favorable hydrogen bonding between methoxy and amino groups (not possible in the ground-state conformation leading to **5b**) as well as between amino and hydroxyl groups. Matsumoto, *et al.*,[24] have presented evidence for the importance of RO···HO bonding in *o*-alkoxy glycols, and molecular models indicate that this might be a favorable arrangement in the present instance; the nmr spectrum of **1** shows shielding of the methoxy group compared with precursors which lack the amino group, but we do not regard this as definitive. This argument assumes that migration is competitive with central C–C bond rotation.[19,23] Second, we feel that the products **3** and **4** do not completely reflect the amount of starting meterial reacting through ion **5b**; we believe that "polymer" (*i.e.*, yellow material lost by filtration of the reaction products through alumina) is formed mainly, though not exclusively, through ion **6** in Scheme I. Our reasoning is as follows. Curtin and Crew[9f] showed that, in the *p*-methoxy analog of **1** and in related semipinacols, ketones were recovered in 97–100% of the theoretical yield. (See Results section for comments on the stabilities of our products to the reaction conditions.) Thus it appears that, in the absence of oxygen involvement of the type depicted in **6**, deamination proceeds cleanly to ketonic (and monomeric) products. Furthermore, comparison of the results at 30° with those at 0° appears to reinforce this argument. At the higher temperature the proportion of phenyl migration (**5a** → **2**) decreases, *o*-methoxyphenyl migration (**5b** → **3**) increases slightly, and production of **4** decreases substantially while "polymer" formation increases markedly; these results are in general agreement with expectations of increased polymer formation at higher temperature. The nature of this polymeric material has not been explored, but several possibilities for diversion of **6** to products other than **4** can be envisaged; for example, capture of **6** by water or acetic acid could give either glycol or hydroxy acetate which could undergo various acid-catalyzed decompositions.

We are presently conducting further experiments which we hope will shed more light on the role of the *o*-methoxyphenyl group in rearrangements of a nature similar to that reported here.

Experimental Section

All melting points were determined in open capillary tubes in a Thomas-Hoover melting-point apparatus and are uncorrected. Infrared (ir) spectra were recorded on Beckman IR-8 and Perkin-Elmer 700 spectrophotometers. Nuclear magnetic resonance (nmr) spectra were recorded on a Hitachi Perkin-Elmer R-20 60-MHz spectrometer. Ultraviolet (uv) spectra were recorded on a Perkin-Elmer 202 spectrophotometer in solvent ethanol. Gas–liquid partition chromatography (glpc) was performed on a 6 ft × 0.25 in. SE-30 column at 209° in a Loenco 2400 gas chromatograph with a helium carrier gas flow rate of about 60 cm³/min.

2-Bromo-2′-methoxyacetophenone.—The procedure of Buckman, *et al.*,[25] was followed. The yield of bromo ketone was 80%: bp 130° (1 mm); ir (neat) 1680 cm^{-1} (C=O); nmr (CCl_4) δ 7.3 (4 H, m, ArH), 4.39 (2 H, s, CH_2Br), and 3.96 (3 H, s, OCH_3).

2-Azido-2′-methoxyacetophenone.—A solution of sodium azide (0.975 g, 15.0 mmol) in water (3 ml) was added at once with stirring to the above bromo ketone (3.00 g, 13.1 mmol) dissolved in ethanol (7.5 ml). Within 30 min there appeared a suspension of pale yellow oil which solidified on cooling. The solid was filtered and washed repeatedly with water until a silver nitrate test for bromide ion in the wash water was negative. After drying, 2.24 g (89%) of crude azide was recovered. It was recrystallized to constant melting point from methanol: mp 45–46°; ir (Nujol) 2130 (strong, N_3), 2210 (weak, N_3), and 1675 cm^{-1} (C=O); nmr (CCl_4) δ 7.3 (4 H, m, ArH), 4.32 (2 H, s, CH_2N_3), and 3.95 (3 H, s, OCH_3).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.82; H, 4.93; N, 21.96 (Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.).

2-Amino-2′-methoxyacetophenone Hydrochloride.—A suspension of 5% palladium on charcoal (0.375 g) in absolute ethanol (2 ml) was stirred under hydrogen at 1 atm pressure and room temperature for 10 min. A solution of the above azido ketone (1.00 g) in acidified ethanol (2.6 ml of 36% hydrochloric acid in 7.8 ml of absolute ethanol) was admitted into the catalyst–ethanol mixture and allowed to react for 29 hr. The mixture was filtered, the catalyst was washed with three small portions of absolute ethanol, and the solution was concentrated on a rotary evaporator. Absolute ether was added until moderate precipitation of product occurred. After 9 days of refrigeration the solid was collected, washed with absolute ether, and dried to yield 0.763 g (72%) of the white, crystalline salt: mp (methanol–benzene) 165.0–165.6° dec; ir (CCl_4) 2700 (NH_3^+), 2580 (NH_3^+), and 1665 cm^{-1} (C=O); nmr (DMSO-d_6) δ 8.62 (3 H, s, NH_3^+), 7.4 (4 H, m, ArH), 4.35 (2 H, s, $COCH_2$), and 3.56 (3 H, s, OCH_3).

2-Amino-1-(2-methoxyphenyl)-1-phenylethanol (1).—The Grignard reagent was prepared in flame-dried apparatus, and these procedures were carried out under an atmosphere of dry nitrogen. Phenylmagnesium bromide was prepared by reaction of dry bromobenzene (1.87 g, 11.9 mmol) with magnesium turnings (0.29 g, 12.1 mmol) in absolute ether (5 ml). The finely powdered amine salt from the previous procedure (0.402 g, 2.0 mmol) was added in small portions with stirring over 65 min, and the mixture was allowed to reflux gently in an oil bath for 4.5 hr. The reaction mixture was then poured into a solution of ammonium chloride (0.5 g) in water (10 ml plus one drop of concentrated ammonium hydroxide). After hydrolysis was complete, the layers were separated, the aqueous layer was extracted twice with ether, and the ether extracts were pooled with the original organic phase. After drying ($MgSO_4$), the solution was filtered, diluted with absolute ether (40 ml), and acidified with gaseous hydrogen chloride. A white precipitate formed at once, and after prolonged addition of hydrogen chloride a pink solid began to appear. At this point addition of the gas was stopped and the flask was refrigerated for 2 days. The product was then filtered, washed with ether, and allowed to dry, yield 0.298 g (53%), mp 168–169° (lit.[13] mp 175–176°).

The free amine **1** was obtained by dissolving the hydrochloride (0.500 g) in water (5 ml) and adding 1 *M* sodium hydroxide (*ca.* 2 ml) dropwise. The resulting suspension was extracted with chloroform and the organic phase was dried ($MgSO_4$) and solvent was removed on a rotary evaporator. After recrystallization to constant melting point from chloroform–ether, the amine was obtained as white crystals: mp 104–106° (lit.[13] mp 107–108°); ir ($CDCl_3$) 3485 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 7.0 (9 H, m, ArH), 3.48 (3 H, s, OCH_3), 3.37 (1 H, d, J = 13 Hz, $CHNH_2$), 3.09 (1 H, d, J = 13 Hz, $CHNH_2$), and 2.0 (3 H, s, broad, NH_2 and OH).

2-Methoxydeoxybenzoin (2).—The reaction of 2-methoxybenzamide with benzylmagnesium bromide was carried out according to the procedure of Faroog, *et al.*[14] Purification of the product was effected by application of 15 g of the crude product to a column of 575 g of silica gel and elution with ether–pentane (1:4): ir (neat) 1675 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.2 (9 H, m, ArH),

(24) K. Matsumoto, R. Goto, T. Asano, and H. Wada, *Nippon Kagaku Zasshi*, **88**, 92 (1967).

(25) S. J. Buckman, J. D. Pera, and F. W. Raths, German Patent 1,174,017 (1964); *Chem. Abstr.*, **61**, 9987*d* (1964).

4.27 (2 H, s, $COCH_2$), 3.83 (3 H, s, OCH_3); uv λ_{max}^{EtOH} 207, 247, 313 nm.

2-Methoxybenzil.—By the procedure of Faroog, *et al.*,[14] 2-methoxydeoxybenzoin (2) (3.930 g, 17.39 mmol) was oxidized with selenium dioxide (2.12 g, 19.13 mmol) in acetic anhydride (35 ml). Chromatography of the resulting oil on silica gel with petroleum ether (bp 30–60°)–chloroform (1:1) provided 2.867 g (69%) of nearly pure 2-methoxybenzil as a yellow oil which slowly crystallized, mp 67–69°, plus *ca.* 0.6 g of impure material.

The material prepared as above was identical with another sample prepared by benzoin condensation between 2-methoxybenzaldehyde and benzaldehyde, followed by oxidation of the product with potassium permanganate, as described by Brass, *et al.*:[26] mp 70.1–7° (lit.[26] mp 71–72°); ir (CCl_4) 1655 and 1676 cm^{-1} (C=O); nmr (CCl_4) δ 7.4 (9 H, m, ArH) and 3.45 (3 H, s, OCH_3).

2-Hydroxybenzil.—By the procedure of Somin and Kuznetsov,[27] 2-methoxybenzil was fused with several times its volume of freshly prepared pyridine hydrochloride under nitrogen at 180° for 2 hr. 2-Hydroxybenzil was obtained as an amber oil (64%) which was only slightly impure as judged by thin layer chromatographic analysis on silica gel: ir (neat) 3350 (OH, very broad), 1720, 1675, 1630 cm^{-1} (C=O); nmr ($CDCl_3$) δ 12.4 (1 H, broad s, ArOH) and 7.6 (9 H, m, ArH).

2′-Hydroxydeoxybenzoin.—2-Hydroxybenzil was reduced by the procedure of Spetz[15] to give 2′-hydroxydeoxybenzoin as a yellow solid (60%). This was crystallized from ethanol–water to give tan flakes: mp 126–130° (lit.[15] mp 110–120° dec); ir (CCl_4) 3490 (OH) and 1675 cm^{-1} (C=O); nmr (acetone-d_6) δ 8.6 (1 H, broad s, OH), 7.5 (9 H, m, ArH), and 4.33 (2 H, s, CH_2).

2′-Methoxydeoxybenzoin (3).—2′-Hydroxydeoxybenzoin was methylated by the procedure of Spetz[15] to provide **3** as a light yellow, crystalline solid (94%): mp 56–58° [crystallization from a small volume of methanol raised the melting point to 58.5–59.5°; successive crystallizations of a portion of the solid from small quantities of methanol gave mp 60–61° (lit.[15] mp 61.5–62°)]; ir (CCl_4) 1683 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.4 (9 H, m, ArH), 4.27 (2 H, s, CH_2), and 3.74 (3 H, s, OCH_3); uv λ_{max}^{EtOH} 204, 243 nm.

3-Phenylbenzofuran (4).—The procedure of Davies and Middleton[16] was followed: bp 115° (1 mm) [lit.[16] bp 110° (0.3 mm)]; $n^{25}D$ 1.6308 (lit.[28] $n^{26}D$ 1.6296); ir (neat) 860 cm^{-1} (furan band[29]); nmr δ 7.4 (m); uv λ_{max}^{EtOH} 205, 270 nm.

The ir spectrum of this authentic 3-phenylbenzofuran was identical with that of the deamination product **4**; its retention time on glpc, which was the same as that of **4** (6.3 min), was unchanged on admixture with **4**.

Deamination of 1.—The aminoethanol **1** (199.6 mg) was dissolved in 50% aqueous acetic acid and the solution was placed in an ice bath. A solution of sodium nitrite (284 mg, a fivefold excess) in water (2 ml) was added dropwise with stirring over 5 min, and the mixture was allowed to stir for 24 hr at 0°. At the end of this period, the reaction was quenched by adding a 10% aqueous sulfamic acid solution dropwise until the solution no longer gave a positive test with starch–iodide paper. The reaction mixture was transferred to a continuous extractor, diluted with water (21 ml), and subjected to continuous extraction with petroleum ether for approximately 8 hr. The extract was stirred with anhydrous potassium carbonate until the solution was neutral; then it was filtered and the potassium carbonate residue was dissolved in water and extracted with chloroform. These extracts were dried ($MgSO_4$) and combined with the original organic phase. After removal of the solvent on a rotary evaporator, the crude product weighed 160.5 mg. This mixture was dissolved in 5 ml of ether and filtered through 2 g of neutral alumina. The nonpolymeric products were readily eluted with *ca.* 20 ml of ether; removal of solvent left 151.6 mg of an oil. This mixture was subjected to the analysis described below; results are recorded in Table I.

A similar run was carried out with 200.2 mg of **1** in an oil bath at 30 ± 1° for 4 hr. After continuous extraction the crude product weighed 162.4 mg; after elution through alumina, 133.0 mg of mixture was recovered. This was subjected to the analysis described below; results are recorded in Table I. Repeat runs gave similar results.

The 3-phenylbenzofuran could be separated from the deoxybenzoins by chromatography on silica gel (100–200 mesh). Product **4** was eluted with ether–petroleum ether (2:98), and **2** and **3** were eluted with ether.

Determination of the Ratio of 4 to 2 + 3 in Deamination Products.—A mixture of known composition was prepared from **4** and the deoxybenzoins separated on column chromatography; this was dissolved in ether and analyzed by glpc to determine detector response to each of the two peaks in the chromatogram. The retention time for **4** was 6.3 min, and that of the deoxybenzoin mixture was 12.1 min. Then the product mixtures from the deamination runs were analyzed by glpc with appropriate detector-response corrections applied to the measured peak areas (planimeter).

Determination of Proportions of 2 and 3 in Deamination Products.—Standard mixtures of the two deoxybenzoins **2** and **3** were prepared such that each mixture weighed *ca.* 50 mg. These mixtures were 75.8, 79.6, and 83.6% in **2**. Each of these deoxybenzoin mixtures was dissolved in 0.3 ml of $CDCl_3$ and its nmr spectrum was recorded. The methoxy proton peaks of the two compounds differ in chemical shift by 6.4 Hz in this solvent and at this concentration, and expansion of the sweep to 120 Hz separates the two signals. The integrations of the expanded methoxy peaks of the standards were used for comparison with those of the deamination samples. Peak-height ratios of these signals in the standard mixtures, determined at both 600- and 120-Hz sweep widths, were also determined and plotted against composition. The ratio of **2** to **3** in the alumina-filtered deamination mixture was determined by the nmr integration and by comparison with the peak-height ratio plots. Agreement between the values determined by these methods was within ±1%. It was demonstrated that presence of **4** in the deamination spamles had no effect on this analysis.

Control Experiment.—Compound **3** (50 mg) was subjected to the deamination conditions described above. Similar work-up followed by continuous extraction recovered 44 mg of crystalline material; this was filtered through alumina and then analyzed by glpc. The material was indicated to be pure **3**.

Registry No.—**1**, 34589-94-1; **2**, 33470-10-9; **3**, 27356-33-8; **4**, 1839-72-1; 2-bromo-2′-methoxyacetophenone, 31949-21-0; 2-azido-2′-methoxyacetophenone, 34635-38-6; 2-amino-2′-methoxyacetophenone HCl, 34589-97-4; 2-methoxybenzil, 34082-43-4; 2-hydroxybenzil, 34589-99-6; 2′-hydroxydeoxybenzoin, 2491-31-8.

Acknowledgments.—One of us (C. E. S.) gratefully acknowledges the award of a summer fellowship (1971) provided by Merck Sharp and Dohme; F. L. H. wishes to thank the San Fernando Valley State College Foundation for the award of a Faculty Fellowship (Half), (1970–1971). Dr. H. L. Nyquist provided helpful suggestions regarding preparation of the manuscript.

(26) K. Brass, E. Willig, and R. Hansen, *Ber.*, **63**, 2615 (1930).

(27) I. N. Somin and S. G. Kuzentsov, *Zh. Obshch. Khim.*, **30**, 220 (1960); **30**, 1842 (1960).

(28) J. N. Chatterjea, *J. Indian Chem. Soc.*, **33**, 339 (1956).

(29) K. Nakanishi, "Infrared Absorption Spectroscopy—Practical," Nankodo, Tokyo, 1966, p 52.

The Synthesis of Some Quinoxaline Ring Systems

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Received November 2, 1971

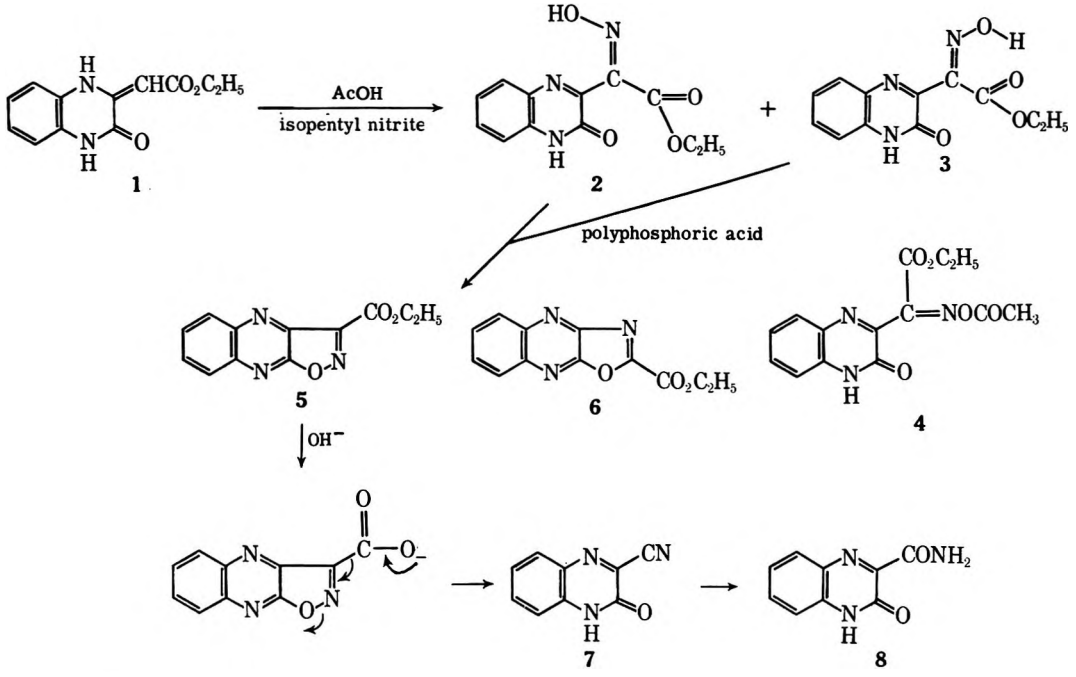
2-Ethoxycarbonylmethylene-1,2,3,4-tetrahydroquinoxalin-3-one was used as an intermediate to prepare both the isoxazolo[4,5-*b*]- and *v*-triazolo[1,5-*a*]quinoxaline ring systems. Some furo[2,3-*b*]- and pyrrolo[2,3-*b*]quinoxalin-2-one derivatives were synthesized and their behavior on alkylation is described. The tautomerism of some quinoxaline acetic acid derivatives is discussed.

We have reported previously on the tautomerism of product **1** obtained by the interaction of ethyl ethoxalylacetate with *o*-phenylenediamine[1] and now describe the use of this readily available starting material to prepare some fused quinoxaline ring systems.

The nitrosation of **1** by isopentyl nitrite according to the procedure described by Biekert and Kössel[2] yielded a mixture of isomeric products. One (A) precipitated from the reaction mixture and the other (B) was isolated by concentration of the mother liquor. These isomers are thought to be the two hydroxyimino derivatives, one in which the hydroxyl group is syn to the quinoxaline ring **2** and the other in which it is anti

Both A and B on acetylation with acetic anhydride and pyridine gave the same acetoxyimino compound **4**. The stereochemistry of this acetate could not be established.

Ring closure between the hydroxyimino and quinoxalone functions to form an isoxazole ring could be accomplished for both isomers by heating with polyphosphoric acid. The new isoxazolo[4,5-*b*]quinoxaline ring system was thereby formed in good yield. In view of the acidic conditions used for this cyclization, the possibility of a Beckmann rearrangement prior to ring closure could not be overlooked. This would lead to the isomeric oxazoloquinoxaline **6**. However,



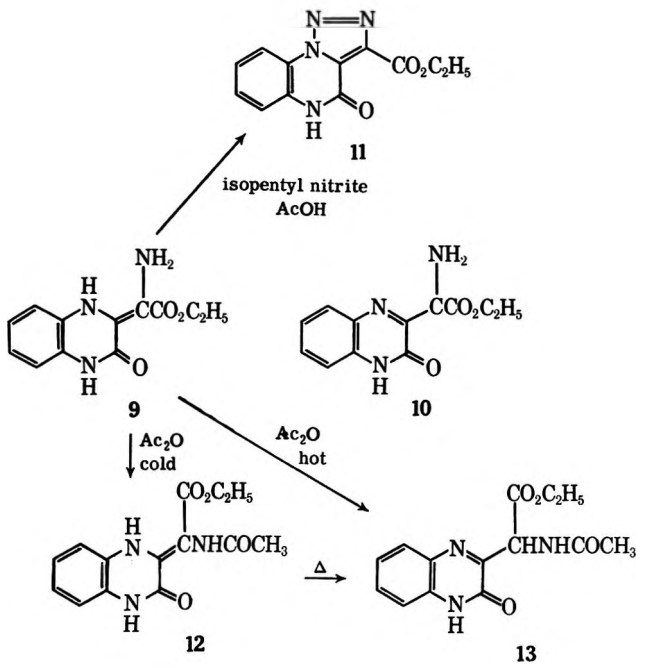
(**3**). It was not possible to study these isomers rigorously by spectroscopic means owing to their lack of solubility in suitable solvents; however, a tentative assignment of structure can be made. Isomer A can be converted into isomer B by prolonged boiling in ethanol or by treatment with methanolic HCl. Isomer B appears to have a more strongly hydrogen bonded structure than A, as evidenced by the appearance of a peak at δ 14 in its nmr spectrum (DMSO) which is absent from that of A.

The ester carbonyl frequency in B is lower than that in A, 1730 *vs.* 1740 cm^{-1}, suggesting hydrogen bonding to the carbonyl. Assuming the correctness of this suggestion, isomer A would have structure **2** and isomer B would have structure **3**.

treatment of the product with cold 5% sodium hydroxide solution showed that structure **5** was correct. After hydrolysis of the ester, decarboxylation with ring opening occurred, forming the nitrile **7**. Prolonged base treatment gave the amide **8**, whereas, if the oxazoloquinoxaline structure had been correct, 2-amino-3,4-dihydroquinoxalin-3-one would have been produced. A small amount of the amide **8** was also found as a by-product in large-scale cyclizations of **2** and **3**. This series of reactions provides convenient syntheses for both the nitrile **7** and the amide **8**.

The hydroxyimino compounds could also be used as a means to enter the *v*-triazolo[1,5-*a*]quinoxaline series. This was accomplished by catalytic reduction to the amino compound **9**, which was cyclized with isopentyl nitrite in acetic acid solution to give ethyl 4,5-dihydro-4-oxo-*v*-triazolo[1,5-*a*]quinoxaline-3-carboxylate (**11**) in

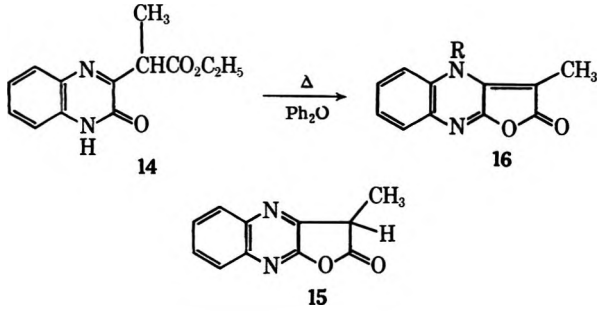
(1) D. D. Chapman, *J. Chem. Soc.*, 806 (1966).
(2) E. Biekert and H. Kössel, *Justus Liebigs Ann. Chem.*, **662**, 83 (1963).



reasonable yield. In an earlier synthesis of this ring system, the quinoxaline ring is closed as the final step.[3]

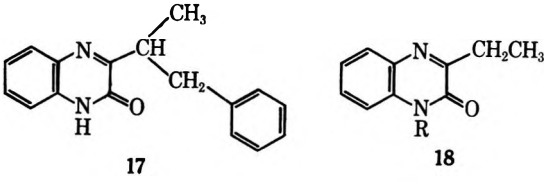
Although **9** could not be purified by recrystallization owing to decomposition, its structure was apparent from its spectral properties and an examination of its acetylation products. Its molecular weight was established as 247 from its mass spectrum; and, as its ir spectrum did not show a peak above 1700 cm^{-1}, this ruled out an alternative structure **10** which would be expected to have a carbonyl absorption in the 1730–1750-cm^{-1} range. With acetic anhydride in the cold a yellow monoacetate was formed, whereas in the hot a colorless isomeric product was isolated. The yellow product was formulated as **12** because again the ir spectrum lacked a peak in the saturated ester range. The colorless product had ir and nmr spectra which were consistent with structure **13**. In particular, the ester carbonyl appeared at 1755 cm^{-1} and the methine proton was a doublet at δ 5.98 owing to coupling with the adjacent NH. This doublet collapsed to a singlet on addition of D_2O to the solution. Attempts to run the nmr spectrum of **12** in DMSO solution were unsuccessful, as rapid rearrangement to the more stable form **13** took place.

In connection with the problems of tautomerism in quinoxaline acetic acid derivatives, it is of interest to recall that a methyl group may have a large effect. Whereas compound **1** exists in the solid as the exocyclic tautomer and in solution as a mixture of the exo- and endocyclic tautomers, **14** is completely in the endocyclic form both in the solid phase and in solution.[1] However, as will become apparent shortly, if the ester function is part of a ring, the equilibrium shifts toward the tautomer with the double bond exocyclic to the quinoxaline ring.



L'Italien and Banks[4] first obtained ester **14** from *o*-phenylenediamine and ethyl ethoxalylpropionate; they also reported that heating **14** in diphenyl ether caused it to cyclize to the furoquinoxalone **15**. However, repetition of this latter reaction and spectral examination of the product showed that structure **15** was incorrect. The ir spectrum in KBr showed bands at 3200 cm^{-1} attributable to an NH stretch and at 1745 cm^{-1} for the carbonyl group. The nmr spectrum had a three-proton peak at δ 1.75 assigned to a methyl group. This latter piece of evidence is sufficient to rule out the presence of structure **15** in solution, and with the ir evidence indicates that structure **16**, R = H, is correct. Methylation with methyl iodide and potassium carbonate gave the *N*-methyl compound **16**, R = CH_3. The nmr spectrum of this latter compound showed two peaks of equal intensity at δ 2.12 and 3.84 for the two methyl groups. Additional evidence for the assignment of structure **16**, R = H, was obtained by a comparison of its ultraviolet spectrum with that of **16**, R = CH_3. The two spectra were very similar, both in the position of the peaks and in intensity. Thus, a consideration of all the evidence leads to the conclusion that the product arising from the cyclization of **14** has structure **16**, R = H, both in the solid phase and in solution.

The *N*-octyl derivative was prepared similarly by reaction of **16**, R = H, with octyl bromide. However, when benzyl bromide was employed, the reaction took a different course and the major product isolated was **17**, identified by its elemental analysis and nmr spectrum, which showed a methyl doublet at δ 1.34 (J = 5 Hz), a nonequivalent methylene at δ 3.15 split by an adjacent proton, and a methine proton as a complex multiplet centered at δ 4.04. This product must have arisen by C-alkylation at position 3 prior to ring opening and decarboxylation because the reaction of **18**, R = H, under the same conditions gave only the *N*-benzyl derivative **18**, R = CH_2Ph, and no product resulting from C-alkylation.

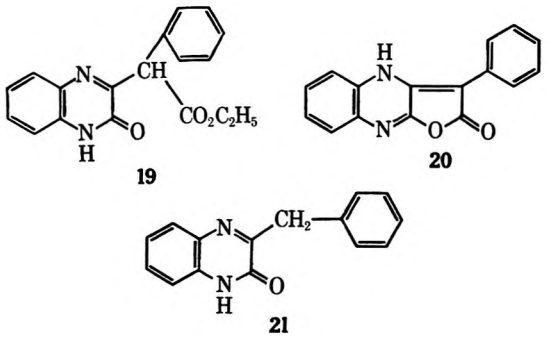


The 3-phenyl analog of **16**, R = H, was prepared in a similar manner. Ethyl phenyloxalacetate was condensed with *o*-phenylenediamine to yield the ester **19**, which was cyclized to a furoquinoxalone whose nmr spectrum in DMSO was in agreement with structure **20**; no peak corresponding to a methine proton was seen. Compound **20** could also be prepared from **21** by reaction with diethyl carbonate in the presence of sodium hydride.

The nature of the substituent on the α carbon of quinoxaline acetic acid derivatives has therefore been shown to have a profound effect on the position of the

(3) J. C. Kaver, U. S. Patent 3,262,943 (1966).

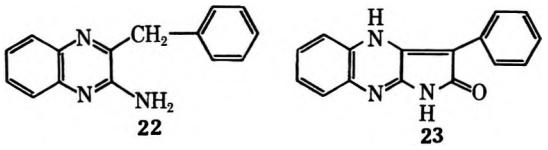
(4) Y. J. L'Italien and C. K. Banks, *J. Amer. Chem. Soc.*, **73**, 3246 (1951).


19 20 21

tautomeric equilibrium in these systems. In the case of an acetamido substituent, both tautomers can be isolated, although the exocyclic form is less stable and is readily converted to the endocyclic form. When the substituent is methyl or phenyl, the endocyclic form is the only one observed; and, when there is no substituent, a mixture of the two tautomers is present in solution. Also, if the ester function is part of a ring, the tautomeric stability is reversed in the methyl and phenyl cases as the tautomer with the double bond exocyclic to the quinoxaline ring is the stable one.

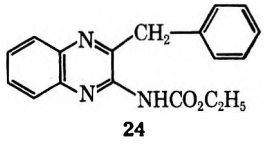
It was also of interest to compare the alkylation of the furoquinoxalones with that of the corresponding pyrroloquinoxalones.

A suitable intermediate for the synthesis of the pyrroloquinoxalone **23** appeared to be the amino compound **22**, which should react with diethyl carbonate


22 23

and sodium hydride to give **23**. Accordingly, the benzylquinoxalone **21** was converted to **22** *via* the chloro compound.

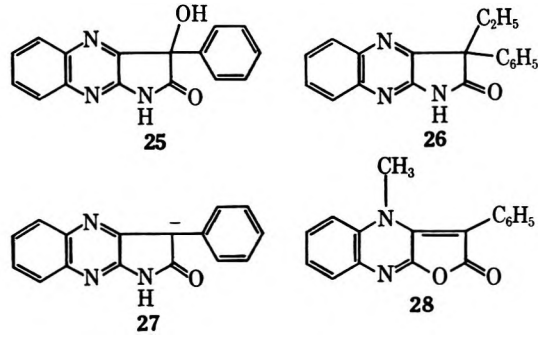
Unfortunately, the cyclization of the amino compound **22** with diethyl carbonate gave a mixture of four products. Two of these were identified as the desired compound **23** and the urethane **24**. The third product


24

contained one oxygen atom more than **23** and structure **25** is proposed. This is by analogy with the reaction of 3-phenyloxindoles with oxygen in alkaline solution.[5a] The basic hydrolysis of **25** gave 2-amino-3-benzoylquinoxaline, generated by decarboxylation followed by aerial oxidation.

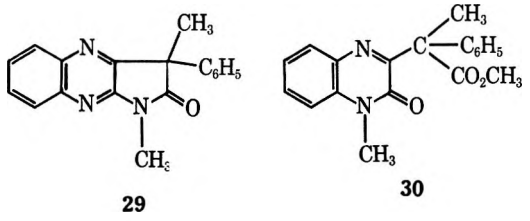
The fourth product, isolated in very low yield, surprisingly contained an ethyl group attached to a tertiary carbon atom, with the methyl appearing at δ 0.88 and the methylene at δ 2.55, and showed an infrared band at 1740 cm^{-1}. When the empirical formula is taken into consideration, the structure most favored is **26**, which could arise from alkylation of **27** by diethyl

(5) (a) P. Aeberli and W. J. Houlihan, *J. Org. Chem.*, **33**, 1640 (1968). (b) D. D. Chapman and J. W. Gates, Jr., U. S. Patent 883,018 (1970); U. S. Defensive Publication T883018.


25 26 27 28

carbonate. Accordingly, **23** was heated with diethyl carbonate and sodium hydride and the alkylated product was obtained in 50% yield.

The pyrroloquinoxalone **23** differs from its oxygen analog **20** in its behavior on alkylation. Compound **23** undergoes methylation at position 3 and at position 1 to give only the C-alkylated product **29**, whereas under


29 30

the same conditions **20** gives mainly the N-4 methylated product **28**. However, the mass spectrum of the crude product from the latter reaction shows a peak that corresponds to a structure such as **30**, which could result from C-3 methylation followed by ring opening and further methylation. In this case the anion derived from **20** is behaving as an ambident nucleophile. Thus, a replacement of an oxygen atom by a nitrogen on going from the furoquinoxalone **20** to the pyrroloquinoxalone **23** is sufficient to change the position of methylation from mainly N- to completely C-methylation.

Many of the quinoxalin-2-one compounds described in this paper are highly fluorescent and have been considered as optical brighteners.[5b] However, the furo[2,3-*b*]quinoxalin-2-one **20** and the corresponding pyrrolo compound **23**, although fluorescent, had their emission at too long a wavelength to be useful for this purpose.

Experimental Section

All melting points are uncorrected. Nmr spectra were recorded in deuteriochloroform solutions except where noted otherwise. Infrared spectra were run as potassium bromide disks.

2-Ethoxycarbonylmethylene-1,2,3,4-tetrahydroquinoxalin-3-one (1) was prepared as described previously.[4]

Reaction of 1 with Isopentyl Nitrite.—The ester (23.2 g) was suspended in glacial acetic acid (500 ml) containing trichloroacetic acid (3 g). After the addition of isopentyl nitrite (15 g), the mixture was stirred and all the solid dissolved. A white solid precipitated and after 1 hr the solution was filtered, yielding 9.5 g of ethyl 2-(3,4-dihydro-3-oxo-2-quinoxalinyl)-2-hydroxyiminoacetate (A), mp 227–229° after recrystallization from ethanol, ir 1740 and 3300 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.2; H, 4.2; N, 16.1. Found: C, 55.0; H, 4.5; N, 16.1.

The acetic acid mother liquor was evaporated to dryness at 55° under vacuum and the residue was triturated with ethyl acetate. The isomeric ethyl 2-(3,4-dihydro-3-oxo-2-quinoxalinyl)-2-hydroxyiminoacetate (B, 14 g) was obtained as a powder,

which was recrystallized from ethanol, mp 218–219°, ir 1730 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}N_3O_4$: C, 55.2; H, 4.2; N, 16.1. Found: C, 55.2; H, 4.3; N, 16.1.

Ethyl 2-(3,4-dihydro-3-oxo-2-quinoxalinyl)-2-acetoxyiminoacetate.—Ethyl 2-(3,4-dihydro-3-oxo-2-quinoxalinyl)-2-hydroxyiminoacetate (A, 1 g) was suspended in acetic anhydride (5 ml) and sufficient pyridine was added to give solution. After 15 min a pale yellow product (0.8 g) precipitated. After recrystallization from ethanol the acetate melted at 161–163°, ir 1790 and 1735 cm^{-1}, mass spectrum *m/e* 303.

Anal. Calcd for $C_{14}H_{13}N_3O_5$: C, 55.4; H, 4.3; N, 13.9. Found: C, 55.5; H, 4.4; N, 14.1.

The same acetate was obtained from the hydroxyimino isomer B in similar yield. On hydrolysis by cold methanolic HCl, isomer B was regenerated.

3-Ethoxycarbonylisoxazolo[4,5-*b*]quinoxaline (5).—A mixture of A and B (10 g) was added to polyphosphoric acid (200 g) and the mixture was heated on the steam bath with intermittent stirring for 4 hr. The solution was cooled and diluted with water, and the product was filtered off. The ester 5 (7 g) melted at 139–140° after recrystallization from ethanol, ir 1730 cm^{-1}.

Anal. Calcd for $C_{12}H_9N_3O_3$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.0; H, 4.0; N, 17.3.

In some larger scale runs, some of the amide 8 was also formed. This was separated by taking advantage of its insolubility in chloroform.

3-Cyano-1,2-dihydroquinoxalin-2-one (7).—The ester 5 (2 g) was added to 5% sodium hydroxide solution with stirring. After 2 hr the solution was filtered and the filtrate was acidified with hydrochloric acid, giving the nitrile 7 (1.3 g), mp 290° after recrystallization from ethanol (lit.[6] mp 288°), mass spectrum *m/e* 171.

Anal. Calcd for $C_9H_5N_3O$: C, 63.2; H, 2.9; N, 24.6. Found: C, 63.5; H, 3.1; N, 24.8.

3-Carbamoyl-1,2-dihydroquinoxalin-2-one (8).—The previous experiment was repeated with the reaction time increased to 24 hr. Acidification gave the amide 8, mp 307–308°. The infrared spectrum of the product was identical with that of an authentic sample.[7]

Hydrogenation of Ethyl 2-(3,4-Dihydro-3-oxo-2-quinoxalinyl)-2-hydroxyiminoacetate.—The hydroxyiminoacetate (9.7 g) was dissolved in tetrahydrofuran and hydrogenated at atmospheric pressure over platinum until the uptake of hydrogen ceased. The catalyst was removed by filtration and washed with ethanol and the filtrate was evaporated under vacuum at 25°. The orange-yellow product 9 separated when nearly all the solvent had been removed, and was filtered off. Attempts to recrystallize this product were unsuccessful (6.3 g), mp 159–161°, mass spectrum *m/e* 247.

Anal. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.2; H, 5.3; N, 17.0. Found: C, 57.4; H, 5.7; N, 16.8.

Acetylation of the Reduction Product 9. A.—The amine 10 (2.3 g) was dissolved in acetic anhydride (15 ml) and the yellow acetyl derivative 12 was filtered off, yield 2.2 g, mp 227–229°, with change from yellow to colorless at *ca.* 180°. Recrystallization from ethanol did not change the melting point.

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.1; H, 5.2; N, 14.5. Found: C, 57.9; H, 5.4; N, 14.5.

B.—The amine 10 (1 g) was heated on the steam bath with acetic anhydride (20 ml) for 45 min. After being cooled, the reaction mixture was filtered and the product *N*-acetyl-3,4-dihydro-3-oxo-2-quinoxalinylglycine ethyl ester (13, 0.9 g) was recrystallized from ethanol, mp 230–231°.

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.1; H, 5.2; N, 14.5. Found: C, 57.8; H, 5.2; N, 14.4.

2,4-Dihydro-3-methylfuro[2,3-*b*]quinoxalin-2-one (16, R = H) was prepared as described by L'Italien and Banks:[4] mp 310° (lit. mp 310°); ir 1745 and 3200 cm^{-1}; nmr (DMSO) δ 1.75; uv (ethanol) 268 nm (ε 1.69 × 10^4), and 380 (1.71 × 10^4).

2,4-Dihydro-3,4-dimethylfuro[2,3-*b*]quinoxalin-2-one (16, R = CH_3).—The furoquinoxalone 16, R = H (9 g), was dissolved in dry acetone (250 ml) and refluxed with methyl iodide (20 ml) in the presence of anhydrous potassium carbonate (9 g) for 36 hr. The solution was filtered and the filtrate was evaporated to dryness. Recrystallization from ethanol gave the 4-methyl derivative (7 g): mp 220–222°; ir 1755 cm^{-1}; nmr (DMSO) two peaks of equal intensity at δ 3.84 and 2.12; uv 270 nm (ε 1.74 × 10^4), 384 (1.81 × 10^4).

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.3; H, 4.7; N, 13.1. Found: C, 67.0; H, 5.1; N, 13.2.

The 4-octyl derivative 16, R = *n*-octyl, was prepared by refluxing 16, R = H, with a slight excess of *n*-octyl bromide and potassium carbonate in acetone solution: yield 42% after recrystallization from ethanol; mp 125–126°; ir 1750 cm^{-1}.

Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.0; H, 7.7; N, 9.0. Found: C, 72.9; H, 7.7; N, 8.7.

The Alkylation of 16, R = H, with Benzyl Bromide.—The furoquinoxalone 16, R = H (4.0 g), benzyl bromide (3.4 g), and potassium carbonate (8 g) were refluxed in acetone for 48 hr. The solution was filtered and the filtrate was evaporated to dryness. Trituration of the residue with ethyl acetate gave a trace of a yellow product (50 mg) that was presumably the 4-benzyl derivative. The ethyl acetate filtrate was evaporated to dryness and the residue was recrystallized from aqueous ethanol to give 3,4-dihydro-3-oxo-2-(1-phenyl-2-propyl)quinoxaline (17, 5.1 g), mp 174–175°.

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.2; H, 6.1; N, 10.6. Found: C, 76.9; H, 6.2; N, 10.6.

1-Benzyl-1,2-dihydro-3-ethylquinoxalin-2-one (18, R = CH_2Ph) was prepared from 1,2-dihydro-2-oxo-3-ethylquinoxaline[4] by alkylation with benzyl bromide under conditions similar to those of the previous reaction. After recrystallization from ethanol it melted at 98–99°, yield 60%.

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.2; H, 6.1; N, 10.6. Found: C, 77.2; H, 6.3; N, 10.6.

Ethyl (3,4-Dihydro-3-oxo-2-quinoxalinyl)phenylacetate (19).—The sodium salt of ethylphenyloxalacetate (5.8 g) was dissolved in water and a solution of *o*-phenylenediamine (2 g) in acetic acid (10 ml) was added. After being heated on the steam bath for 1 hr, the reaction mixture was cooled and filtered to give 19 as a colorless solid, mp 190–191°. Recrystallization from ethanol raised the melting point to 191–192°.

Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2; N, 9.1. Found: C, 70.1; H, 5.5; N, 9.2.

2,4-Dihydro-3-phenylfuro[2,3-*b*]quinoxalin-2-one (20).—The ester 19 (5 g) was dissolved in refluxing diphenyl ether (100 ml) and, after the ethanol had boiled off, the solution was cooled and diluted with petroleum ether (bp 30–60°). Filtration yielded 2,4-dihydro-3-phenylfuro[2,3-*b*]quinoxalin-2-one as a bright yellow powder (3 g), mp 271–272°, unchanged on recrystallization from ethanol.

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.3; H, 3.8; N, 10.7. Found: C, 73.0; H, 3.8; N, 11.0.

Methylation as for the 3-methyl analog gave 2,4-dihydro-4-methyl-3-phenylfuro[2,3-*b*]quinoxalin-2-one (28) as yellow prisms from ethanol: mp 229–230°; yield 45%; ir 1745 cm^{-1}; nmr δ 3.40.

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.9; H, 4.4; N, 10.1. Found: C, 73.9; H, 4.4; N, 10.0.

The mass spectrum of the crude product showed peaks at *m/e* 276 and 322.

2-Benzyl-3,4-dihydroquinoxalin-3-one (21).—Crude hydroxyiminophenylpyruvic acid[8] (115 g) was added to a solution of *o*-phenylenediamine (90 g) in water (1:1) and concentrated hydrochloric acid (200 ml). The reaction mixture was stirred and heated on a steam bath for 3 hr. After being cooled, the product (98 g) was filtered off and recrystallized from ethanol, mp 197–198° (lit.[9] mp 197°).

The above product (1.7 g) was heated in toluene with diethyl carbonate (10 ml) and sodium hydride (0.79 g, 53% oil dispersion) for 18 hr. The reaction mixture was evaporated to dryness. The residue was dissolved in water and the solution was acidified with acetic acid. The product (1.3 g) was recrystallized from ethanol and had an infrared spectrum identical with that of 20.

2-Benzyl-3-chloroquinoxaline.—The quinoxaline 21 (34 g) was added to phosphoryl chloride (200 ml), refluxed for 5 hr, and poured onto ice. The pH was adjusted to 6 (ammonia), the mixture was allowed to stand overnight, and the product was filtered off, yield 31 g, mp 86–87° after recrystallization from ethyl acetate–ligroin (lit.[10] mp 86–87°).

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2-Amino-3-benzylquinoxaline (22).—2-Benzyl-3-chloroquinoxaline (10 g) was added to ethanol (400 ml) that had been saturated with ammonia gas at 0° and the solution was heated at 170° for 8 hr. The reaction mixture was concentrated, filtered to remove ammonium chloride, and evaporated to dryness. Recrystallization from ethanol gave the aminoquinoxaline (4 g), mp 155–157°.

Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.1; H, 5.6; N, 17.9. Found: C, 76.1; H, 5.3; N, 17.8.

Interaction of 2-Amino-3-benzylquinoxaline with Diethyl Carbonate.—The amino compound (5 g) was dissolved in toluene (250 ml) containing sodium hydride (2.1 g of 53% mineral oil dispersion). The apparatus was arranged such that any ethanol formed could be removed after condensation. Diethyl carbonate (25 ml) was added dropwise over 30 min to the boiling reaction mixture and refluxing was continued for 4.5 hr. The solution was then evaporated to dryness and acidified with dilute acetic acid. The solid was filtered off, dissolved in chloroform, and extracted with 2 *N* potassium hydroxide. The dried chloroform solution was passed through an alumina column and the major fraction was recrystallized from ethanol to give the urethane **24** (2 g): mp 132°; nmr δ 4.43 ($C_6H_5CH_2$), 4.22 (q), 1.26 (t, C_2H_5O).

Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.3; H, 5.6; N, 13.7. Found: C, 70.2; H, 5.5; N, 13.7.

The alkaline extract was acidified with hydrochloric acid and the yellow solid was filtered off and dried. After three recrystallizations from isopropyl alcohol, the yellow pyrroloquinoxalone **23** (0.6 g), mp 296–300°, was obtained: mass spectrum *m/e* 261; ir 3360, 3200, 1660 cm^{-1}.

Anal. Calcd for $C_{16}H_{11}N_3O$: C, 73.6; H, 4.2; N, 16.1. Found: C, 73.3; H, 4.0; N, 16.0.

The mother liquors were evaporated and the residue was recrystallized successively from acetic acid and isopropyl alcohol (Norit) to give colorless crystals (1.2 g) of **25**: mp 297–298°; ir 3350 and 1745 cm^{-1}; mass spectrum *m/e* 277.

Anal. Calcd for $C_{16}H_{11}N_3O_2$: C, 69.3; H, 4.0; N, 15.2. Found: C, 69.0; H, 4.4; N, 15.1.

The mother liquors were again evaporated and the residue was extracted with chloroform. The extract gave a solid (120 mg) which, when recrystallized from ethanol, yielded 2,3-dihydro-3-ethyl-3-phenyl-1*H*-pyrrolo[2,3-*b*]quinoxalin-2-one (**26**): mp 217–218°; ir 1740 cm^{-1}; mass spectrum *m/e* 289.

Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.7; H, 5.2; N, 14.5. Found: C, 74.4; H, 5.3; N, 14.4.

Reaction of 22 with Diethyl Carbonate and Sodium Hydride.—The pyrroloquinoxalone **22** (320 mg), diethyl carbonate (7 ml), and sodium hydride (0.15 g, 53% oil dispersion) were refluxed in toluene (100 ml) for 36 hr. The solution was evaporated to dryness and acidified with dilute acetic acid. The product was dissolved in chloroform and the solution was extracted with 1 *N* potassium hydroxide. Acidification of the alkaline extract gave **26** (180 mg) having an infrared spectrum identical with that obtained previously.

Hydrolysis of 2,3-Dihydro-3-hydroxy-3-phenyl-1*H*-pyrrolo[2,3-*b*]quinoxalin-2-one.—Compound **25** (0.6 g) was dissolved in 2 *N* potassium hydroxide solution (15 ml) and heated on the steam bath overnight. The precipitated material was collected, dissolved in chloroform, chromatographed on silica gel, and recrystallized from ethanol to give 2-amino-3-benzoylquinoxaline (0.12 g), mp 168–169°, mass spectrum *m/e* 249.

Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.3; H, 4.5; N, 16.9. Found: C, 71.9; H, 4.2; N, 16.9.

Methylation of 2,4-Dihydro-3-phenyl-1*H*-pyrrolo[2,3-*b*]quinoxalin-2-one (22).—The pyrroloquinoxalone (0.33 g) was dissolved in acetone (75 ml) and, after the addition of methyl iodide (3 ml) and anhydrous potassium carbonate (1.5 g), the mixture was refluxed overnight. The product was worked up in the usual manner and chromatographed on neutral alumina in chloroform. 1,3-Dimethyl-2,3-dihydro-3-phenylpyrrolo[2,3-*b*]quinoxalin-2-one (**29**) (0.25 g) was eluted and recrystallized from aqueous ethanol to give colorless crystals: mp 129–130°; nmr δ 3.47 (NCH_3) and 1.95 (CCH_3); ir 1740 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.7; H, 5.2; N, 14.5. Found: C, 74.4; H, 5.2; N, 14.8.

Registry No.—**2**, 34731-45-8; **3**, 34712-59-9; **4**, 34712-60-2; **5**, 34731-46-9; **7**, 34731-47-0; **9**, 34731-48-1; **12**, 34731-49-2; **13**, 34712-61-3; **16** (R = CH_3), 34731-50-5; **16** (R = *n*-octyl), 32444-98-7; **17**, 34731-52-7; **18** (R = CH_2Ph), 34731-53-8; **19**, 30747-72-9; **20**, 32444-97-6; **22**, 34731-56-1; **23**, 34731-57-2; **24**, 34712-62-4; **25**, 34731-58-3; **26**, 34731-59-4; **28**, 33904-61-9; **29**, 34731-61-8; 2-amino-3-benzylquinoxaline, 34731-62-9.

Acknowledgment.—I wish to thank Dr. T. H. Regan and Mr. R. L. Young for the nmr spectra, Mr. G. Happ and Mr. D. Maier for the mass spectra, and Mr. D. F. Ketchum and his staff for the microanalyses.

Notes

Reactions of Arylcyclopropanes with *N*-Bromosuccinimide in Hydroxylic Solvents[1]

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Received January 13, 1972

Earlier we observed that the reactivity of bromine with arylcyclopropanes in hydrocarbon and halogenated hydrocarbon solvents is very sensitive to light, temperature, and solvent. These reactions resulted in the formation of aryldibromopropanes and products of aromatic ring substitution.[2] It was also of interest to explore the action of electropositive bromine on arylcyclopropanes in more polar, hydroxylic solvents. Therefore phenylcyclopropane (**1a**), *p*-bromophenylcyclopropane (**2a**), and *cis*- (**3a**) and *trans*-1,2-diphenylcyclopropane (**4a**) were treated with *N*-bromosuccinimide (NBS) in methanol solution. In addition, the diphenylcyclopropanes were treated with NBS in 1,2-dimethoxyethane–water. The distributions of product components were determined in most cases by glc analyses and are summarized in Table I. The principal products were isolated and the structures were determined by spectral and elemental analyses

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for their support of this work. (b) Paper X in a series dealing with carbon–carbon bond fission in cyclopropanes. For paper IX, see ref 2.

(2) R. T. LaLonde, P. B. Ferrara, and A. D. Debboli, Jr., *J. Org. Chem.*, **37**, 1094 (1972).

TABLE I

REACTANTS AND PRODUCTS. THE REACTION OF ARYLCYCLOPROPANES (ACP) WITH *N*-BROMOSUCCINIMIDE (NBS)[a]

ACP	NBS/ACP[b]	Product mixture, % composition[c] ACP	Aromatic substitution Product	Product
1a, A = H; B = H	1.05	**1a**, 11	**2a**, 9	**1c**, A = B = H; Y = OCH_3; Z = Br, 80
2a, A = Br; B = H	1.1	**2a**, 12		**2c**, A = Br; B = H; Y = OCH_3; Z = Br, 83
3a, A = H; B = *cis*-C_6H_5	1.11	**3a**, 5		**3c**, A = H; B = C_6H_5; Y = Z = OCH_3, 86
3a	1.0[d]	**3a**, 20[e]		**3d**, A = H; B = C_6H_5; Y = Z = OH, 40
				3e, A = H; B = C_6H_5; Y = Br; Z = OH, 34
4a, A = H; B = *trans*-C_6H_5	1.0	**4a**, 55	**5a**, 32	**3c**, 9
4a	2.0		**5a**, 72	**3c**, 19
4a	2.0[f]		**5a**, 100	
5a, A = Br; B = *trans*-BrC_6H_4				

[a] Reaction conditions were NBS and ACP in methanol for 7 days at room temperature in the dark unless indicated otherwise. [b] Mole ratio of NBS to ACP. [c] The distribution of unconsumed reactant and products was determined by glc analysis unless indicated otherwise. [d] The reaction was carried out in water–dimethoxyethane for 3 days at room temperature in the dark. [e] The product distribution was determined by weight. Minor products are given elsewhere. [f] The reaction was carried out in water–dimethoxyethane for 5 days at room temperature in the dark.

and in some cases were correlated with known compounds.

As the results of Table I show, phenyl-, *p*-bromophenyl-, and *cis*-diphenylcyclopropanes give mainly the products resulting from addition across the cyclopropane ring. The action of NBS on *cis*-diphenylcyclopropane in dimethoxyethane–water gives a complex mixture which consists not only of **3d** and **3e** but also 4% 3-hydroxy-1,3-diphenyl-1-propanone and 2% benzalacetophenone, products likely resulting from subsequent NBS oxidation and oxidation and elimination, respectively.

In contrast to phenylcyclopropanes **1a**, **2a**, and **3a**, *trans*-diphenylcyclopropane (**4a**) undergoes largely aromatic ring substitution giving *trans*-1,2-di-*p*-bromophenylcyclopropane (**5a**). In methanol some small amount of addition product is formed, and, like the cis isomer, addition occurs across the σ bond joining the two substituted carbons. In dimethoxyethane–water **5a** is the only detectable product.

The formation of para-substituted **5a** and **2a** is consistent with many previous examples of the directional influence of a cyclopropyl group and also with uv studies showing that cyclopropyl groups attached to aromatic rings are electron donors.[3] Seemingly the dissimilarity in the principal mode of *cis*- and *trans*-diphenylcyclopropane reactivity can be traced back to differences in the ground state levels. The cis isomer is known to be less stable.[4] According to molecular models, the difference in stability would seem to result from the crowding of the two phenyl groups in the cis isomer coupled with the more favorable conformation of the trans isomer wherein both phenyl groups bisect the plane of the cyclopropane ring and thereby allow maximum overlap of p-rich σ bonds of the cyclopropane ring with the π bonds of the phenyl groups.[5] Consequently an element of strain, not present in the trans isomer, is relieved in the addition to the cis isomer. As for the trans isomer, the second phenyl group can better donate electrons to the phenyl group undergoing attack in the electron-demanding process of electrophilic aromatic substitution. Therefore the energy of the transition state is lowered relative to that for aromatic substitution of the cis isomer.

Interestingly, the dimethoxydiphenylpropane addition products from *cis*- and *trans*-diphenylcyclopropane differ in diastereomeric composition. The cis isomer largely undergoes overall trans addition, resulting in a mixture of dimethoxypropanes rich in the *dl* diastereomer (*dl*/meso = 2). The trans cyclopropane gives equal amounts of *dl* and meso dimethoxypropanes. Selective isomer stereospecificity was previously observed in the dark, bromine addition to the diphenylcyclopropanes in carbon tetrachloride solution. There, the cis isomer gave predominantly the meso dibromide, indicating cis addition to the σ bond,[2] whereas the trans isomer again gave meso and *dl* dibromides in equal amounts. Presently we have insufficient evidence to offer an explanation for predominant cis addition in carbon tetrachloride and overall trans addition in methanol. The nature of the addition products first formed and the stereochemistry of subsequent solvolysis, including the ramifications of possible 1,3 neighboring group participation,[6] are imponderables at this time.

Experimental Section

Spectra were obtained as follows: nmr in $CDCl_3$ solution (unless otherwise indicated), 1% TMS (10.00 τ), Varian A-60A, symbols s, d, t, q, and m used in connection with nmr refer to singlet, doublet, triplet, quartet, and multiplet, respectively; ir in CCl_4 solution, 0.05-mm sample and reference cells (unless otherwise indicated), Perkin-Elmer 137, symbols s, m, w, sh, br, and sp used in connection with ir refer to strong, medium, weak, shoulder, broad and sharp, respectively.

Melting points were determined on a Köfler micro hot stage and are uncorrected. Glc was performed on a Varian Aerograph Model 200 using columns 5 ft × 0.25 in. containing the liquid

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phase on Chromosorb W. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

All reactions carried out in methanol solution were run for 7 days at room temperature in the dark and are referred to as standard reaction conditions. The standard procedure for processing the reaction mixture consisted of pouring the methanol solution into 50–100 ml of water and extracting the resulting mixture with ether (2–3 × 25 ml). The combined ether extracts were washed with water (2 × 25 ml) and dried (anhydrous $MgSO_4$). Evaporation of the ether at the rotary evaporator gave the crude product mixture.

Phenylcyclopropane.—Phenylcyclopropane was prepared by a known method.[7] A 473-mg sample (4.0 mmol) in 8 ml of absolute MeOH was treated with 750 mg (4.2 mmol) of NBS in 8 ml of MeOH under the standard reaction conditions. Processing by the standard procedure gave 776 mg of a clear, colorless liquid. Quantitative glc analysis using a 15% XF-1 at 130° established the presence of three components in 9, 11, and 80%. Comparative glc on 10% QF-1 (150°), 15% XF-1 (130°) and 20% Se-30 (180°) established the identity of the two minor components as phenylcyclopropane (11%) and *p*-bromophenylcyclopropane (9%). The major component was isolated and purified by preparative glc and was identified as 1-methoxy-3-bromo-1-phenylpropane: nmr τ 2.60 (s, 5 H, ArH), 5.60 (q, J = 5.5, 7.5 Hz, 1 H, $ArCHOCH_3$), 6.1–6.7 (m, 2 H, CH_2Br), 6.73 (s, 3 H, OCH_3), 7.3–8.2 (m, 2 H, CH_2); ir 2900 (m, sp), 1620 (w, sp), 1100 (s, br) 700 cm^{-1} (s, br).

Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72; Br, 34.88. Found: C, 52.62; H, 5.76; Br, 35.04.

***p*-Bromophenylcyclopropane.**—*p*-Bromophenylcyclopropane was prepared by a known method.[8] A 394-mg sample (2.0 mmol) in 4 ml of absolute MeOH was treated with 390 mg (2.2 mmol) of NBS in 4 ml of absolute MeOH under the standard reaction conditions. Processing by the standard procedure afforded 513 mg containing 12% unconverted *p*-bromophenylcyclopropane and 83% of the major component according to glc. A third unidentified component was detected by nmr (m, τ 8.18–8.40, and m, τ 8.6–8.7). Purification of the major component by preparative glc using a 10% QF-1 column (175°) gave 1-methoxy-3-bromo-1-*p*-bromophenylpropane: nmr τ 2.82 (A_2 of A_2B_2 m, 2 H, ArH), 2.75 (B_2 of A_2B_2 m, 2 H, ArH), 5.62 (q, J = 8, 5.5 Hz, 1 H, $ArCHOCH_3$), 6.3–6.7 (m, 2 H, CH_2Br), 6.75 (s, 3 H, CH_3O), 7.6–8.1 (m, 2 H, CH_2).

Anal. Calcd for $C_{10}H_{12}Br_2O$: C, 38.98; H, 3.98; Br, 51.89. Found: C, 38.89; H, 3.99; Br, 51.89.

***cis*-1,2-Diphenylcyclopropane. A. Methanol.**—A mixture of *cis*- and *trans*-1,2-diphenylcyclopropane was prepared by a known method.[9] Isomers were separated on a spinning band column to obtain pure cis, bp 116° (0.2 mm), and trans isomers, bp 125° (0.2 mm). A 970-mg sample (5.0 mmol) of the cis isomer in 10 ml of absolute MeOH was treated with 1.0 g (5.6 mmol) of NBS in 10 ml of the same solvent under standard reaction conditions. Processing by the standard procedure afforded 933 mg of product mixture consisting of 5% unconverted cyclopropane, 9% of an unidentified component, and 86% of the major component according to glc. Isolation of the major component from a sample by preparative glc using a 20% Se-30 column at 215° gave the known 1,3-dimethoxy-1,3-diphenylpropane:[10] mp 57–58°; nmr τ 2.69 (s, 10 H, ArH), 5.46 (q, J = 6, 7 Hz, *dl*-$ArCHOCH_3$),[11] 5.86 (J = 7 Hz, *meso*-$ArCHOCH_3$), 6.78 (s, OCH_3), 6.90 (s, OCH_3), 7.98 (q, J = 6, 7 Hz, *dl* CH_2), 7.5–8.3 (m, *meso*-CH_2), ratio of integrated intensities, τ 5.46/5.83 and 6.78/6.90 = *dl*/meso = 2; ir 2900 (s, sp), 1350 (s, sp), 1100 (s, br), and 700 cm^{-1} (s, br). Recrystallization of a sample of the crude product mixture from pentane gave 1,3-dimethoxy-1,3-diphenylpropane, mp 57–58°; nmr *dl*/meso = 2.

A solution of 1,3-dibromo-1,3-diphenylpropane (*dl*/meso = 1.0)[2] (2.08 g, 5.3 mmol), 1.08 g (6.0 mmol) of NBS, and 600 mg of succinimide in 24 ml of absolute MeOH was kept at room temperature for 7 days in the dark. Processing in the standard manner gave 1.19 g of crude 1,3-dimethoxy-1,3-diphenylpropane: nmr as above, 5.46/5.83 and 6.78/6.90 = *dl*/meso = 1.

B. Dimethoxyethane–Water.—To 3.492 g (18 mmol) of *cis*-1,2-diphenylcyclopropane in 300 ml of 1,2-dimethoxyethane and 110 ml of water was added in one portion 3.45 g (18 mmol) of NBS. This solution was then stirred at room temperature for 3 days in the dark. Thereafter the mixture was poured into 500 ml of water and the resulting mixture was extracted repeatedly with ether. The ether extract was washed with water and dried (anhydrous $MgSO_4$). Removal of the ether at the rotary evaporator gave 4.51 g of crude product mixture which was separated by glc using silica gel GF-254 and 97% $CHCl_3$–3% EtOAc. Thereby was obtained 925 mg of *dl*- and *meso*-1,3-dihydroxy-1,3-diphenylpropane [R_f 0.18; nmr (CD_3COCD_3) τ 2.5–2.9 (10 H, ArH), 4,9–5.3 (m, 2 H, ArCHOH), 6.57 (2 H, OH), 7.7–8.3 (m, 2 H, CH_2); ir 3300 (s, br), 1400 (m, sp), 1150 (br, d), 935 cm^{-1} (m, sp) and consistent with spectra of *dl* and meso diols obtained by another method],[2] 74 mg of 3-hydroxy-1,3-diphenylpropan-1-one [R_f 0.37; mp 49–51° from petroleum ether (bp 30–60°); semicarbazone mp 179–180°;[12] nmr τ 2.0–2.9 (m, 10 H, ArH), 4.70 (q, J = 6 Hz, 2 H, CH_2); ir 3600 (m, br), 1625 (s, br), 1455 (s, sp), 1210 cm^{-1} (s, br)], 760 mg of 1-bromo-3-hydroxy-1,3-diphenylpropane [R_f 0.57; nmr (CCl_4) 2.6–2.9 (m, 10 H, ArH), 5.13 (m, 1 H, ArCHOH), 5.60 (q, J = 5.8 Hz, ArCHBr), 7.25 (s, 1 H, OH), 7.0–8.0 (m, 2 H, CH_2); ir 3600 (m, br), 1300 (s, br)], 50 mg of benzalacetophenone (R_f 0.70), and 460 mg of *cis*-1,2-diphenylcyclopropane (R_f 0.95). Samples of 1-bromo-3-hydroxy-1,3-diphenylpropane darkened rapidly even when extreme precautions were taken to prevent it. Attempts to obtain a satisfactory analysis were unsuccessful.

Hydrolysis of 1-Bromo-3-hydroxy-1,3-diphenylpropane.—To 58 mg (0.2 mmol) of 1-bromo-3-hydroxy-1,3-diphenylpropane obtained as indicated above, in 3.7 ml of acetone was added in one portion 450 mg (0.2 mmol) of silver nitrate in 3.7 ml of water and the resulting slurry was stirred overnight at room temperature. The silver bromide (calcd: 38 mg; found: 34 mg) was filtered off and the acetone was removed from the filtrate at the rotary evaporator. The aqueous residue was extracted with ether and the extract was washed with water, 5% aqueous $NaHCO_3$, and water and then dried (anhydrous $MgSO_4$). Vacuum evaporation of the ether gave 45 mg of 1,3-diphenyl-1,3-propanediol whose spectra were consistent with those from a sample of meso and *dl* diol obtained earlier.[2]

***trans*-1,2-Diphenylcyclopropane. A. Methanol.**—*trans*-1,2-Diphenylcyclopropane was obtained as described above. A solution of 970 mg (5.0 mmol) of the cyclopropane in 10 ml of absolute MeOH was treated with 2.0 g (11 mmol) of NBS in 8 ml of absolute MeOH under standard reaction conditions. Processing by the standard procedure afforded 1.526 g of a moist, white solid. Glc analysis (20% Se-30, 225°) established the presence of 72% *trans*-1,2-*p*-bromophenylcyclopropane, 19% 1,3-dimethoxy-1,3-diphenylpropane, and 9% of at least six unidentified substances. Isolation of the 1,3-dimethoxy-1,3-diphenylpropane by glc and subsequent nmr analyses of the purified sample showed *dl*/meso = 1.

The remaining portion of crude product mixture was triturated several times with cold ether to obtain *trans*-1,2-*p*-bromophenylcyclopropane: mp 114–115°; nmr (CCl_4) τ 2.66 (A_2 of A_2B_2 m, 4 H, ArH), 3.10 (B_2 of A_2B_2 m, 4 H, ArH), 7.98 (A_2 of A_2B_2 m, 2 H, ArCH), 8.69 (B_2 of A_2B_2 m, 2 H, CH_2); ir 1490 (s, sp), 1010 cm^{-1} (s, sp).

Anal. Calcd for $C_{15}H_{12}Br_2$: C, 51.17; H, 3.44; Br, 45.39. Found: C, 51.31; H, 3.57; Br, 45.40.

In a similar manner 970 mg (5.0 mmol) of *trans*-1,2-diphenylcyclopropane was treated with 1.0 g (5.6 mmol) of NBS in a total of 20 ml of absolute MeOH in the standard manner and the reaction mixture was processed according to the standard procedure. Thereby was obtained 946 mg of a product mixture which consisted of 55% unconverted *trans*-1,2-diphenylcyclopropane, 32% *trans*-1,2-*p*-bromophenylcyclopropane, and 9%

(7) T. F. Corbin, R. C. Hahn, and H. Shechter, *Org. Syn.*, **44**, 30 (1964).

(8) R. Yu. Levina, P. A. Gembitskii, V. N. Kostin, S. M. Shostakovskii, and E. G. Treschchova, *Zh. Obshch. Khim.*, **33**, 365 (1963).

(9) S. G. Beech, J. H. Turnbull, and W. Wilson, *J. Chem. Soc.*, 4686 (1952).

(10) J. W. Copenhaver, U. S. Patent 2,768,212 (1956); *Chem. Abstr.*, **52**, 433c (1958).

(11) The combination of the low-field quartet (τ 5.46) with the high-field quartet (τ 7.98) was taken as an A_2X_2 resonance pattern stemming from the four methylene and methine protons of *dl*-1,3-dimethoxy-1,3-diphenylpropane. The low-field triplet (τ 5.86) in conjunction with the high-field complex multiplet (τ 7.5–8.3) constituted the ABX_2 pattern which originated from the four methylene and methine protons of *meso*-1,3-dimethoxy-1,3-diphenylpropane.

(12) D. S. Noyce, W. A. Pryor, and A. H. Bottini, *J. Amer. Chem. Soc.*, **77**, 1402 (1955).

1,3-dimethoxy-1,3-diphenylcyclopropane according to glc analysis (20% Se-30, 225°).

B. Dimethoxyethane–Water.—To 2.036 g (11 mmol) of *trans*-1,2-diphenylcyclopropane in 132 ml of 1,2-dimethoxyethane and 48 ml of water was added in one portion 4.1 g (23 mmol) of NBS. The resulting solution was kept at room temperature for 5 days in the dark. Thereafter the solution was poured into 1 l. of water and the mixture was extracted with ether (3 × 250 ml). The ether extract was washed with water and dried (anhydrous $MgSO_4$). Vacuum evaporation of the ether left a white solid whose glc analysis (Se-30, 225°) showed a single peak in addition to solvent. Two recrystallizations from ethanol–water gave 2.4 g of *trans*-1,2-*p*-bromophenylcyclopropane whose spectral properties were identical with those given above.

Registry No.—**1a**, 873-49-4; **1c**, 34733-61-4; **2a**, 1124-14-7; **2c**, 34733-62-5; **3a**, 1138-48-3; (±)-**3c**, 34733-63-6; *meso*-**3c**, 34733-64-7; **3e**, 34712-58-8; **4a**, 1138-47-2; **5a**, 34733-66-9; NBS, 128-08-5.

Rearrangement and Cleavage Processes in Crowded Cyclohexadienyl Carbonium Ions

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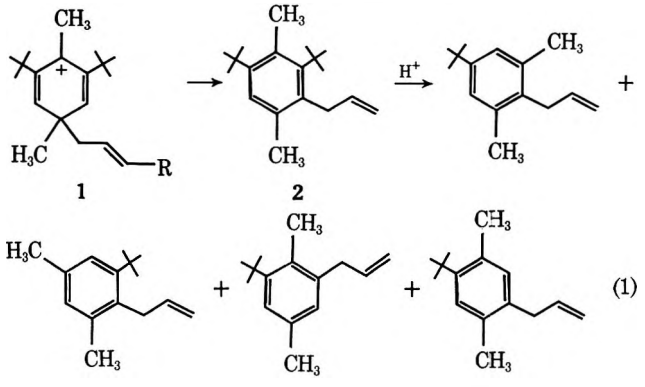
Received January 18, 1972

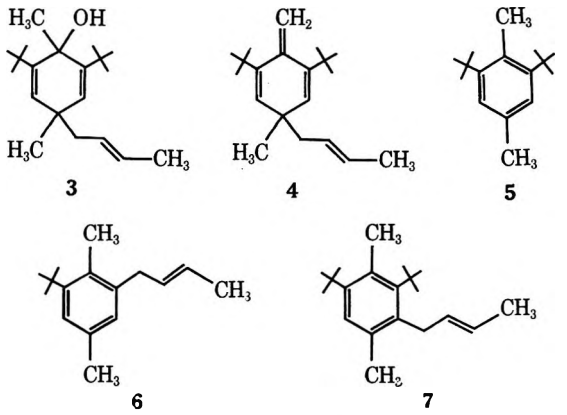
In an earlier paper[1a] we reported that carbonium ion **1** (R = H) rearranges to give the normal [1,2] migration product **2**. Rearrangement of **2**, in turn,



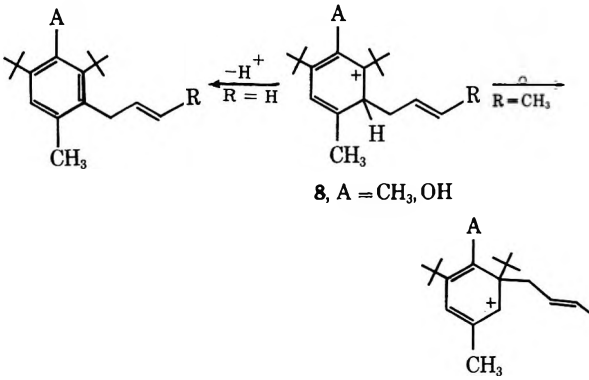
(1)

proceeds in surprisingly mild acid conditions to give the products shown in eq 1. The ease of rearrangement of **2** and the unusual nature of its rearrangement products were attributed to steric effects favoring protonation at the most hindered position on the ring.[1] We have now prepared several additional highly crowded cyclohexadienyl carbonium ions, in order to compare their reactions with those of **1**.

We first substituted a crotyl group (a better migrating group[2]) for the allyl group in **1**. Reaction of cyclohexadienol **3**[3] with 10% sulfuric acid in acetic acid gave two products in the ratio 6:1. These products were isolated by preparative vpc. The major product was identified as 2,6-di-*tert*-butyl-*p*-xylene (**5**),[3] while the minor product was assigned the structure 2-(*trans*-2-butenyl)-6-*tert*-butyl-*p*-xylene (**6**). (Evidence for structural assignments is discussed below.) When either **3** or the semibenzene **4**[3] was refluxed in benzene solution in the presence of Florisil (magnesium fluorosilicate), a mildly acidic heterogeneous catalyst,[4] **5** was again the major product, constituting from 60 to 75% of the total product, while **6** was obtained in 8–10% yield. A third component, constituting 20–30% of the product, was obtained under these conditions, however, and was assigned structure **7**. Compound **7** was found to be unchanged on prolonged refluxing in the presence of Florisil. Furthermore, on prolonged standing in sulfuric acid in acetic acid, **7** reacted to give a complex mixture of products. These were not isolated due to the small amount of **7** available. Vpc analysis, however, showed that **6** was only a minor component of the mixture. Thus, formation of **6** in the Florisil catalyzed reaction occurs predominantly during the initial rearrangement of carbonium ion **1** (R = CH_3) rather than as a result of further rearrangement of **7**.



The products obtained from carbonium ion **1** closely resemble those obtained from reactions of 2,6-di-*tert*-butylcyclohexadienones in acid.[2] With either the dienone or **1** no cleavage of an allyl group from the ring takes place,[1,2] while crotyl groups undergo appreciable cleavage.[2] That a higher yield of cleavage product is obtained from **1** than from the cyclohexadienone may be attributed to the fact that the energy gained by formation of an aromatic ring from **1** is greater than that resulting from formation of a phenol from a protonated cyclohexadienone. With either the dienone or cyclohexadienyl carbonium ion, initial [1,2] migration of a crotyl group to form **8** is immediately



followed, in sulfuric acid–acetic acid solution, by a second [1,2] migration of the crotyl group to the carbon

(1) (a) K.-H. Lai and B. Miller, *Tetrahedron Lett.*, 3575 (1971); (b) K.-H. Lai and B. Miller, *Tetrahedron*, **28**, 2221 (1972).

(2) B. Miller and H. Margulies, *J. Amer. Chem. Soc.*, **87**, 5106 (1965); B. Miller, *ibid.*, **87**, 5115 (1965).

(3) B. Miller and K.-H. Lai, *ibid.*, **94**, 3471 (1972).

(4) M. J. Gentles, J. B. Moss, H. L. Herzog, and E. B. Hershberg, *ibid.*, **80**, 3702 (1958).

TABLE I

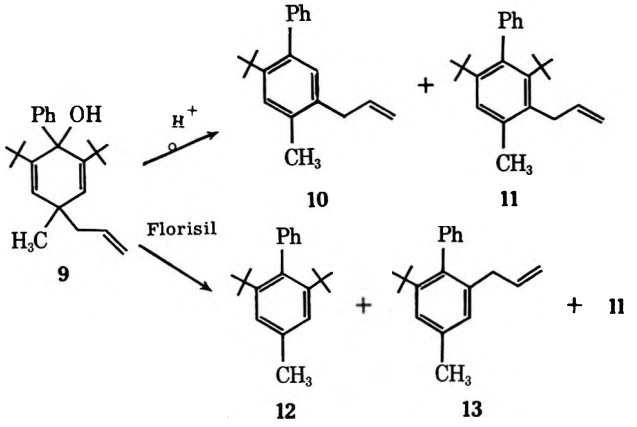
MAJOR PEAKS IN NMR SPECTRA (CHEMICAL SHIFTS IN UNITS OF δ)

Compd	ArH	t-Bu (s)	$-CH_2CH=C$	$ArCH_3$ (s)	$C=CHCH_3$
7	7.00 (s)	1.52 (9 H)	3.59 (d, J = 6.0 Hz)	2.51 (3 H)	1.65 (d, J = 6.0 Hz)
		1.41 (9 H)		2.23 (3 H)	
6	6.99 (d, J = 2 Hz)	1.44 (9 H)	3.22 (d, J = 5.5 Hz)	2.40 (3 H)	1.68 (d, J = 5.0 Hz)
	6.75 (d, J = 2 Hz)			2.25 (3 H)	
9	5.44 (s, 2 H)[a]	0.87 (18 H)	2.05 (d, J = 7.0 Hz)[b]	1.16 (3 H)[b]	
	7.1 (m, 5 H)				
10	7.1 (m, 7 H)	1.20 (9 H)	3.20 (b d, J = 6.0 Hz)	2.24 (3 H)	
11[c]	7.06 (s, 7 H)	0.99 (9 H)	3.72 (m)	2.28 (3 H)	
	7.14 (s, 5 H)	1.04 (9 H)			
12[c]	7.1 (b s, 7 H)	1.02 (18 H)		2.31 (3 H)	
13[c]	7.1 (m, 7 H)	1.11 (9 H)	2.73 (d, J = 6.0 Hz)	2.29 (3 H)	
14	5.45 (s, 2 H)[a]	0.92 (18 H)	2.02 (d, J = 6.0 Hz)[b]	1.19 (3 H)[b]	1.63 (d, J = 4.5 Hz)
	7.1 (m, 5 H)				
15[c]	7.12 (s, 1 H)	0.99 (9 H)	3.71 (m)	2.28 (3 H)	1.67 (d, J = 5.0 Hz)
	7.17 (b s, 5 H)	1.04 (9 H)			

[a] Vinyl protons on ring. [b] Substituents at C-4. [c] The chemical shifts for these compounds are slightly different from those previously reported,[5] due to recalibration of the instrument.

bearing the *tert*-butyl group. In contrast, migration of an allyl group in either case is sufficiently slow so that loss of a proton from **8** competes effectively with allyl migration.

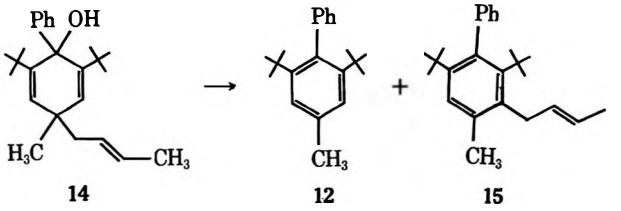
The effect of substituting a phenyl group for the methyl at C-1 in **1** seemed of interest. Reaction of 4-allyl-2,6-di-*tert*-butyl-4-methylcyclohexadienone with phenyllithium gave the corresponding cyclohexadienol **9**, apparently as a single isomer. Reaction of **9** with 10% sulfuric acid for 18 hr gave rise to two products, in the ratio 5:95.[5] The products were isolated by preparative vpc and assigned structures **10** and **11** (see



below). In contrast, rearrangement of **9** in refluxing benzene in the presence of Florisil gave three products in the ratio 7:20:73. These were isolated by preparative vpc. The major product was found to be **11**. The product present in lowest yield was assigned the structure **12**, and the product obtained in 20% yield was assigned structure **13**.

Reaction of **11** with 20% sulfuric acid in acetic acid for 24 hr gave rise to a very complex mixture containing at least six significant components. These had very similar vpc retention times, and could not be separated or identified. It could be determined, however, that the peak with retention time equal to that of **10** accounted for no more than 20% of the total area. Since **10** was the sole product other than **11** obtained from rearrangement of **9**, it could not have arisen as a secondary product from further reaction of **11**, but must have been formed directly from **9** by migration of a proton in carbonium ion **8** (R = H, A = C_6H_5). Similarly, formation of **13** during the Florisil-catalyzed rearrangement of **9** must have occurred during the initial rearrangement process, since **11** was unchanged by prolonged refluxing in the presence of Florisil.

Finally, rearrangement of dienol **14** in 10% sulfuric acid in acetic acid gave rise to **12** and a to new compound assigned structure **15**, in the ratio 89:11, respectively. Rearrangement of **14** in refluxing benzene



in the presence of Florisil gave **12** and **15** in the ratio 2:1.

The absence of any product analogous to **13** from rearrangement of **14** is presumptive evidence that **13** is formed by a [3,3] shift of the allyl group in the carbonium ion derived from **9**, rather than by two [1,2] shifts, since the crotyl group should undergo [1,2] shifts more readily than an allyl group. That a crotyl group in **8** (R = CH_3) apparently undergoes further migration more readily when A = CH_3 than when A = C_6H_5 can be accounted for by destabilization of **8** by the inductive effect of the phenyl group. Resonance stabilization of the carbonium ion by the phenyl substituent would presumably be minor, since the two rings are nearly perpendicular to one another.

Structural Assignments.—Most of the rearrangement products were assigned structures on the basis of their nmr spectra. The salient features of these spectra are outlined in Table I. (In addition to the resonances listed in the table, all compounds showed appropriate absorptions for vinyl protons of the allyl and crotyl groups. These absorptions were not of appreciable use for identifying products, and are therefore not listed in Table I.)

As has previously been pointed out,[1,6] resonances for

(5) A preliminary account of the formation of 2,6-di-*tert*-butylbiphenyls has been reported: B. Miller and K.-H. Lai, *Tetrahedron Lett.*, 2957 (1971).

(6) W. A. Gibbons and V. M. S. Gil, *Mol. Phys.*, **9**, 163, 167 (1965).

aromatic substituents (including hydrogen) ortho to *tert*-butyl groups exhibit significant downfield shifts compared to "normal" positions for resonances of these substituents when they are not located ortho to *tert*-butyl groups. Similarly, the resonances for *tert*-butyl groups ortho to groups other than hydrogen atoms exhibit slight downfield shifts. On the basis of these downfield shifts it can be seen that one methyl group in **7** is ortho to two *tert*-butyl groups and one methyl group in **6** is ortho to one *tert*-butyl group, while the other methyl groups in these molecules and in the other products are not ortho to *tert*-butyl groups. Similarly, the positions of the resonances for the allylic methylene groups demonstrate that the allyl group in **11** and the crotyl groups in **7** and **15** are ortho to *tert*-butyl groups, while those in **6**, **10**, and **13** are not. The aromatic hydrogen in **7** and *one* of the two aromatic hydrogens in **6** must be ortho to *tert*-butyl groups, while the coupling between the aromatic hydrogens in **6** demonstrates that they are meta to each other.

Further useful structural evidence is provided by the marked upfield shifts of substituents ortho to a phenyl group. As has been noted above, the two aromatic rings in the biphenyl derivatives are essentially perpendicular to one another, and ortho substituents will thus lie in the shielding cone of the unsubstituted phenyl ring. The high field locations of the resonances for the *tert*-butyl groups in **10**–**13** and **15** show that they remain ortho to the phenyl group. Similarly, the allyl group in **13** is clearly ortho to the *tert*-butyl group, while that in **10** is not.

Thus, the nmr spectra serve to unequivocally identify most of the rearrangement products. The only remaining ambiguity concerns the relative positions of the crotyl group and one of the methyl groups in **6**, and of the allyl group and the methyl group in **10**. In view of the strong evidence that allyl and crotyl groups are far better migrators than methyl groups,[2] it has been assumed that the methyl groups in **6** and **10** remain at C-4, and that these structures result from "normal" sequences of [1,2] migrations of the allyl and crotyl groups.

Experimental Section

All nmr spectra were taken in $CDCl_3$ solution on a Varian A-60 spectrometer, except where otherwise indicated. Ir spectra were taken on a Perkin-Elmer Model 237 spectrometer, using films of oils and liquids, and mineral oil mulls of solids. Vpc analyses were carried out on a Varian 202c chromatographic instrument equipped with a thermal conductivity detector, using the following columns: column A, 6 ft × 0.25 in., 3% SE-30 on Chromosorb W, at a He flow rate of 64 ml/min; column B, 5 ft × 0.375 in., 20% SE-30 on Chromosorb W, at a He flow rate of 155 ml/min; and column C, 1.5 × 0.375 in., 30% SE-30 on Chromosorb W, at a He flow rate of 186 ml/min. Elementary analyses were carried out by the University of Massachusetts Microanalytical Laboratory.

Synthesis of 4-Allyl-2,6-di-*tert*-butyl-4-methyl-1-phenylcyclohexa-2,5-dien-1-ol (9).—To a solution of 4-allyl-2,6-di-*tert*-butyl-4-methylcyclohexa-2,5-dien-1-one[2] (3.9 g, 0.015 mol) in 20 ml of benzene was added with stirring 15 ml of phenyllithium solution (2.11 *M* in 3:7 ether–benzene). After 0.5 hr, the solvent was evaporated under reduced pressure, and the residue was heated at 50° for 1 hr. The residue was shaken with 3:1 methanol–water solution and extracted with methylene chloride. The organic layer was washed with water, dried over magnesium sulfate, and evaporated under vacuum to give 5.6 g of a colorless fluid. Its ir spectrum showed a sharp OH peak at 2.7 μ, and no carbonyl peak. Vpc on column A at 200° showed three peaks with retention times of 1.1, 4.1, and 6.2 min, in the relative areas 1:1:13. These three products were isolated by preparative vpc on column B at 175°. The component with the lowest retention time was identified by its ir and nmr spectrum as biphenyl. The component with intermediate retention time was obtained as a white solid, mp 121–123°. Its ir spectrum showed peaks at 3.4 (s), 6.25 (m), 7.0 (m), 7.1 (m), 8.1 (w), 8.4 (m), 8.55 (w), 9.35 (m), 11.6 (s), 12.8 (w), 12.9 (s), 13.5 (s), and 14.0 μ (s). On the basis of its nmr spectrum (see Table I) it was assigned the structure **3,5-di-*tert*-butyl-4-phenyltoluene (12)**.

Anal. Calcd for $C_{21}H_{28}$: C, 89.9; H, 10.1. Found: C, 90.2; H, 10.2.

The component with highest retention time was obtained as a pale yellow oil. Its ir spectrum showed peaks at 2.7 (m), 3.35 (s), 6.05 (w), 6.2 (w), 6.75 (s), 6.9 (s), 7.18 (m), 7.35 (s), 7.55 (m), 8.1 (m), 8.35 (m), 8.45 (w), 8.65 (m), 9.15 (w), 9.65 (s), 9.85 (m), 10.05 (m), 10.75 (s), 10.9 (s), 11.5 (m), 12.9 (s), 13.7 (s), 14.2 (s), and 14.5 μ (m). On the basis of its nmr spectrum (see Table I) it was assigned the structure **4-allyl-2,6-di-*tert*-butyl-4-methyl-1-phenylcyclohexa-2,5-dien-1-ol (9)**. The presence of small peaks around δ 1.5, however, suggested the presence of aromatic impurities, to the extent of 2–3%.

The crude reaction product remaining (4.6 g) was chromatographed on silica gel (66 g). Elution with 5% benzene in *n*-pentane gave 3.2 g of oil. Vpc analysis on column A at 200° showed the presence of one major component, with a retention time of 9.5 min, as well as traces of biphenyl and **12**. The major component was isolated as a colorless oil by vpc on column B at 215°. Its ir spectrum showed peaks at 3.37 (s), 5.08 (w), 5.22 (w), 5.43 (w), 6.05 (w), 6.2 (w), 6.71 (w), 6.9 (s), 7.05 (m), 7.15 (m), 7.33 (s), 7.90 (w), 8.09 (w), 8.3 (s), 8.4 (m), 8.59 (w), 9.1 (w), 9.3 (w), 9.7 (m), 10.04 (m), 10.35 (w), 10.65 (w), 10.95 (s), 11.43 (m), 12.5 (w), 12.88 (s), 13.55 (w), and 14.1 μ (s). On the basis of its nmr spectrum (see Table I) it was assigned the structure **2-allyl-3,5-di-*tert*-butyl-4-phenyltoluene (11)**, yield 0.01 mol (73%).

Anal. Calcd for $C_{24}H_{32}$: C, 89.9; H, 10.1. Found C, 89.7; H, 10.2.

Further elution with 1:1 ether–pentane gave 0.8 g (2.2 mmol, 16%) of **9** as a colorless oil.

Synthesis of 4-(*trans*-2-Butenyl)-2,6-di-*tert*-butyl-4-methyl-1-phenylcyclohexa-2,5-dien-1-ol (14).—Phenyllithium solution (20 ml, 2.11 *M*) in 3:7 ether–benzene was added to 4-(*trans*-2-butenyl)-2,6-di-*tert*-butyl-4-methylcyclohexa-2,5-dien-1-one[2] (5.0 g, 0.0182 mol) in 20 ml of benzene. The mixture was stirred for 0.5 hr and then evaporated to dryness under reduced pressure, while being heated in a water bath at 50°. A mixture of water and methanol was then added, and the resulting mixture was extracted with *n*-pentane. The organic layer was washed with water, dried over magnesium sulfate, and evaporated to give 6.3 g (0.0179 mol, 98%) of **14** as a yellow oil. Its ir spectrum showed peaks at 2.73 (w), 3.35 (s), 6.2 (w), 6.75 (s), 6.9 (s), 7.15 (m), 7.35 (m), 7.65 (w), 8.1 (m), 8.35 (m), 8.65 (m), 9.15 (w), 9.65 (s), 9.86 (m), 10.35 (s), 10.8 (s), 11.5 (w), 12.4 (m), 13.7 (m), 14.2 (s), and 14.5 μ (m). Its nmr spectrum (see Table I) showed it to be essentially pure **14**.

Reaction of 4-(*trans*-2-Butenyl)-2,6-di-*tert*-butyl-1,4-dimethylcyclohexa-2,5-dien-1-ol (3) with Acid.—A solution of dienol **3** (0.14 g) in 2 ml of 10% sulfuric acid (by volume) in glacial acetic acid was kept at room temperature for 15 hr. Water was then added, and the mixture was extracted with *n*-pentane. The organic layer was washed with water, then with sodium bicarbonate solution, again with water, and then dried over magnesium sulfate and evaporated under vacuum to give 0.11 g of a brown oil. Vpc analysis on column A at 155° showed the presence of two components with retention times of 4.4 and 5.1 min, in the area ratio 6:1. The products were isolated by preparative vpc on column B at 175°. The major product was a white solid, mp 91–93°, which was identified as **2,6-di-*tert*-butyl-*p*-xylene (5)** by comparison of its ir and nmr spectra and vpc retention times with those of an authentic sample.[3] The minor component showed peaks at 3.4 (s), 6.2 (m), 6.85 (s), 6.92 (s), 7.35 (m), 9.55 (w), 8.2 (w), 8.4 (w), 9.5 (w), 9.7 (w), 9.95 (w), 10.4 (s), 11.7 (s), 13.5 (w), and 13.7 μ (w) in its ir spectrum. On the basis of its nmr spectrum, it was assigned the structure **2-(*trans*-2-butenyl)-6-*tert*-butyl-*p*-xylene (6)**.

Anal. Calcd for $C_{16}H_{24}$: C, 88.8; H, 11.2. Found: C, 88.7; H, 11.1.

Reactions of 4-(*trans*-2-Butenyl)-2,6-di-*tert*-butyl-1,4-dimethylcyclohexa-2,5-dien-1-ol (3) and 4-(*trans*-2-Butenyl)-2,6-di-*tert*-butyl-4-methyl-1-methylenecyclohexa-2,5-diene (4) in the Pres-

ence of Florisil —Florisil (0.50 g) was added to a solution of **3** (0.20 g) in 10 ml of benzene, and the mixture was refluxed for 15 hr. The mixture was then cooled and filtered, and the solvent was evaporated to give 0.15 g of a pale yellow oil. Vpc on column A at 175° showed the presence of three peaks with retention times of 2.6, 3.0, and 8.3 min, with relative areas in the ratio 10:52, respectively. The three products were isolated by preparative vpc on column B at 200°. The two components with lower retention times were identified as **5** and **6** by comparison of their nmr and ir spectra and vpc retention times with those of samples previously prepared.

The component with the highest retention time showed maxima in its ir spectrum at 3.35 (s), 6.3 (w), 6.8 (s), 6.9 (s), 7.05 (m), 7.17 (m), 7.3 (m), 7.35 (s), 7.98 (m), 8.25 (s), 8.4 (m), 8.75 (w), 9.45 (w), 9.7 (w), 10.05 (m), 10.35 (s), 10.55 (m), 11.5 (m), 12.7 (w), and 12.9 μ (w). On the basis of its nmr spectrum (see Table I) it was assigned the structure **3-(*trans*-2-butenyl)-2,6-di-*tert*-butyl-*p*-xylene (7)**.

A suspension of Florisil (0.20 g) in a solution of **4**[3] (0.20 g) in 10 ml of benzene was refluxed for 24 hr. Work-up as above gave 0.18 g of pale yellow oil. Vpc analysis on column A at 150° showed the presence of three components, with retention times of 2.6, 3.0, and 8.2 min, with relative areas of 9:3:1 The three products were isolated by preparative vpc on column B, and identified as **5**, **6**, and **7** by their ir and nmr spectra.

Rearrangement of 4-Allyl-2,6-di-*tert*-butyl-4-methyl-1-phenylcyclohexa-2,5-dien-1-ol (9) in Acid.—Dienol **9** (0.20 g) was dissolved in 4 ml of a 10% (by volume) solution of sulfuric acid in acetic acid. An insoluble layer immediately separated above the acetic acid layer. The mixture was allowed to stand at room temperature overnight, and the two layers then separated. The upper layer was dissolved in *n*-pentane, washed with water, sodium bicarbonate solution, and water, and dried over magnesium sulfate. The mixture was filtered and the filtrate was evaporated to give 0.16 g of a clear oil. Vpc analysis on column A at 200° showed the presence of only one peak with a retention time of 9.5 min. The ir and nmr spectra and vpc retention time of the product showed it to be 2-allyl-3,5-di-*tert*-butyl-4-phenyltoluene (**11**). The acetic acid layer was extracted with *n*-pentane, and the pentane layer was washed with water and sodium bicarbonate solution. It was dried over magnesium sulfate and the solvent was evaporated to give 0.05 g of brown oil. Vpc on column A at 200° showed the presence of two components with retention times of 3.6 and 9.6 min, with relative areas in the ratio 1:4. The two products were isolated by preparative vpc on column C at 175°. The major product was again shown to be **11**. The low retention time component had peaks in its ir spectrum at 3.4 (s), 6.1 (m), 6.2 (m), 6.75 (s), 6.85 (s), 6.95 (s), 7.15 (w), 7.35 (m), 8.05 (m), 8.3 (m), 9.35 (m), 9.7 (m), 10.5 (m), 11.0 (s), 11.4 (m), 13.0 (s), and 14.35 μ (s). On the basis of its nmr spectrum (see Table I) it was assigned the structure **2-allyl-5-*tert*-butyl-4-phenyltoluene (10)**.

Rearrangement of 9 in the Presence of Florisil —A mixture of **9** (0.20 g) and Florisil (0.20 g) in 10 ml of benzene was refluxed overnight. After filtration evaporation of the solvent gave 0.17 g of a clear oil. Vpc analysis on column A at 200° showed the presence of three peaks with retention times of 3.4, 4.1, and 9.8 min, with relative areas in the ratio 3:1:11. The products were isolated by preparative vpc on column C at 175°. The product with lowest retention time was a pale yellow oil with ir peaks at 3.35 (s), 6.05 (m), 6.2 (m), 6.4 (w), 6.85 (w), 6.95 (s), 7.1 (w), 7.2 (w), 7.35 (m), 8.2 (m), 8.3 (m), 8.5 (w), 8.7 (w), 9.35 (m), 9.7 (w), 9.9 (m), 10.05 (w), 10.95 (s), 11.65 (s), 12.6 (w), 13.1 (s), and 14.2 μ (s). On the basis of its nmr spectrum (see Table I) it was assigned the structure **3-allyl-5-*tert*-butyl-4-phenyltoluene (13)**.

Anal. Calcd for $C_{20}H_{24}$: C, 90.9; H, 9.15. Found: C, 90.9; H, 9.17.

The other two products were identified by their ir and nmr spectra and vpc retention times as **12** and **11**.

Reaction of 4-(*trans*-2-Butenyl)-2,6-di-*tert*-butyl-4-methyl-1-phenylcyclohexa-2,5-dien-1-ol (14) with Acid.—Dienol **14** (0.20 g) was dissolved in 10% sulfuric acid in glacial acetic acid solution. A white solid formed immediately. Water was added and the mixture was extracted with *n*-pentane. The pentane solution was washed with water and sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to give 0.18 g of oily crystals. Vpc on column A at 200° showed the presence of two components with retention times of 4.1 and 11.0 min, in the area ratio 10:1. Recrystallization from methanol gave white crystals, mp 122–124°, which were identified by their vpc retention time and ir and nmr spectra as **12**. The oil obtained from the mother liquor after recrystallization showed two peaks with the same retention times as before recrystallization. The peak with the higher retention time was isolated as a pale yellow oil by preparative vpc. The ir spectrum of the product had peaks at 3.35 (s), 5.8 (w), 6.22 (m), 6.3 (w), 6.75 (s), 6.95 (s), 7.1 (m), 7.2 (m), 7.65 (w), 7.9 (w), 8.15 (w), 8.3 (s), 8.4 (m), 8.6 (w), 9.3 (m), 9.7 (m), 9.85 (m). 10.3 (s), 10.7 (w), 10.8 (w), 11.4 (m), 12.75 (s), 13.55 (w), and 14.05 μ (s). On the basis of its nmr spectrum (see Table I) this compound was assigned the structure **2-(*trans*-2-butenyl)-3,5-di-*tert*-butyl-4-phenyltoluene (15)**.

Anal. Calcd for $C_{25}H_{34}$: C, 89.7; H, 10.2. Found: C, 89.9; H, 9.86.

Reactions of 14 in the Presence of Florisil.—A mixture of **14** (0.20 g) and Florisil (0.20 g) in 10 ml of benzene was refluxed overnight and then filtered. The filtrate was evaporated to give 0.15 g of colorless oil. Vpc on column A at 200° showed the presence of two components with retention times of 4.1 and 10.1 min, with areas in the ratio 2:1. The two components were isolated by preparative vpc on column C at 175°. Comparison of their vpc retention times and ir spectra with those of the products previously showed them to be **12** and **15**, respectively.

Registry No.—**3**, 34731-37-8; **6**, 34731-38-9; **7**, 34731-39-0; **9**, 34712-56-6; **10**, 34731-40-3; **11**, 34014-53-4; **12**, 34014-54-5; **13**, 34014-56-7; **14**, 34712-57-7; **15**, 34731-44-7.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant in support of this work.

The Reaction of 1-Azirines with 1,3-Diphenylisobenzofuran. Ring Expansion to Isoquinoline, Dihydroisoquinoline, and Azanorcarane Derivatives

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Received January 28, 1972

Under appropriate reaction conditions advantage can be taken of the inherent reactivity of the rigid C=N bond of 1-azirines to effect cycloadditions. The 2-π electrons of this system can participate in thermally allowed [$_{\pi}4 + {}_{\pi}2$] reactions as dienophiles[1,2] or as dipolarophiles.[3-5] Thus, reaction of 1-azirines with cyclopentadienones proceeds *via* the cycloadduct to furnish after decarbonylation, valence tautomerism, and 1,5-sigmatropic shift, 3*H*-azepine derivatives. 1,3-Dipolar cycloaddition to the three-orbital 4-π electron system of diazomethane and nitrile oxides transforms these 1-azirines into allylic azides and carbodiimides, respectively. The apparent photochemical [2 + 2] cycloaddition with electron-deficient olefins actually proceeds through thermal addition of a 1,3-dipolar species generated by cleavage of the electronically excited singlet state of the appropriate azirine.[6]

(1) V. Nair, *J. Org. Chem.*, **37**, 802 (1972).
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(3) V. Nair, *J. Org. Chem.*, **33**, 2121 (1968).
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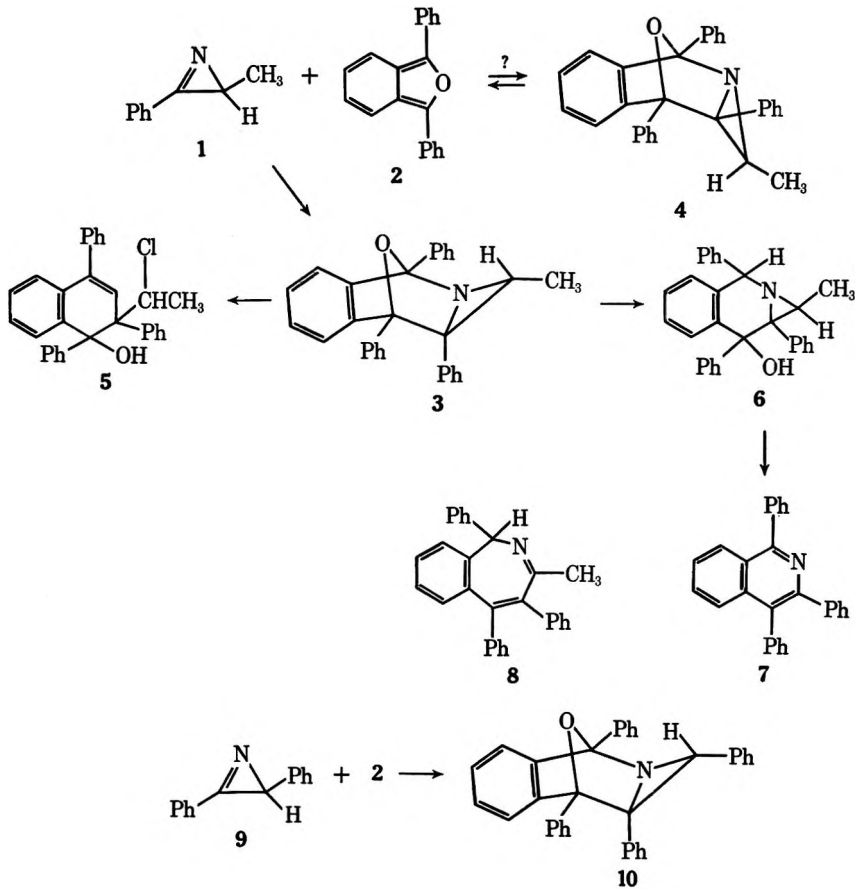


As part of this program, we embarked on some further cycloadditions of 1-azirines with dienes. We were particularly interested in the isolation and examination of the initially formed cycloadduct, a feature that had been absent from our previous studies on cycloadditions due to the inherent instability of these adducts. We selected to examine the cycloaddition of the reactive diene[7] 1,3-diphenylisobenzofuran (**2**)[8] with a model azirine, 3-methyl-2-phenyl-1-azirine (**1**).[3] When azirine **1** was treated with **2** in toluene at reflux temperatures for 18 hr, column chromatography and crystallization furnished a white, crystalline compound in 73% isolated yield. Mass spectral data and elemental analysis were consistent with the molecular formula $C_{29}H_{23}NO$. The nmr spectrum (in $CDCl_3$) showed absorptions at δ 1.05 (d, J = 5.8 Hz, 3 H) and 3.52 (q, J = 5.8 Hz, 1 H) and multiplets in the aromatic region between δ 6.48 and 7.96 (19 H, aromatic).

On the basis of the spectral evidence and the chemical transformations discussed below, the compound was assigned the cycloadduct structure **3**. The exo stereochemistry was inferred from its nmr spectrum, which showed considerable deshielding (>1 ppm) of the aziridine hydrogen (δ 3.52) by the oxido bridge, implying that this hydrogen is syn to the oxygen. Further support for this assignment comes from work on cyclopropene adducts with 1,3-diphenylisobenzofuran by Cava,[9] Breslow,[10] Battiste,[11] and coworkers.

The lone pair of electrons on the nitrogen of the cycloadduct **3** undergoes protonation readily in anhydrous HCl–benzene and the protonated species suffers subsequent cleavage to furnish the HCl salt of **5**, from which the free base **5** can be easily obtained. No dihydroazepine derivatives were isolated or detected. The protonated species resulting from **3** undergoes C–N and not C–C bond cleavage. There is discrimination between the two C–N bonds and cleavage of presumably the weaker aziridine bond takes place, giving the dihydroisoquinoline derivative **5**. That **5** is indeed the product of this ring cleavage was substantiated further by examination of the nmr spectrum of **5** HCl, which showed a downfield shift for both the H and CH_3 (of $ClCHCH_3$) consistent with a positive center situated β to the carbon carrying them.

Reductive cleavage of the exo adduct **3** with $LiAlH_4$ gave a compound to which we have assigned the benzoazanorcarane structure **6** on the basis of its spectral and analytical data. Its nmr spectrum showed considerable deshielding of the benzylic hydrogen (δ 5.68), suggesting that the central six-membered ring retains its boat conformation, the deshielding being from the hydroxyl group. When **6** was treated with anhydrous HCl at room temperature, a white, crystalline compound precipitated out of the reaction mixture within a few minutes. Its nmr spectrum was consistent with its being the hydrochloride salt of **6**. Treatment of **6** with anhydrous HCl in refluxing benzene converted it to the triphenylisoquinoline **7**.

When 2,3-diphenyl-1-azirine (**9**) was treated with 1,3-diphenylisobenzofuran (**2**), conversion to the exo adduct **10** occurred in ~70% yield.

The isolation of the exo adducts exclusively from these Diels–Alder reactions may be explained in terms

(7) Attempted cycloaddition with furan and with butadiene derivatives, such as methyl *trans*-2,4-pentadienoate, were unsuccessful.

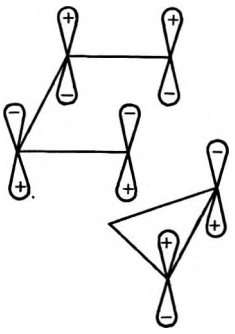
(8) M. S. Newman, *J. Org. Chem.*, **26**, 2630 (1961).

(9) M. P. Cava and K. Narasimhan, *ibid.*, **36**, 1419 (1971).

(10) R. Breslow, G. Ryan, and J. T. Groves, *J. Amer. Chem. Soc.*, **92**, 988 (1970).

(11) M. A. Battiste and C. T. Sprouse, *Tetrahedron Lett.*, 4661 (1970).

of an unfavorable increase in energy for the endo transition state as a result of secondary orbital interactions (11).[5] In 11, a mixing of the highest occupied diene



11

orbital with the lowest unoccupied cyclopropene or azirine orbital occurs.

It is possible that the endo adduct 4 is formed to a small extent but is unstable and undergoes a retro Diels–Alder reaction.[9]

We are currently examining the possible dehydrative rearrangement of the azanorcarane 6 to the 2*H* azepine 8.

Experimental Section

Reaction of 3-Methyl-2-phenyl-1-azirine with 1,3-Diphenylisobenzofuran. Formation of Exo Adduct 3.—A solution of 1.048 g (8 mmol) of 3-methyl-2-phenyl-1-azirine (1)[3,12] in 10 ml of toluene was treated with a solution of 1.620 g (6 mmol) of 1,3-diphenylisobenzofuran (2)[8] in 15 ml of toluene. The reaction mixture was heated under reflux for 18 hr and then chromatographed over silica gel. Unreacted 1,3-diphenylisobenzofuran was eluted with pentane and the adduct with 10% ether–pentane. Crystallization from ether–pentane gave the exo adduct 3 as white plates (1.75 g, 73%): mp 192–194°; nmr $\delta_{TMS}^{CDCl_3}$ 1.05 (d, J = 5.8 Hz, 3 H), 3.52 (q, J = 5.8 Hz, 1 H), 6.48–7.96 (m, 19 H).

Anal. Calcd for $C_{29}H_{23}NO$: C, 86.75; H, 5.77; N, 3.49. Found: C, 86.43; H, 5.51; N, 3.53.

Thermal Stability of Exo Adduct 3.—The adduct 3 in $CDCl_3$ was heated in a sealed nmr tube at 100° and the reaction was monitored by periodic nmr spectral determinations. Even after 1 week, about 85 ± 5% of 3 remained undestroyed.

3-Chloroethyl-4-hydroxy-1,3,4-triphenyl-3,4-dihydroisoquinoline (5).—A solution of 500 mg of the adduct 3 in 5 ml of anhydrous benzene was treated with 10 ml of a saturated solution of anhydrous HCl in benzene. The reaction mixture darkened immediately. After the mixture was stirred for 3 hr, the yellow crystalline compound that precipitated out (5·HCl) was collected (510 mg): mp 168°; nmr $\delta_{TMS}^{CD_3OD}$ 1.43 (d, J = 6.2 Hz, 3 H), 5.24 (s, broad, 2 H), 6.06 (q, J = 6.2 Hz, 1 H), 6.58–7.95 (19 H).

The product from the foregoing reaction was dissolved in 5 ml of methanol and treated with 20 ml of 2 *N* aqueous NaOH. The reaction mixture was diluted with 100 ml of water and extracted with benzene (3 × 50 ml). The combined organic extract was washed with water and dried (Na_2SO_4). The solution was concentrated and treated with pentane when pale yellow plates of the dihydroisoquinoline 5 crystallized out (335 mg, 76%): mp 178–180°; nmr $\delta_{TMS}^{CDCl_3}$ 1.28 (d, J = 6.2 Hz, 3 H), 4.10 (s, 1 H), 4.72 (q, J = 6.2 Hz, 1 H), 6.84–8.00 (m, 19 H).

Anal. Calcd for $C_{29}H_{24}NOCl$: C, 79.53; H, 5.52; N, 3.20. Found: C, 79.50; H, 5.32; N, 3.22.

Reductive Cleavage of Exo Adduct 3 with $LiAlH_4$. Isolation of Benzoazanorcarane (6).—A solution of 300 mg of the adduct 3 in 5 ml of anhydrous ether was reduced with $LiAlH_4$. Purification of the product by preparative layer chromatography on silica gel PF_{254} with 50% benzene–pentane as the developing solvent gave benzoazanorcarane (6) as a viscous, pale yellow oil which crystallized slowly from ether–pentane as pale yellow plates (280 mg, 93%): mp 85°; nmr $\delta_{TMS}^{CDCl_3}$ 0.95 (d, J = 5.5 Hz, 3 H), 2.32 (q, J = 5.5 Hz, 1 H), 2.52 (s, broad, 1 H), 5.69 (s, 1 H), 6.60–7.90 (m, 19 H).

Anal. Calcd for $C_{29}H_{25}NO$: C, 86.32; H, 6.24; N, 3.47. Found: C, 86.62; H, 6.41; N, 3.50.

Treatment of Benzoazanorcarane (6) with Anhydrous HCl in Benzene. Isolation of Isoquinoline (7).—A solution of 403 mg (1 mmol) of 6 in 20 ml of anhydrous benzene was treated with anhydrous HCl at reflux temperatures for 0.5 hr. The solution was concentrated and subjected to preparative layer chromatography using silica gel PF_{254} with 50% ether–pentane as the developing solvent. The isoquinoline (7) crystallized from ether–pentane as pale yellow plates (197 mg, 55%): mp 184–185; nmr $\delta_{TMS}^{CDCl_3}$ 7.08–8.18 (m, 19H).

Anal. Calcd for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.79; H, 5.59; N, 3.83.

In a separate experiment the benzoazanorcarane (6) was treated with anhydrous HCl in benzene at 25°, and the precipitated white crystalline compound (6 HCl) was collected: mp 178–181°; nmr $\delta_{TMS}^{CD_3OD}$ 1.45 (d, J = 5.8 Hz, 3 H), 5.12 (s, broad, 2 H), 5.94 (q, J = 5.8 Hz, 1 H), 6.60–8.13 (m, 20 H). Basification of this salt gave 6 quantitatively.

Reaction of 2,3-Diphenyl-1-azirine (9) with 1,3-Diphenylisobenzofuran. Formation of Exo Adduct 10.—A solution of 386 mg (2 mmol) of 2,3-diphenyl-1-azirine (9)[13] and 405 mg (1.5 mmol) of 1,3-diphenylisobenzofuran (2) was heated under reflux for 44 hr and then chromatographed using preparative plates (silica gel PF_{254}). Crystallization from ether–pentane gave the exo adduct 10 as white plates (490 mg, 70.5%): mp 198–200°; nmr $\delta_{TMS}^{CDCl_3}$ 4.52 (s, 1 H), 6.27–7.97 (m, 24 H).

Anal. Calcd for $C_{34}H_{25}NO$: C, 89.03; H, 5.00; N, 2.78. Found: C, 88.62; H, 5.22; N, 2.70.

Registry No.—2, 5471-63-6; 3, 34806-16-1; 5, 34806-17-2; 5 HCl, 34806-18-3; 6, 34792-35-3; 6 HCl, 34792-36-4; 7, 30081-56-2; 10, 34806-20-7.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society (Grant No. 1871-G1), for partial support of this research.

(12) An excess of the azirine was used in all runs because of the instability of the azirines at elevated temperatures.

(13) A. Hassner and F. W. Fowler, *J. Amer. Chem. Soc.*, **90**, 2869 (1968).

Selectivity in the Reaction of Azodicarboxylate Esters with Sulfides[1]

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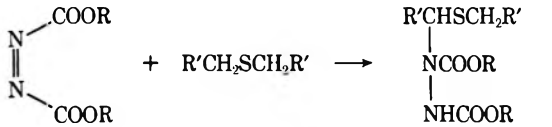
Received January 7, 1972

In the course of studies of other reactions which result in substitution at the α-carbon atom of sulfides, we have examined the reactions of azodicarboxylate esters with a number of sulfides. This reaction was used initially by Woodward in the synthesis of cephalosporin C.[2,3] The transformations, which proceed as

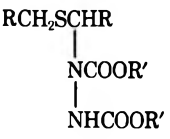


(1) Taken from the thesis of J. H. E. Martin submitted in partial fulfillment of the degree of Master of Science at the Polytechnic Institute of Brooklyn.

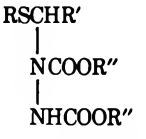
(2) R. B. Woodward, H. Heusler, J. Gosteli, P. Naegeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbruggen, *J. Amer. Chem. Soc.*, **88**, 852 (1966).

(3) R. B. Woodward, *Science*, **153**, 487 (1966).

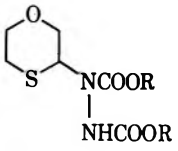
shown to produce derivatives of bicarbamic acid, were in general carried out by warming a mixture of sulfide and azo compound with or without added benzoyl peroxide, thus providing the derivatives I–III. However, for benzyl methyl sulfide, better yields were obtained using uv irradiation to realize the functionalization of the methylene group. A similar reaction has been carried out with ethers, but in this case irradiation was necessary to effect reaction.[4] In a competition experiment 1,4-oxathiane underwent reaction only adjacent to the sulfur atom. This may indicate that the initial complexation between azo acceptor and heteroatom donor is stabilized by polarizability interactions or that it involves selective hydrogen abstraction as an initiating step. In this regard radicals are



Ia, R = Ph; R′ = Me
b, R = Ph; R′ = CH_2Ph
c, R = *n*-Pr; R′ = Me
d, R = *n*-Pr; R′ = CH_2Ph



IIa, R = CH_3; R′ = Ph; R″ = Me
b, R = Me; R′ = Ph; R″ = CH_2Ph
c, R = $PhCH_2$; R′ = COOMe; R″ = Me
d, R = $PhCH_2$; R′ = COOMe; R″ = CH_2Ph

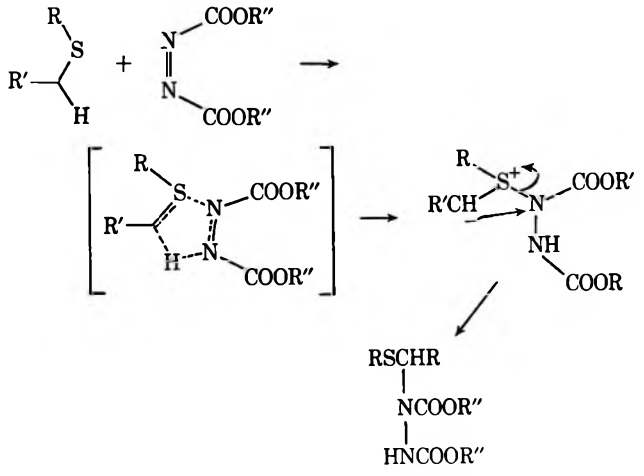


IIIa, R = Me
b, R = *t*-Bu

known to be better stabilized by adjacent sulfur than by adjacent oxygen.[5] The nature of the ester function did not seem to be an important factor; *tert*-butyl azodicarboxylate reacted with the same facility as the methyl ester. By contrast the reaction appears quite sensitive to substitution on the α carbon atom. Thus, di-*n*-butyl sulfide reacted readily, but di-*sec*-butyl sulfide failed to provide the bicarbamate esters under any conditions. The reactivity order for protons adjacent to sulfur appears to be CH_2COOR > benzyl > methyl, and this order is most consistent with proton removal to provide a transition state or intermediate with carbanionic character. A similar order of methylene reactivities was found by Tuleen for the chlorination of sulfides with *N*-chlorosuccinimide, and they arrived at a similar conclusion.[6] By contrast, in the Pummerer reaction of sulfoxides, methyl groups are attacked more easily than benzyl functions.[7]

(4) R. C. Cookson, I. D. R. Stevens, and C. T. Watts, *Chem. Commun.*, 259 (1965).
(5) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, p 27.
(6) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969).
(7) C. R. Johnson, J. C. Sharp, and W. G. Phillips, *Tetrahedron Lett.*, 5299 (1967).

In view of the vacant bonding orbital of azodicarboxylic esters[8] and in concert with the original proposal by Woodward,[3] we consider that the association of sulfide with the azo linkage might be accompanied by proton transfer to generate an ylide in one step. Functionalization of the α position might take place by a nitrogen migration from the sulfur atom to the electron-rich ylide carbon atom similar to that initially suggested for the Pummerer reaction[9] as shown below. The expected low acidity of the hydrazine moiety makes unattractive a mechanism involving ejection of the $ROOCNH\bar{N}COOR$ function from the ylide and its subsequent attack on the sulfocarbonium ion thus formed.



Experimental Section

Materials and Procedures.—The esters of azodicarboxylic acid and the sulfides were obtained from Aldrich Chemical Co. and used without further purification. Tlc silica gel F_{254} plates, available from Brinkmann Instruments Inc., were used for all thin layer chromatography. Mass spectral data were obtained on an Associated Electric Industries MS9 instrument using a direct inlet. All nmr curves were obtained with a Varian A-60 spectrometer at 60 MHz. All melting points were obtained on a Fisher-Johns hot stage apparatus and are reported uncorrected. All pure samples were dried *in vacuo* at 56–57° for 16 hr before microanalysis. Solutions were allowed to cool slowly to 4° for all crystallizations.

The Photochemical Apparatus.—The photochemical apparatus consisted of a water-jacketed quartz irradiation vessel equipped with a bubbler for a continuous flow of nitrogen through the reaction chamber. A Hanovia 140-W mercury lamp was used as the source of ultraviolet light, and a General Electric 275-W sunlamp was used for reactions with visible light. Tap water was allowed to flow through the jacket for the dissipation of heat. The current of ultrahigh purity nitrogen through the reaction chamber served to keep the system free of oxygen and agitated.

Chromatography on Silica Gel.—The crude reaction mixtures and preparations from the interaction of azodicarboxylate esters and sulfides were purified by chromatography on silica gel. All columns were prepared in the same manner. Silica gel (Grade No. 62 from Davison Chemical Co., Baltimore, Md.) (100 g) was suspended in heptane–chloroform (1:1 by volume) and poured into a 1.25-in. glass column, after which the excess solvent was allowed to drain away. The preparations to be purified were dissolved or suspended in chloroform–heptane (1:1 by volume) and applied to the top of the column. The column was eluted first with chloroform–heptane (1:1 by volume), then successively with chloroform, chloroform–ethyl acetate (1:1 by volume), and finally ethyl acetate. Fractions (40 ml) were collected in erlenmeyer flasks and allowed to evaporate at room temperature. The presence of a peak in the infrared in the range 3200–3600

(8) F. Yoneda, K. Suzuki, and Y. Nitta, *J. Org. Chem.*, **32**, 727 (1967).
(9) F. G. Bordwell and B. M. Pitt, *J. Amer. Chem. Soc.*, **77**, 572 (1955).

cm^{-1} (NH) was used to determine which fractions were to be retained and worked up further.

Dimethyl [α-(Methylthio)benzyl]bicarbamate.—A solution of benzyl methyl sulfide (3 ml) and dimethyl azodicarboxylate (0.4 ml) was irradiated with a sun lamp in a Pyrex apparatus for 8 hr. The reaction mixture was concentrated *in vacuo* to about 1/2 volume, and hexane (15 ml) was added to the concentrate, leading to a white crystalline precipitate. The supernatant was decanted, and the residue was washed with several portions of fresh hexane. The air-dried product weighed 444 mg (48%). The air-dried solid was dissolved in carbon tetrachloride (7 ml), and hexane was added until a precipitate formed. The suspension was redissolved by heating over a steam cone and then allowed to cool slowly to 4°, giving 237 mg of dimethyl [α-(methylthio)-benzyl]bicarbamate as a white, crystalline solid: mp 126°; nmr (DMSO-d_6) δ 2.30 (s, 3), 3.67 (s, 1), 3.80 (s, 6), 6.54 (s, 1), 7.40 (m, 5); mass spectrum *m/e* (rel intensity) 284 (<1), 239 (2.3), 238 (17.4), 237 (100), 193 (27.9), 161 (26.7), 139 (8.0), 138 (11.0), 137 (125.6), 122 (5.8), 121 (12.8), 118 (15.1), 105 (8.1), 104 (18.6), 103 (12.8), 92 (5.2), 91 (16.9), 90 (19.8), 89 (3.5), 78 (5.8), 77 (18.6), 65 (6.4), 58 (5.8), 51 (5.8), m* at 157.1 (237 → 193), 134.3 (193 → 161); ir ν_{max} (KBr) 1510, 1670, 1750, 3350, 3450 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.64; N, 9.86; S, 11.28, mol wt, 284.3. Found: C, 50.77; H, 5.98; N, 9.99; S, 11.08; mol wt, 284 (mass spectrum).

Dibenzyl [α-(Methylthio)benzyl]bicarbamate.—A solution of benzl methyl sulfide (1.5 ml) and dibenzyl azodicarboxylate (448 mg) was irradiated in a Pyrex vessel for 16 hr using a sunlamp. Petroleum ether–diethyl ether (1:1 by volume) was added to the reaction mixture and the resulting suspension was stored for 2 days at 4°. The resulting white, crystalline solid was collected on a filter, washed with fresh petroleum ether–diethyl ether solution, and air dried. The air-dried solid weighed 457 mg (69%). A portion (264 mg) was recrystallized from heptane–carbon tetrachloride (10:3 by volume) to give 208 mg of dibenzyl [α-(methylthio)benzyl]bicarbamate: mp 116–119°; nmr ($CDCl_3$) δ 2.20 (s, 3), 5.10 (s, 1), 5.20 (s, 4), 6.60 (s, 1), 7.30 (m, 15); ir ν_{max} (KBr) 1525, 1680, 1760, 3350, 3450 cm^{-1}.

Anal. Calcd for $C_{24}H_{24}N_2O_4S$: C, 66.06; H, 5.50; N, 6.42; S, 7.34; mol wt, 436.7. Found: C, 65.82; H, 5.53; N, 6.32; S, 6.82.

Using a mercury lamp and a quartz apparatus, a 60% yield was obtained.

Dimethyl (1,4-Oxathian-3-yl)bicarbamate.—A solution of 1,4-oxathiane (4 ml) and dimethyl azodicarboxylate (0.4 ml) was heated under reflux at 80° for 16 hr in the presence of 15 mg of benzoyl peroxide. A white, crystalline product (104 mg, 13%) was isolated by chromatography on silica gel. The material was recrystallized from heptane–chloroform (5:1), giving 53 mg of dimethyl (1,4-oxathian-3-yl)bicarbamate: mp 118–120°; nmr ($CDCl_3$) δ 2.70 (t, 2), 3.65 (s, 3), 3.70 (s, 3), 4.00 (m, 4), 5.20 (t, 3), 9.50 (s, 1); ir ν_{max} (KBr) 1540, 1720, 2950, 3300, 3350 cm^{-1}.

Anal. Calcd for $C_8H_{14}N_2O_5S$: C, 38.52; H, 5.64; N, 11.19; S, 12.81; mol wt, 250.3. Found: C, 37.92; H, 5.39; N, 11.04; S, 11.50.

Dimethyl [(Benzylthio)carboxymethyl]bicarbamate.—A solution of dimethyl azodicarboxylate (0.5 ml), methyl *S*-benzylthioglycollate (2.1 ml), and benzoyl peroxide (25 mg) was heated under reflux at 80° for 16 hr. The reaction was protected from atmospheric moisture by a calcium chloride drying tube. Chromatography on silica gel gave dimethyl [(benzylthio)carboxymethyl]bicarbamate (295 mg, 21%). The white solid was recrystallized from heptane–carbon tetrachloride (2:1) to give 124 mg of crystalline solid: mp 79–81°; nmr ($CDCl_3$) δ 3.65 (s, 6), 3.70 (s, 3), 3.90 (s, 2), 5.80 (s, 1), 7.30 (s, 5), and 9.50 (s, 1); ir ν_{max} (KBr) 1600, 1695, 1735, 2995, 3200, 3500 cm^{-1}; mass spectrum *m/e* (rel intensity) 344 (<1), 343 (<1), 342 (2.9), 283 (10.8), 235 (13.1), 234 (9.6), 222 (1.8), 221 (10.8), 220 (100), 195 (8.1), 175 (40), 161 (56.2), 147 (3.9), 146 (32.3), 143 (17.7), 135 (11.2), 123 (10.8), 122 (<1), 115 (38.5), 101 (7.8), 92 (24.3), 91 (111.7), 90 (6.2), 77 (6.2), 76 (16.2), 69 (3.2), 59 (32.3), 51 (5.3).

Anal. Calcd for $C_{14}H_{18}N_2O_6S$: C, 49.12; H, 5.30; N, 8.18; S, 9.36; mol wt, 342.3. Found: C, 49.01; H, 5.42; N, 8.19; S, 11.72; mol wt, 342 (mass spectrum).

Dibenzyl [(Benzylthio)carboxymethyl]bicarbamate.—A solution of methyl *S*-benzylthioglycollate (2 ml) and dibenzyl azodicarboxylate (538 mg) was heated at 80° under reflux for 80 hr. The reaction mixture was chromatographed on silica gel to give a white solid weighing 272 mg (30%). The white solid was recrystallized from carbon tetrachloride–heptane (1:1 by volume) to dibenzyl [(benzylthio)carboxymethyl]bicarbamate weighing 132 mg: mp 85–88°; nmr ($CDCl_3$) δ 3.70 (s, 3), 4.05 (s, 2), 5.10 (s, 4), 5.95 (s, 1), 7.00 (s, 1), 7.33 (s, 15); ir ν_{max} (KBr) 1520, 1680, 1750, 3350, 3450 cm^{-1}.

Anal. Calcd for $C_{26}H_{26}N_2O_6S$: C, 63.14; H, 5.30; N, 5.67; S, 6.48; mol wt, 494.6. Found: C, 63.35; H, 5.45; N, 5.86; S, 6.12.

Di-*tert*-Butyl (1,4-Oxathian-3-yl)bicarbamate.—A solution of 1,4-thioxane (5 ml) and di-*tert*-butyl azodicarboxylate (530 mg) was heated under reflux at 80° for 20 hr. Chromatography on silica gel gave a white solid weighing 440 mg (54%). A portion was recrystallized from carbon tetrachloride to give 126 mg of di-*tert*-butyl (1,4-oxathian-3-yl)bicarbamate: mp 162–163°; nmr (DMSO-d_6) δ 1.40 (s, 18), 2.15 (t, 2), 3.80 (m, 4), 5.00 (m, 1), 8.50 and 8.96 (s, 1); ir ν_{max} (KBr) 1255, 1260, 1520, 1725, 1750, 3030, 3350, 3550 cm^{-1}.

Anal. Calcd for $C_{14}H_{26}N_2O_5S$: C, 50.30; H, 7.78; N, 8.38; S, 9.58. Found: C, 49.98; H, 7.70; N, 8.61; S, 7.69.

Dibenzyl [1-(Butylthio)butyl]bicarbamate.—A solution of *n*-butyl sulfide (10 ml) and dibenzyl azodicarboxylate (800 mg) was irradiated in the quartz apparatus with a mercury lamp for 24 hr. The reaction mixture was chromatographed on silica gel, yielding 1.13 g (95%) of a white waxy solid. This material was crystallized from 18 ml of carbon tetrachloride–heptane (1:5) to give 403 mg of dibenzyl [1-(butylthio)butyl]bicarbamate: mp 68–70°; nmr ($CDCl_3$) δ 0 to 1.80 (m, 14), 2.50 (t, 2), 5.10 (s, 4), 5.50 (m, 1), 6.80 (s, 1), 7.30 (s, 10); ir ν_{max} (KBr) 1310, 1410, 1460, 1515, 1665, 1720, 1740, 3350, 3550 cm^{-1}.

Anal. Calcd for $C_{24}H_{32}N_2O_4S$: C, 64.86; H, 7.21; N, 6.31; S, 7.21. Found: C, 64.88; H, 6.96; N, 6.25; S, 6.90.

Registry No.—Id, 34792-31-9; IIa, 34804-18-7; IIb, 34804-19-8; IIc, 34804-20-1; IId, 34804-21-2; IIIa, 34804-22-3; IIIb, 34804-23-4; benzyl methyl sulfide, 766-92-7; dimethyl azodicarboxylate, 2446-84-6; dibenzyl azodicarboxylate, 2449-05-0; 1,4-oxathiane, 15980-15-1; methyl *S*-benzylthioglycollate, 17277-59-7; di-*tert*-butyl azodicarboxylate, 870-50-8; *n*-butyl sulfide, 544-40-1.

Aminothiosulfonates

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Received February 29, 1972

Interest in various biologically active properties of the thiolsulfonate moiety has prompted investigations of compounds containing this group in combination with groups bearing greater or lesser degrees of electronegativity. Thiolsulfonates **1** whose R′ groups

1

consist of electron-withdrawing groups such as trichloromethyl[1,2] and trifluoromethyl[3] have been shown to exhibit biological and chemical properties different

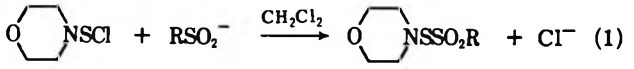
(1) J. E. Dunbar and J. H. Rogers, *Tetrahedron Lett.*, 4291 (1965); *J. Org. Chem.*, **31**, 2842 (1966).

(2) B. G. Boldyrev and S. A. Kolesnikova, *Zh. Obshch. Khim.*, **35**, 198 (1965).

(3) J. P. Weidner and S. S. Block, *J. Med. Chem.*, **10**, 1167 (1967).

from those of thiolsulfonates, having R′ groups consisting of simple alkyl and aryl groups.

This paper reports the synthesis and several reactions of a novel class of compounds, represented by three 4-morpholinethiolsulfonates (**2a–c**). Treatment of alkali metal salts of sulfinic acids with 4-morpholinesulfenyl chloride at ambient temperature in methylene chloride gave the aminothiolsulfonates in good yields (eq 1).

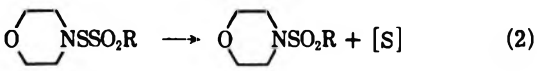


(1)

2a, R = CH_3
b, R = p-$CH_3C_6H_4$
c, R = p-$CH_3CONHC_6H_4$

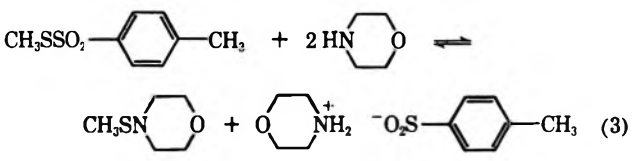
The infrared absorption by the sulfonyl groups of the aminothiolsulfonates occurs at slightly longer wavelengths (1105–1110 and 1293–1297 cm^{-1}) than do those of alkyl and aryl esters of thiosulfonic acids (1150 and 1340 cm^{-1}).[4]

Extrusion of sulfur from the aminothiolsulfonates (**2a–c**) occurred slowly at room temperature and rapidly at boiling temperatures in polar solvents such as acetone, methanol, and 2-propanol to give the corresponding sulfonmorpholides (eq 2). 4-(Methanesulfonylthio)morpholine (**2a**) converted in the solid state to methanesulfonmorpholide in less than 10 days on standing in a capped vial at room temperature, while 4-(*p*-acetamidophenylsulfonylthio)morpholine (**2c**) was stable for several months under similar conditions.



(2)

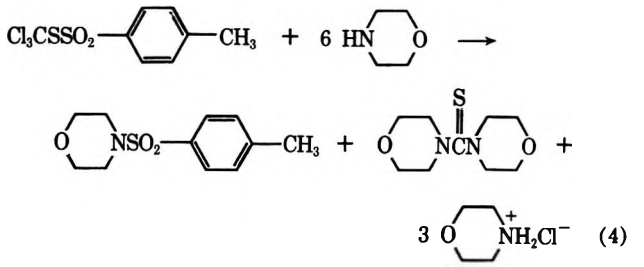
The reaction of primary and secondary amines with thiolsulfonates has been shown by one of us to give different products, depending upon the type of thiolsulfonate employed.[1] Alkyl and aryl thiolsulfonic acid esters are cleaved by the attack of the amine on the divalent sulfur atom with subsequent formation of sulfenamides, exemplified in eq 3. Thiolsulfonates



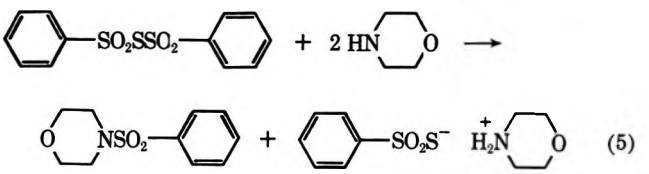
(3)

1, where the electron-withdrawing effects of R′ are similar in magnitude to those of RSO_2, react with morpholine by attack of the nucleophile on the sulfonyl moiety, exemplified in eq 4 and 5.

It was therefore of interest to us to determine the nature of a base attack upon a thiolsulfonate **1** where R′ is an electron-rich basic group, as in the aminothiolsulfonates **2a–c**. When 4-(*p*-acetamidophenylsulfonylthio)morpholine (**2c**) was treated with 2 equiv of morpholine in carbon tetrachloride at room temperature, quantitative amounts of 4-morpholinosulfide

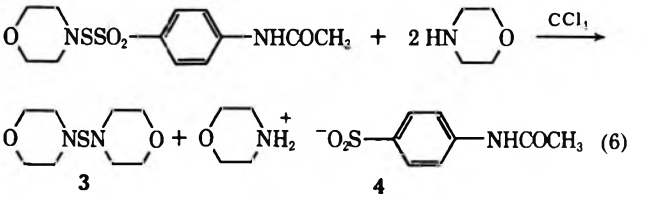


(4)



(5)

(**3**) and morpholinium *p*-acetamidobenzenesulfinate (**4**) were formed (eq 6).



(6)

We therefore conclude that when R′ of thiolsulfonate **1** is an electron-rich group such as morpholino, the site of the nucleophilic attack remains at the divalent sulfur atom.

Experimental Section[5]

4-(Methylsulfonylthio)morpholine (2a).—A solution of 8.2 g (0.053 mol) of 4-morpholinesulfenyl chloride[6] in 50 ml of methylene chloride was added to a stirred suspension of 6.3 g (0.053 mol) of potassium methanesulfinate in 30 ml of methylene chloride. After the mixture had been stirred for 18 hr at ambient temperature, the potassium chloride by-product was removed by filtration. The filtrate was washed with water, dried (Na_2SO_4), and concentrated *in vacuo*, leaving 5.3 g (50%) of white crystalline solid. Recrystallization from a mixture of benzene and petroleum ether (bp 60–70°) gave the pure product as colorless crystals: mp 83–83.5°; nmr ($CDCl_3$) δ 3.28 (s, 3, CH_3), 3.38–3.87 (m, 8, morpholine ring protons).

Anal. Calcd for $C_5H_{11}NO_3S_2$: C, 30.44; H, 5.62; N, 7.10; S, 32.50. Found: C, 30.50; H, 5.62; N, 7.10; S, 32.23.

4-(p-Tolylsulfonylthio)morpholine (2b).—Morpholinesulfenyl chloride (25 g, 0.16 mol) was treated with 35 g (0.16 mol) of sodium *p*-toluenesulfinate dihydrate by the same procedure used in the preparation of **2a** to obtain 36.5 g (84%) of product as colorless crystals. Recrystallization from 2-propanol gave the pure, colorless, crystalline product: mp 104.5–105°; nmr ($CDCl_3$) δ 2.50 (s, 3, CH_3), 3.22–3.82 (m, 8, morpholine ring protons), 7.33–8.08 (m, 4, aromatic protons).

Anal. Calcd for $C_{11}H_{15}NO_3S_2$: C, 48.33; H, 5.53; N, 5.13; S, 23.46. Found: C, 48.20; H, 5.52; N, 5.13; S, 23.57.

Repeated recrystallization of **2b** from 2-propanol resulted in the formation of *p*-toluenesulfonmorpholide, mp 148° (lit.[7] mp 147°).

4-(p-Acetamidophenylsulfonylthio)morpholine (2c).—A solution of 27 g (0.17 mol) of 4-morpholinesulfenyl chloride in 150 ml of methylene chloride was added to a stirred suspension of 38 g (0.17 mol) of sodium *p*-acetamidobenzenesulfinate in 150 ml of methylene chloride. The reaction mixture was stirred at room

(4) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 359.

(5) All melting points are uncorrected. Infrared spectral data were obtained on a Perkin-Elmer 337 grating infrared spectrophotometer as Nujol and Fluorolube mulls. All nmr spectra were obtained on a Varian A-60 spectrometer in deuteriochloroform using TMS as the internal standard. Elemental analyses were obtained from the Analytical Services Laboratory of The Dow Chemical Company.

(6) G. Weiss and G. Schulze, German Patent, 1,131,222 (1962); *Chem. Abstr.*, **57**, 13777e (1962).

(7) J. Sand, *Ber.*, **34**, 2906 (1901).

temperature for 36 hr, an additional 400 ml of methylene chloride was added, and the mixture was washed with water. Much of the product was insoluble in the organic layer and was collected on a filter (34 g). An additional 18 g of crystalline product was obtained by evaporation of the methylene chloride filtrate. The combined crude product (52 g, 95%) was dried and recrystallized from a mixture of benzene and petroleum ether to give colorless crystals: mp 133–133.5° dec; nmr ($CDCl_3$) δ 2.15 (s, 3, CH_3), 3.17–3.73 (m, 8, morpholine ring protons), 7.87 (s, 4, aromatic protons), 10.25 (m, 1, NH).

Anal. Calcd for $C_{12}H_{16}N_2O_4S_2$: C, 45.55; H, 5.10; N, 8.86; S, 20.27. Found: C, 45.61; H, 5.11; N, 8.90; S, 20.35.

Reaction of Morpholine with 4-(*p*-Acetamidophenylsulfonylthio)morpholine (2c).—Morpholine (2.75 g, 0.0316 mol) was added to a suspension of 5.00 g (0.0158 mol) of 4-(*p*-acetamidophenylsulfonylthio)morpholine in 100 ml of carbon tetrachloride, and the mixture was stirred at ambient temperature for 17 hr. The precipitated morpholinium *p*-acetamidobenzenesulfinate was collected on a filter, washed with carbon tetrachloride, and dried. The salt, obtained in quantitative yield (4.5 g), was recrystallized from 2-propanol to give colorless crystals, mp 171.5–172.5°.

Anal. Calcd for $C_{12}H_{18}N_2O_4S$: C, 50.33; H, 6.34; N, 9.79; S, 11.20. Found: C, 50.03; H, 6.28; N, 9.66; S, 11.23.

The carbon tetrachloride filtrate was concentrated *in vacuo*, leaving 3.0 g (94%) of crystalline 4-morpholinosulfide, mp 123.5–124.5°. Recrystallization from ethanol gave the pure substance, mp 124.5–125.5° (lit.[8] mp 125–126°).

Anal. Calcd for $C_8H_{16}N_2O_2S$: C, 47.03; H, 7.90; N, 13.72; S, 15.70. Found: C, 47.05; H, 7.87; N, 13.67; S, 15.72.

Registry No.—**2a**, 34764-81-3; **2b**, 34764-82-4; **2c**, 34764-83-5; **3**, 5038-11-9; **4**, 23837-27-6.

(8) E. S. Blake, *J. Amer. Chem. Soc.*, **65**, 1267 (1943).

Synthesis of 1,2-Dithiolane-3,5-diones and Thietane-2,4-diones[1a]

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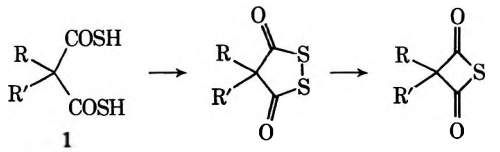
Received October 5, 1971

Although 1,2-dioxolane-3,5-diones (malonyl peroxides)[2] and oxetane-2,4-diones (malonic anhydrides)[3] are known, the sulfur analogs have not been reported. Herein we describe a simple sequence for obtaining dialkylated 1,2-dithiolane-3,5-diones and thietane-2,4-diones *via* the pyridinium salts of the corresponding bisthio acids (**1**) (Scheme I).

SCHEME I



1 **2** **3**

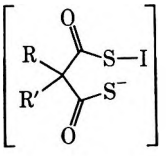
a, R = R′ = CH_3
b, R = R′ = CH_3CH_2
c, R, R′ = $(CH_2)_3$

Although bisthiomalonic acid has been reported to result by reaction of malonyl chloride with hydrogen sulfide in pyridine solution, followed by acidification of the reaction mixture,[4] we were unable to effect this preparation. Parallel attempts to prepare the bisthio acids (or the intermediate pyridinium salts) from monoalkylmalonyl chlorides also failed.[5] However, reaction of disubstituted malonyl chlorides under similar conditions afforded the bisthio acids **1a–c** as low-melting solids.

Since it is well documented that salts of monothiocarboxylic acids undergo oxidation with halogens to give diacyl disulfides,[6] it was anticipated that formation of 1,2-dithiolane-3,5-diones could be carried out analogously by oxidation of salts of the bisthiomalonic acids (**1**). Reconversion of the thio acids to their pyridinium salts,[7] followed by oxidation with iodine in anhydrous ether solution,[8] gave the cyclic disulfides **2a–c** in 55–80% yields, accompanied by small amounts (5%) of the corresponding thietane-2,4-diones **3a–c**. The thietanes were observed by gc, ir, and nmr analysis on the crude reaction mixtures and were identified by comparison with data obtained on pure samples obtained by alternate procedures (*vide infra*).

The ir spectra for the 1,2-dithiolane-3,5-diones **2a–c** exhibit strong absorptions at approximately 1720 and 1680 cm^{-1}, apparently as a result of vibrational coupling for the diacyl disulfide group. The structures for **2a–c** are further supported by elemental analysis and nmr and mass spectral data.

Oxidation of the salts of the bisthiomalonic acids with iodine presumably involves formation of intermediate sulfenyl iodides of type **4**,[9] which undergo



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intramolecular displacement of iodide by thiocarboxylate ion to provide the expected 1,2-dithiolane-3,5-diones. The unexpected formation of thietane-2,4-diones **3a–c** appears to be the result of intramolecular displacement of the –SI group from the sulfenyl iodide intermediate. The possibility that **3a–c** might result from overoxidation of the disulfides was ruled out by subjecting **2a** to the conditions of the oxidation.

Reaction of the cyclic disulfides **2a–c** with triphenylphosphine in benzene at 60° gave the colorless, distillable thietanes **3a–c** in high yields.[10] The ir spectra of **3a–c** exhibit bands at 1850 and 1750 cm^{-1} which are attributed to vibrational coupling of the thioanhydride function.

(1) (a) Presented at the 7th Middle Atlantic Regional Meeting of the American Chemical Society, Philadelphia, Pa., Feb 1972. (b) NDEA Fellow, 1968–1971.

(2) W. Adam and R. Rucktaschel, *J. Amer. Chem. Soc.*, **93**, 557 (1971).

(3) A. C. Duckworth, *J. Org. Chem.*, **27**, 3146 (1962).

(4) S. Sunner, *Svensk Kem. Tidskr.*, **62**, 204 (1950).

(5) Considering the ease with which the acid chlorides undergo elimination in basic media [M. Rabjohn and H. M. Molotsky, *J. Org. Chem.*, **23**, 1642 (1958)], these results are not too surprising.

(6) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. 4, Chemical Publishing Co., New York, N. Y., 1962, p 22.

(7) Isolation of the free thioacids was carried out in order to obtain pure pyridinium salts.

(8) It was necessary to run these reactions in a nonnucleophilic medium in order to avoid solvolysis of the disulfides.

(9) J. P. Danehy, C. P. Egan, and J. Switalski, *J. Org. Chem.*, **36**, 2530 (1971), have demonstrated the intermediacy of sulfenyl iodides during the oxidation of thiols.

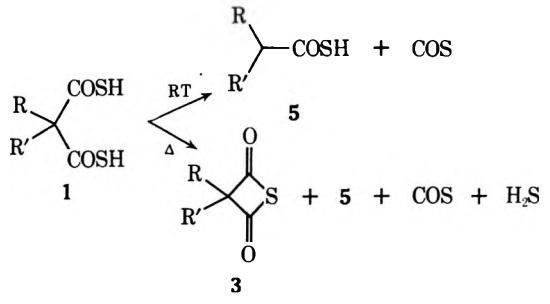
(10) D. N. Harpp and J. G. Gleason, *J. Amer. Chem. Soc.*, **93**, 2437 (1971), have described the desulfurization of 1,2-dithiolanes to thietanes by treatment with tris(diethylamino)phosphine.

Extensive fragmentation of **3a–c** to carbonyl sulfide and the corresponding ketenes occurred during gc analysis employing inlet port temperatures above 150°. Samples of the peaks assigned as ketenes were collected and found to possess the characteristic ketene ir absorptions at 2100 cm^{-1}. Thermal decomposition of a neat sample of diethylthietane-2,4-dione (**3b**) in a microdistillation apparatus provided diethylketene in high yield. Similar treatment of dimethylthietane-2,4-dione (**3a**) by heating in an unsealed tube gave the dimethylketene dimer, 2,2,4,4-tetramethylcyclobutane-1,3-dione.[11]

The thietane **3a** was also obtained in high yield by treatment of the pyridinium salt of the bisthio acid **1a** with trifluoroacetic anhydride at room temperature.

Although the bisthio acids **3a–c** are stable in the solid state at −15°, ir and nmr studies indicate that the neat liquids undergo facile loss of carbonyl sulfide at room temperature to yield monothio acids[12] (Scheme II).

SCHEME II



a, R = R′ = CH_3
b, R = R′ = CH_3CH_2
c, R, R′ = $(CH_2)_3$

At temperatures above 80° formation of thietane-2,4-diones **3** by loss of hydrogen sulfide is also observed.[13]

Experimental Section[14]

Preparation of the Bisthiomalonic Acids 1a–c.—In a 250-ml round-bottom flask equipped with gas inlet and outlet tubes, pressure-equalizing funnel, ice bath, and magnetic stirrer was placed 36 g of anhydrous pyridine. The pyridine was saturated with hydrogen sulfide for 30 min; then a solution of 0.05 mol of the appropriate disubstituted malonyl chloride in 20 ml of anhydrous ether was added *via* the dropping funnel over a period of 2–3 hr (bath temperature 0–10°). Hydrogen sulfide addition was continued during addition of the malonyl chloride. The reaction mixture was then poured into a mixture of 400 g of cracked ice and 20 ml of concentrated H_2SO_4 and extracted with three 75-ml portions of ether. The combined extract was washed with ice water, dried ($MgSO_4$), and evaporated *in vacuo* to provide the liquid bisthio acids, which solidified to white solids at 20–25°. The bisthio acids were not further purified due to their lability at room temperature. The ir and nmr spectra of these compounds (Table I) verified the assigned structures.

TABLE I
PHYSICAL DATA[d]

Compd	Bp, °C (mm)	Yield, %	Ir,[a] cm^{-1}	Nmr[b]	
1a	c	50	2600, 1680	1.55 (s, 6 H)	4.70 (s, 2 H)
1b	c	70	2600, 1680	0.9 (t, 6 H)	1.90 (q, 4 H)
				5.0 (s, 2 H)	
1c	c	83	2600, 1680	1.95 (m, 2 H)	2.6 (m, 4 H)
				4.8 (s, 2 H)	
2a	80–82 (5)	57	1720, 1680	1.42 (s, 6 H)	
2b	47–48 (0.5)	80	1720, 1680	0.93 (t, 6 H)	1.90 (q, 4 H)
2c	67–69 (0.1)	82	1760, 1670	2.5 (m, 6 H)	
3a[e]	50–51 (15)	86	1850, 1760	1.53 (s, 6 H)	
3b[e]	32–34 (0.1)	83	1840, 1740	1.15 (t, 6 H)	1.76 (q, 4 H)
3c[e]	39–41 (0.5)	87	1850, 1750	2.02 (m, 2 H)	2.74 (m, 4 H)

[a] Liquid films. [b] CCl_4 solutions, employing TMS as the internal reference. [c] Unstable liquid, mp 20–25°. [d] Satisfactory analyses (±0.25% for C, H, and S) were reported for compounds **2a–c** and **3a–c**: Ed. Nominal molecular weights were determined by mass spectrometry; isotopic abundance of P + 1 and P + 2 peaks were as expected. [e] The mass spectrum indicated COS and the ketene as the principal fragments, due at least in large part to thermal cleavage.

Thermal Decomposition of the Bisthio Acids.—Ir and nmr analysis of a sample of **1a** which had been stored at −15° for 18 months showed 5–8% decomposition to thioisobutyric acid; however, when a neat sample of **1a** was allowed to stand at 26° for 22 hr, spectral analysis indicated 95% decomposition to thioisobutyric acid. The formation of thioisobutyric acid was verified by comparison of the ir and nmr spectra with those obtained on a sample prepared from isobutyryl chloride and H_2S.[15] Gc analysis of **1a** at 280° inlet port temperature resulted in extensive decomposition to thioisobutyric acid, COS, and H_2S accompanied by thietane-2,4-dione (**3a**) in 15–20% yield. Gc analysis at 80° resulted in the formation of only thioisobutyric acid and COS.

The thermal instability of **2a** and **3a** qualitatively paralleled that observed for **1a**.

Preparation of the 1,2-Dithiolane-3,4-diones 2a–c.—To a solution of 0.025 mol of the appropriate bisthiomalonic acid in 300 ml of anhydrous ether was added 3.96 g (0.05 mol) of pyridine. The mixture was titrated with 1.5 *M* iodine in ether until the color of iodine just persisted. The reaction mixture was filtered and the filtrate was washed successively with 10-ml portions of 0.1 *N* $Na_2S_2O_3$ solution, 10% HCl, and 10% Na_2CO_3 solution. The ether extract was then dried ($MgSO_4$) and evaporated at 100 mm pressure, and the residue was distilled *in vacuo*. The physical and analytical data obtained for **2a–c** are listed in Table I.

Distilled samples of **2a–c** prepared by the above procedure contained 1% of the corresponding thietanes **3a–c** which were detected by gc and spectral analysis. Examination of crude samples of **2a** before aqueous work-up and distillation indicated the presence of 4% of **2a**. When a sample of 99% pure **2a** was subjected to the conditions of the oxidation (2 mmol of pyridine, 1 mmol of pyridinium iodide, and 1 mmol of iodine per mmol of **2a** in ether solution) only a trace of the thietane **3a** could be detected in the crude product.

Preparation of the Thietane-2,4-diones 3a–c. A. Reaction of 1,2-Dithiolane-3,5-diones 2a–c with Triphenylphosphine.—In a 25-ml round-bottom flask fitted with a reflux condenser and Drierite drying tube was placed a solution of the appropriate cyclic disulfide (**2a–c**) in 10 ml of benzene. The solution was stirred at 60° and 5.25 g (0.02 mol) of triphenylphosphine was added in small portions over a period of 8 hr. After removal of the triphenylphosphine sulfide by filtration, the filtrate was evaporated at 100 mm pressure and the residue was distilled to provide the desired thietane-2,4-dione. The physical and analytical data for **3a–c** are shown in Table I.

B. Reaction of Dimethylbisthiomalonic Acid (1a) with trifluoroacetic Anhydride.—To a stirred solution of 5.1 g (0.031 mol) of trifluoroacetic anhydride was added 6.1 g (0.031 mol) of dimethylbisthiomalonic acid in 10 ml of anhydrous ether. The mixture was allowed to stand for 10 min, and then was diluted to

(11) By analogy, oxetane-2,4-diones undergo thermal decomposition to give carbon dioxide and ketenes (ref 2). I. L. Knunyants and O. V. Kil'disheva, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 619 (1955), have reported the thermal cleavage of a substituted 2-thietanone to give carbonyl sulfide and the corresponding olefin.

(12) In contrast, 1,1-dicarboxylic acids undergo decarboxylation only at temperatures well above 100°: P. I. Abell and R. Tien, *J. Org. Chem.*, **30**, 4212 (1965).

(13) By comparison, bisthiosuccinic and bisthio-*o*-phthalic acids are not isolable, but undergo rapid loss of hydrogen sulfide to form the cyclic thioanhydrides (ref 6, p 21).

(14) Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Mass spectra were obtained through Schrader Analytical Laboratories, Detroit, Mich. Ir spectra were obtained on a Perkin-Elmer Model 337 instrument. Nmr spectra were determined with a Varian A-60 instrument. Glpc was carried out on a Hewlett-Packard F & M Model 700 instrument, employing a 6 ft × 0.25 in. stainless steel column packed with 10% SE-30 on silanized 60–80 mesh Chromosorb W.

(15) Reference 6, p 61.

160 ml with petroleum ether (bp 30–60°) and 5.2 g (0.066 mol) of pyridine was added with stirring. The reaction mixture was then filtered to remove pyridinium salts and the filtrate was evaporated at 100-mm pressure to give 3.7 g (95% yield) of **3a**.

Thermolysis of 3a and 3b.—A neat sample of 3,3-dimethylthietane-2,4-dione (**3a**) was heated at 145° for 1.5 hr (evolution of gas began at 130°). On cooling, a white, crystalline solid formed. A sample sublimed at atmospheric pressure gave mp 113–115°. The melting point was not depressed upon admixture with 2,2,4,4-tetramethylcyclobutane-1,4-dione (obtained from Aldrich Chemical Co). Nmr (singlet at 1.31 ppm) confirmed the identity.

A neat sample of 3,3-diethylthietane-2,4-dione (**3b**) was placed in a short-path microdistillation apparatus equipped with a Dry Ice cooled receiver and heated under nitrogen, at atmospheric pressure from room temperature to 170° over a 30-min period. Gas evolution was apparent at 145°. The ir spectrum of the pale yellow liquid which distilled into the receiver showed a strong band at 2100 cm^{-1} (diethylketene[3]) and a weak absorption for starting material at 1820 cm^{-1}. Gc analysis indicated the presence of 95% diethylketene and 5% starting material.

Registry No.—**1a**, 34803-94-6; **1b**, 34803-95-7; **1c**, 34803-96-8; **2a**, 34803-97-9; **2b**, 34803-98-0; **2c**, 34803-99-1; **3a**, 34804-00-7; **3b**, 34804-01-8; **3c**, 34804-02-9.

Zinc Reduction of 4-Methylpyridine in Acetic Anhydride

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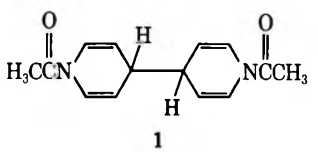
Received November 26, 1971

Mild treatment of pyridine with zinc and acetic anhydride results in the formation of 1,1′-diacetyl-1,1′,4,4′-tetrahydrobipyridine (**1**).[1,2] Pyrolysis of **1** at



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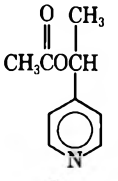

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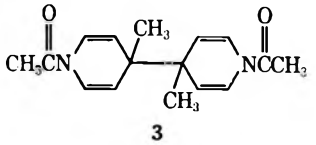
2 mm and 250–275° results in the formation of 1-(4-pyridyl)ethyl acetate[3] (**2**).

The present work is an attempt to prepare 1,1′-diacetyl-4,4′-dimethyl-1,1′,4,4′-tetrahydrodipyridine (**3**)



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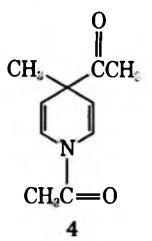

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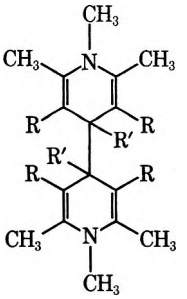
by applying the conditions of the zinc reduction to 4-methylpyridine. We did not obtain the expected product **3**, but instead we obtained 1,4-diacetyl-4-methyl-1,4-dihydropyridine (**4**).

The zinc reduction product of 4-methylpyridine and acetic anhydride was shown not to be structure **3** on the basis of molecular weight and elemental analysis. The assignment of **4** as the structure is based upon the nmr spectrum. Low-field protons assigned to H_2 and H_6 occur as a double doublet at δ 7.28 and 6.77 (J = 7.5 cps) with an area of 1 for each doublet. H_3 and H_5 occur as a single doublet at δ 4.97 (J = 7.5 cps), with an area of 2. Two methyl signals (area of 3) occur as sharp singlets at δ 2.27 and 2.22 and are assigned as the acetyl signals. A third methyl (area of 3) occurs as a singlet at δ 1.27 and is assigned as the 4-methyl group of **4**. The nmr spectrum of **4** in $CDCl_3$ is very similar to that of **1** in $CDCl_3$, in which the 2,2′ and 6,6′ protons occur as a double doublet at δ 7.23 and 6.68 with coupling constant of 11 cps, and the 3,3′,5,5′ protons of **1** occur as a multiplet at δ 4.92.[4] Due to their *N*-acetyl groups the nmr absorptions of the ring protons of **1** and **4** occur at much lower field than the corresponding absorptions of other dihydropyridines. Examples are the chemical shifts for 1-phenyl-1,4-dihydropyridine[5] and 1,4,4-trimethyl-1,4-dihydropyridine,[6] which occur at δ 6.27 and 5.51 for the 2,6 protons and at δ 4.53 and 4.11 for the 3,5 protons.

The infrared spectrum of **4** displays very strong bands at 1670 and 1692 cm^{-1}. The 1670-cm^{-1} band is attributed to the >C=C< by analogy with other dihydropyridine systems.[3,6,7] The 1692 and 1624-cm^{-1} bands are due to carbonyl stretching of **4** and **1**.

The ultraviolet spectrum of **4** in water, 1 *M* HCl, 0.1 *M* HCl, and 0.1 *M* NaOH occurs at 2530 Å with an extinction coefficient of 1.9×10^4 M^{-1} cm^{-1}. An overnight treatment of **4** with 0.1–1 *M* HCl or 0.1–1 *M* NaOH completely abolishes its ultraviolet absorbance, indicating hydrolytic instability of **4**. The ultraviolet absorbance of **4** is similar to that of **1**[4] (λ_{max} 2630 Å, ϵ_{max} 2.4×10^4 M^{-1} cm^{-1}).

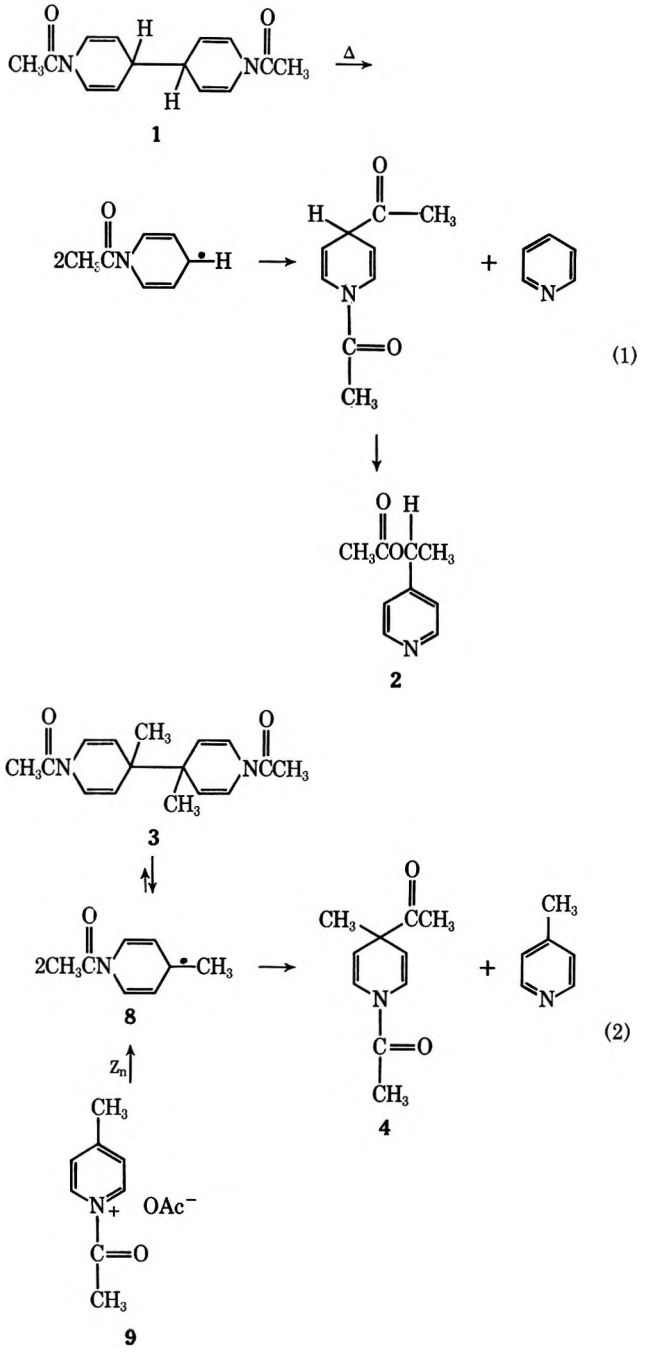
The failure to obtain **3** upon treatment with zinc and acetic anhydride can be ascribed to the instability of bipyridines which are hindered at the 4,4′ positions. The early work of Mumm[8,9] and Emmert[10] clearly indicates that compounds **5**–**7**, formed by reduction of



5, R = CO_2Et; R′ = *i*-Bu
6, R = R′ = CH_3
7, R = H; R′ = CH_3

(1) O. Dimroth and F. Frister, *Ber.*, **55**, 1223 (1922).
(2) O. Dimroth and R. Heene, *ibid.*, **54**, 2934 (1921).
(3) A. T. Nielsen, D. W. Moore, J. H. Mazur, and K. H. Berry, *J. Org. Chem.*, **29**, 2898 (1964).
(4) A. T. Nielsen, D. W. Moore, G. M. Muha, and K. H. Berry, *ibid.*, **29**, 2175 (1964).
(5) M. Saunders and E. H. Gold, *ibid.*, **27**, 1439 (1962).
(6) E. M. Kosower and T. S. Sorensen, *ibid.*, **27**, 3764 (1962).
(7) R. L. Frank, F. Pelletier, and F. W. Starks, *J. Amer. Chem. Soc.*, **70**, 1767 (1948).
(8) O. Mumm and H. Ludwig, *Ber.*, **59B**, 1605 (1926).
(9) O. Mumm, O. Rodel, and H. Ludwig, *ibid.*, **57B**, 865 (1924).
(10) B. Emmert and O. Werb, *ibid.*, **55B**, 1352 (1922).

the corresponding pyridinium ions with sodium amalgam, are unstable upon storage and form compounds of lower molecular weight. The instability of **1** to heating with the resultant formation of **2**,[3] presumably by a disproportionation reaction shown in eq 1, strongly suggests that **3**, if formed, would disproportionate to **4** *via* **8** as shown in eq 2.



Experimental Section

Materials.—4-Methylpyridine, acetic anhydride, and 40 mesh zinc were reagent grade materials from Fisher Scientific Co.

Preparation of 4.—The procedure of Dimroth and Heene[2] was used with the substitution of 4-methylpyridine for pyridine. 4-Methylpyridine (50 ml) and 200 ml of acetic anhydride were mixed together in an erlenmeyer flask. After the addition of 50 g of zinc the reaction mixture was agitated in the stoppered flask with a magnetic stirrer for 16 hr–14 days at 30–35°. The only color change which was noticeable was a yellowing of the reaction mixture. The early precipitate formed was very soluble in water and is $Zn(OAc)_2$ based upon its nmr spectrum in D_2O and the presence of a residue upon burning. The flask and its contents were treated with 200 ml of water and heated to 85° in a water bath in order to dissolve the precipitate. The zinc was separated by filtration using hot acetic anhydride to wash the filter. The filtrate was refrigerated overnight and crystals of **4** were collected and recrystallized from methanol, mp 80–81°. A yield of 15–17% was obtained independent of the time of work-up. *Anal.* Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.81; O, 17.85. Found: C, 67.02; H, 7.44; N, 7.77; O, 17.77 (by difference). The molecular weight of **4** was determined in chloroform by vapor phase osmometry to be 181, agreeing well with the value of 179 calculated for $C_{10}H_{13}NO_2$.

Physical Measurements.—The spectral determination of **4** was made with a Beckman IR-4 infrared spectrometer, a Cary 14 ultraviolet–visible spectrophotometer, and a Varian A-60 nuclear magnetic resonance spectrometer.

Registry No.—**3**, 34803-87-7; **4**, 25463-04-1; 4-methylpyridine, 108-89-4.

The Reaction of Dilithium Cyclooctatetraenide with Phosgene. Preparation of Bicyclo[4.2.1]nona-2,4,7-trien-9-one[1]

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Received December 16, 1971

Although the chemistry of bicyclo[4.2.1]nonatrienols has been explored to a considerable extent,[4] the corresponding parent ketone, bicyclo[4.2.1]nona-2,4,7-trien-9-one (**1**), has not been described. This system has been synthesized by the reaction of dilithium cyclooctatetraenide with phosgene.[5] Cyclooctatetraene was converted into its dianion, which was treated with excess ethereal phosgene at −40° and then quenched with water. The resulting mixture, containing two main products, was subjected to tlc. The component of shorter R_f was formed in about 19% yield and established to be the desired **1** on the basis of the mass spectrum [parent peak, m/e 132 ($C_9H_8O^+$)] and nmr spectrum [τ 4.29 (6 H) and saturated bridgehead proton absorptions centered at τ 7.09 (2 H)]. The ir spectrum shows weak absorption at 3045 cm^{-1} (olefinic C–H) and strong absorption at 1755 cm^{-1} (C=O, similar to that of bridgehead ketones[6]). The addition of CH_3MgI to **1** resulted in the formation of one alcohol, indistinguishable from an authentic sample of *syn*-9-hydroxy-9-methylbicyclo[4.2.1]nona-2,4,7-triene (**2**)[4a] on the basis of vpc comparison on two columns and nmr and ir spectral comparison. The component of longer R_f, formed in 22% yield, was 3-chloroindene (**3**).[7]

(1) Part of this work was described in a Communication to the Editor: M. Sakai, A. Diaz, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 4452 (1970).

(2) Address correspondence to this author at Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada.

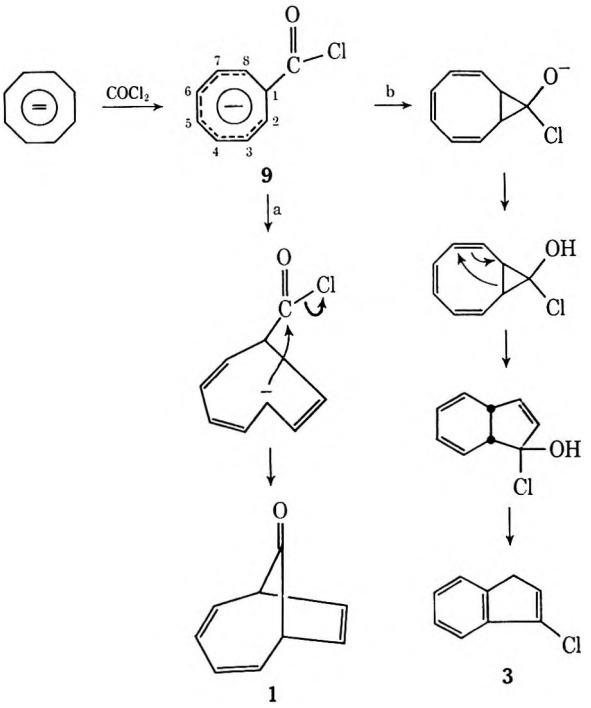
(3) Deceased Nov 23, 1969.

(4) (a) T. S. Cantrell and H. Shechter, *J. Amer. Chem. Soc.*, **89**, 5868 (1967); (b) L. G. Cannell, *Tetrahedron Lett.*, 5947 (1966); (c) A. S. Kende and T. L. Bogard, *ibid.*, 3383 (1967); (d) M. Sakai and S. Winstein, unpublished results.

(5) After the present method had been perfected, we learned that Professor H. Shechter and coworkers made **1** by the reaction of dilithium cyclooctatetraenide with dimethylcarbamoyl chloride.

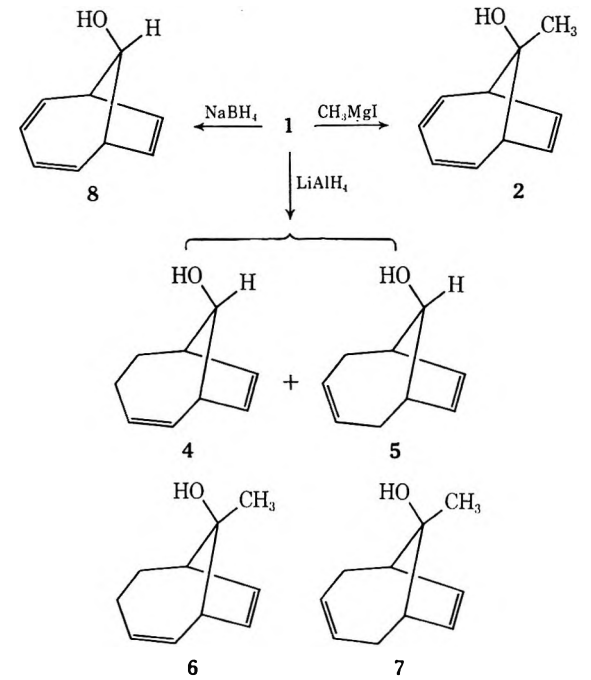
(6) (a) C. D. Gutsche and T. D. Smith, *J. Amer. Chem. Soc.*, **82**, 4067 (1960); (b) H. K. Hall, Jr., and R. Zhinden, *ibid.*, **80**, 6428 (1958); (c) P. G. Gassman and P. G. Pape, *J. Org. Chem.*, **29**, 160 (1964); (d) C. F. H. Allan, T. Davis, D. W. Stewart, and J. A. VanAllan, *ibid.*, **20**, 306 (1955).

(7) E. A. Braude and E. A. Evans, *J. Chem. Soc.*, 3337 (1955).



Formation of **1** and **3** from the dianion and phosgene can be envisaged as proceeding *via* paths a and b. The intermediate **9** undergoes intramolecular reaction at C-4 (a) of the eight-membered ring to give **1**. Compound **3** is derivable *via* ring closure (b) of **9** at C-2, followed by dehydration of 1-chloro-1-hydroxy-8,7-dihydroindene and prototropic rearrangement.

Reaction of **1** with $LiAlH_4$ in ether furnishes *syn*-9-hydroxybicyclo[4.2.1]nona-2,7-diene (**4**) and *syn*-9-hydroxybicyclo[4.2.1]nona-3,7-diene (**5**). The structure of **4** and **5** are assignable from their spectral properties. The nmr spectra are quite similar to those of the analogous alcohols **6** and **7**,[4d] except for the disappearance of methyl absorptions and formation of α-proton absorption. It is probable that **4** and **5** have syn stereochemistry.



The reaction of **1** and $NaBH_4$ in methanol at room temperature has been briefly investigated and found to yield only *syn*-9-hydroxybicyclo[4.2.1]nona-2,4,7-triene (**8**). The identification of **8** rests on its analysis, its ir spectrum, its mass spectrum, and, in particular, its nmr spectrum. The stereochemistry of the hydroxyl group in **8** is assigned as syn to the four-carbon bridge on the basis that the side of the carbonyl group facing the two-carbon bridge is considerably less hindered than the side facing the four-carbon bridge. Hydride attack should occur predominantly from the side of the carbonyl group syn to the two-carbon to give **8**.

Experimental Section

Reaction of Dilithium Cyclooctatetraenide with Phosgene.—Lithium (4.0 g) was added in small pieces to dry DME (250 ml, freshly distilled from $LiAlH_4$) at −78° in nitrogen atmosphere. Freshly distilled COT (26 g) was added, and the mixture was stirred vigorously for 20 hr, allowed to warm to room temperature, and stirred for an additional 48 hr. The deep green solution of LiCOT in DME was added over a 1-hr period to vigorously stirred cold (−40°) phosgene (100 g) in 200 ml of DME under helium. After further stirring for 3 hr at −40°, the mixture was allowed to warm to room temperature and stirred for 5 hr more. The reaction mixture was filtered, water added, and extracted with pentane (3 × 500 ml) to give a red solution. The combined organic layers were washed with water (200 ml) and saturated Na_2CO_3 solution (100 ml) and then dried ($MgSO_4$). Evaporation of the solvent gave a red oil which was chromatographed on 100 ml of neutral alumina (activity III).

The first elution with pentane was 3-chloroindene (9.0 g, 22%): mass spectrum *m/e* 150 (M^+); nmr $\tau_{TMS}^{CS_2}$ 2.67 (m, 4, aromatic), 3.62 (t, 1, vinyl), and 6.67 (d, 2, allyl); ir ν_{max}^{neat} 759 cm^{-1}.

Anal. Calcd for C_9H_7Cl: C, 71.78; H, 4.68. Found: C, 71.92; H, 4.91.

The second elution with 12% ether–pentane was almost pure **1**, yield 6.2 g (19%).

Anal. Calcd for C_9H_8O: C, 81.79; H, 6.10. Found: C, 81.56; H, 6.09.

Some modification of the preparation of **1** gave the results shown in Table I.

TABLE I

YIELDS OF 1 AND 3

Solvent	Temp, °C	Time, hr	Yield, % 1	3
DME	−40	4	19	22
Ether	−30	3	17	20
Ether	0	1	18	25
THF	−30	4	20	?

Reaction of 1 with Methylmagnesium Iodide.—A solution of **1** (100 mg) in ether (2 ml) was added at 0° to stirred methylmagnesium iodide (3 mol excess) in ether (2.5 ml). The mixture was refluxed for 20 min and then poured onto a slurry of ice and saturated aqueous NH_4Cl. The aqueous layer was washed with ether. The combined ether solution was washed with water, dried, and evaporated to give 95 mg of **2** as an oil: ir ν_{max}^{neat} 1394, 1372, 1180, 860, 751 and 687 cm^{-1}; nmr $\tau_{TMS}^{CS_2}$ 4.01 (m, 4, vinyl), 4.82 (m, 2, vinyl), 7.32 (m, 2, bridgehead), 8.13 (s, 1, OH), and 8.67 (s, 3, methyl).

Reaction of 1 with $LiAlH_4$.—A solution of 1.5 g of **1** in 20 ml of ether was added to a solution of 0.8 g of $LiAlH_4$ in 5 ml of ether dropwise at −78°. After the solution was stirred for 2 hr at this temperature, it was decomposed with 10 ml of 20% KOH solution. The ether solution was washed with water and dried (K_2CO_3), and evaporation of the ether gave 1.6 g of a pale yellow oil. Examination by vpc revealed two components, **4** (81.5%) and **5** (18.5%) in order of increasing emerging time. Preparative vpc of a 1.0-g quantity of the above mixture gave 0.4 g of **4** [nmr $\tau_{TMS}^{CDCl_3}$ 4.07 (m, 2, vinyl), 4.43 (m, 2, vinyl), 5.78 (t, 1, α-H), 6.83 (m, 1, bridgehead), 7.33 (m, 1, bridgehead), 8.06 (s, 1, OH), and 8.14 (m, 4, methylene)] and 0.1 g of **5** [nmr $\tau_{TMS}^{CDCl_3}$ 4.22 (m, 2, vinyl), 4.55 (m, 2, vinyl), 5.53 (t, 1, α-H),

7.24 (m, 2, bridgehead), 7.69 (m, 4, methylene), and 8.28 (s, 1, OH)].

Reaction of 1 with $NaBH_4$.—A solution of 0.5 g of 1 in 30 ml of methanol was cooled to 0°. $NaBH_4$ (0.4 g) was added in small portions. After 30 min, the ice bath was removed and the solution was allowed to stir for 1 hr. The reaction mixture was cooled and hydrolyzed with 10 ml of water and 15 ml of 20% KOH solution. The mixture was poured into ice–water and extracted with ether. Evaporation of the ether yielded a residue which was crystallized from hexane at −5° to give 0.48 g (95%) of 8 as white needles: mp 52.0–52.5°; mass spectrum *m/e* 137 (M^+); ir $\nu_{max}^{CHCl_3}$ 3575, 3035, and 1105 cm^{-1}; nmr $\tau_{TMS}^{CDCl_3}$ 3.98 (m, 4, vinyl), 4.75 (m, 2, vinyl), 5.62 (m, 1, α-H), 6.96 (t, 2, bridgehead), and 8.22 (m, 1, OH).

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.56. Found: C, 80.44; H, 7.66.

Registry No.—**1**, 34733-74-9; **2**, 17339-68-3; **3**, 25894-22-8; **4**, 34733-77-2; **5**, 34771-56-7; **8**, 34712-67-9; dilithium cyclooctatetraenide, 34728-91-1; phosgene, 75-44-5.

Novel Synthesis of 1-Hydroxy-1*H*-benzimidazole 3-Oxides and 2,2-Dialkyl-2*H*-benzimidazole 1,3-Dioxides[1]

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Received January 20, 1972

Benzofurazan 1-oxide (**1**) is known to react with enamines[2] and β diketones[3] to yield substituted quinoxaline 1,4-dioxides and with phenolate anions[4,5] to yield substituted phenazine 5,10-dioxides and related compounds. We have recently discovered its utility for the preparation of substituted benzimidazole 1,3-dioxides. The method constitutes a highly convenient preparative procedure.

We have found that benzofurazan 1-oxide (**1**) reacts exothermically with primary nitroalkanes in tetrahydrofuran in the presence of organic amine bases to give good yields of 2-substituted 1-hydroxy-1*H*-benzimidazole 3-oxides (see Table I) and nitrite salts of the amines. The parent compound **2** (R = H) was prepared in 40% yield from nitromethane in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN). This compound was identical with an authentic sample prepared by Katritsky's method.[6] Diethylamine was the base used for the preparation of compounds **3**–**6** (Table I), and in these experiments the other product was characterized as the nitrite salt of diethylamine.

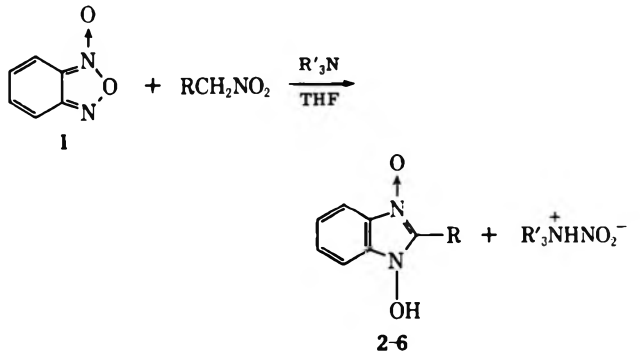


TABLE I[a]

Compd no.	R	Yield, %	Mp, °C[b]
2	-H	40	223
3	$-CH_3$	65	204–205
4	$-CH_2CH_3$	66	194–195
5	$-CH_2CH_2CONH_2$	70	220
6	$-CO_2CH_2CH_3$	35	156.5

[a] All compounds were analyzed for C, H, and N and the results were within ±0.3% of the theoretical values. Spectral data were consistent with assigned structures. [b] Compounds 2–5 were recrystallized from MeOH; 6 from AcOH.

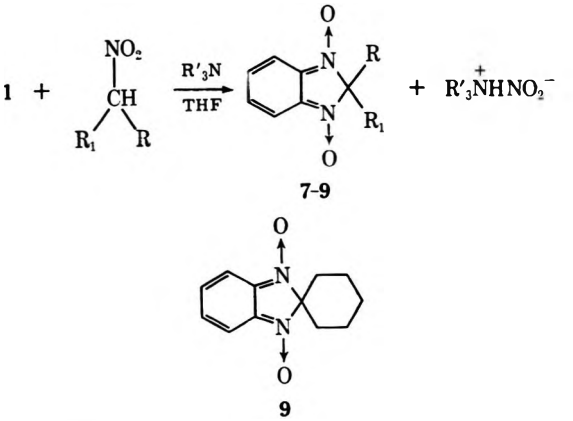
In a typical procedure, 0.1 mol of **1** and 0.12 mol of nitroethane were dissolved in 100 ml of tetrahydrofuran. To this was added at room temperature 0.12 mol of diethylamine over a period of 0.5 hr. An instantaneous exothermic reaction was observed (40°) and within 1 hr the product crystallized from the solution. The solution was allowed to stand overnight at room temperature and filtered to give 9.6 g of **3**. The product was recrystallized from methanol and was found to be identical with authentic material prepared by a known procedure.[7]

Of particular interest was the reaction of secondary nitroalkanes with **1** to afford a novel new class of compounds, 2,2-dialkyl-2*H*-benzimidazole 1,3-dioxides (Table II). These compounds are red with a green fluorescence. The procedure described above gave 2,2-dimethyl-2*H*-benzimidazole 1,3-dioxide (**7**) in 60%

TABLE II[a]

Compd no.	R	R_1	Yield, %	Mp, °C
7	$-CH_3$	$-CH_3$	60	132–134
8	$-CH_3$	$-CH_2CH_3$	52	127–129
9	$-(CH_2)_5-$		75	112–115

[a] All compounds were analyzed for C, H, and N and the results were within ±0.3% of the theoretical values. Spectral data were consistent with assigned structures. Compounds were recrystallized from acetone–hexane.



(1) Presented in part at (a) IUPAC Meeting in London, July 1968, Abstract H4, 437; (b) 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Medicinal Chemistry Abstract 15.

(2) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965).

(3) C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.*, **31**, 4067 (1966).

(4) K. Ley, F. Seng, V. Eholzer, R. Nast, and R. Schubart, *Angew. Chem., Int. Ed. Engl.*, **8**, 596 (1969).

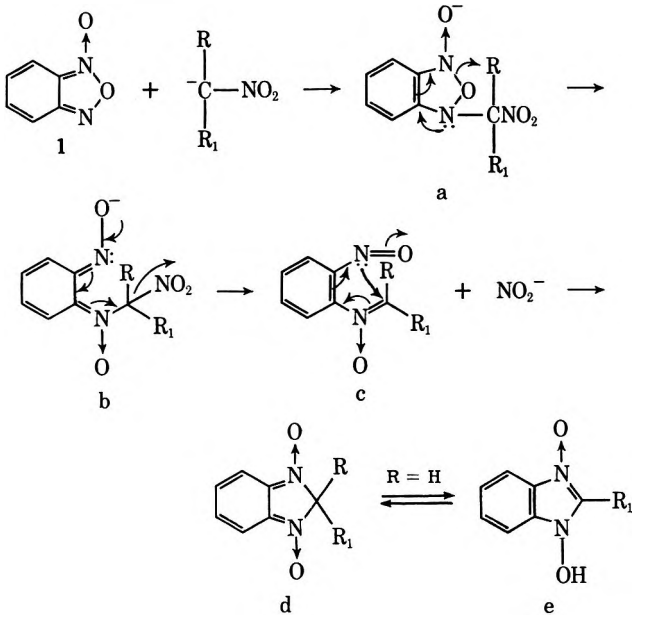
(5) M. J. Abu El-Haj, B. W. Dominy, J. D. Johnston, M. J. Haddadin, and C. H. Issidorides, *J. Org. Chem.*, **37**, 589 (1972).

(6) A. J. Boulton, A. C. Gray, and A. R. Katritsky, *Chem. Commun.*, 741 (1966).

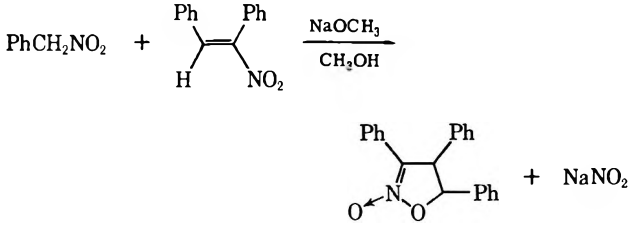
(7) G. La Parola, *Gazz. Chim. Ital.*, **75**, 216 (1945).

yield from 2-nitropropane. The ir spectrum (KBr) exhibited strong absorption bands for the N→O at 1399, 1361, and 1307 cm^{-1}; the uv spectrum (MeOH) exhibited maxima at 510 mμ (ϵ 7.25 × 10^3) and 245 (2.34 × 10^4). The nmr spectrum ($CDCl_3$) showed absorption at δ 1.7 (s, 6 H) due to the dimethyl grouping and two A_2B_2 quartets for the aromatic protons at δ 6.9 (J = 3 Hz) and 7.25 (J = 3 Hz). The spiro compound **9** was obtained by allowing **1** to react with nitrocyclohexane in the presence of DBN.

A possible mechanism for the formation of the above products from **1** and the nitroalkanes is outlined below. The nitroanion probably adds to the N-3 nitrogen to



give a, which can tautomerize to b. Elimination of NO_2^- would give c, which could rearrange to d. The latter is the final product where R and R_1 are alkyl, whereas if R = H, the product tautomerizes to form e. A similar displacement of a nitro group was reported during the formation of 3,4,5-triphenylisoxazoline 2-oxide from phenylnitromethane and *cis*-α-nitrostilbene in the presence of base, as shown below.[8]



The first observation of the displacement of a nitro group from a tertiary carbon atom (by thiophenoxide and malonate anions) was reported by Kornblum, *et al.*[9]

Another route from benzofurazan oxides to 1-hydroxy-1*H*-benzimidazole 3-oxides, using β-keto sulfoxides, has recently been reported.[10]

Registry No.—**2**, 15966-49-1; **3**, 15966-52-6; **4**, 31980-09-3; **5**, 34759-59-6; **6**, 31980-11-7; **7**, 31980-12-8; **8**, 34789-56-5; **9**, 31983-86-5.

(8) A. T. Nielsen and T. G. Archibald, *Tetrahedron Lett.*, 3378 (1968).
(9) N. Kornblum, T. M. Davies, G. W. Earl, G. S. Greene, N. L. Holy, R. C. Kerber, J. W. Manthey, M. T. Musser, and D. H. Snow, *J. Amer. Chem. Soc.*, **89**, 5714 (1967).
(10) D. P. Claypool and D. R. Sidani, *J. Org. Chem.*, in press.

The Rearrangement of 3a,7a-Dihydro-3,3a,5,6-tetraphenylinden-1-one

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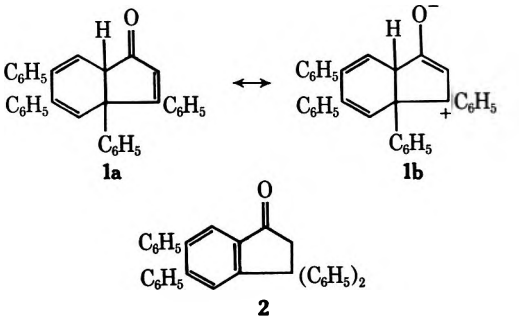
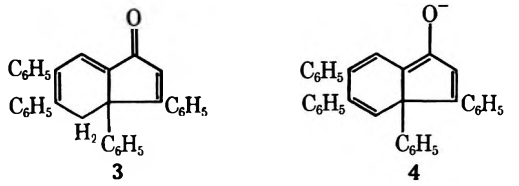
Received January 18, 1972

The thermal rearrangement of 3a,7a-dihydro-3,3a,5,6-tetraphenylinden-1-one (**1a**) to 3,3,5,6-tetraphenyl-



indan-1-one (**2**), which has been considered to proceed through the polarized form **1b**,[1] has now been found to be catalyzed by base and acid. Addition of catalytic amounts of sodium methoxide to an alcohol solution of **1a** forms a purple enolate ion which on heating for a short time gives mainly the less acidic 3a,4-dihydro-3,3a,5,6-tetraphenylinden-1-one (**3**) and a small amount



of **2**. Further heating of this solution converts **3** to **2**. These results preclude the participation of **1b** in this rearrangement and indicates that the enolate ion **4**, which can be formed from both **1a** and **3**, is involved and would allow the rearrangement to proceed by a 1,5-suprafacial sigmatropic shift of the phenyl group.

The behavior of **1a** with acid is similar. Treatment with hydrogen bromide in acetic acid at 100° for 30 min gives **3**.[2] Prolonged heating of **1a** with hydrochloric acid in ethanol gave mainly **2**. This sequence of reactions favors the enol form of **1a** as a precursor of **2**.

The uncatalyzed thermal rearrangement of **1a** may proceed through the enol form even though this form could not be detected by either infrared or nmr spectroscopy. Studies of **1a** using the first technique were carried out at temperatures varying from 25 to 175°. At the melting point **1a**, when present as a film, was found to rearrange to **2**.

Nmr studies of **1a** found no evidence for the enol form; similar peak heights were observed in polar ($DCCl_3$) and nonpolar (C_6D_6) solvents.

The uncatalyzed thermal rearrangement[2] of **3** to **2** would involve first a 1,5 shift of hydrogen and the formation of **1a**. The possibility of a 1,7 shift of

(1) C. F. H. Allen and J. A. VanAllan, *J. Org. Chem.*, **20**, 315 (1955).
(2) C. F. H. Allen and J. W. Gates, Jr., *J. Amer. Chem. Soc.*, **64**, 2120 (1942).

hydrogen directly to the enol exists but would require more energy.

Experimental Section[3]

Action of Sodium Methoxide on 3a,7a-Dihydro-3,3a,5,6-tetraphenylinden-1-one (1a).—The indenone **1a** (1 g) was refluxed with sodium methoxide (0.01 g) in 95% ethanol (60 ml) for 30 min. The resulting brownish yellow solution upon cooling gave **3** (0.48 g) which after successive crystallizations from ethyl acetate and benzene melted at 240–242°. This sample was identical with a sample prepared by the acid isomerization of **1a**:[2] ir (Nujol) 1670 (C=O), 1650 cm^{-1} (C=C); nmr ($DCCl_3$) δ 3.29 (d, J = 16 Hz, H-4), 3.62 (d, J = 16 Hz, H-4), 6.7–7.4 ppm (m, 20 aromatic H and H-2).

The filtrate upon treatment with water and a trace of acid gave **2**, which after recrystallization two times from ethanol melted at 176°, yield 0.16 g. This sample was identical with that obtained by pyrolysis:[4] ir (Nujol) 1720 cm^{-1} (C=O); nmr ($DCCl_3$) δ 3.51 (s, CH_2), 7.0–7.3 (m, 20 aromatic hydrogens), 7.4 (s, H-7), and 7.83 ppm (s, H-4).

Heating a solution of the indenone **1a** (0.62 g) in 95% ethanol (35 ml) with sodium methoxide (0.01 g) for 8.5 hr gave 0.43 g of **2**.

Action of Hydrochloric Acid on 3a,7a-Dihydro-3,3a,5,6-tetraphenylinden-1-one (1a).—The indenone **1a** was heated in ethanol (50 ml) with concentrated hydrochloric acid (1 ml) for 17 hr. Addition of water gave a solid (0.40 g) which, based upon the ir spectrum, consisted mainly of **2** with a small amount of **3**.

3a,7a-Dihydro-3,3a,5,6-tetraphenylinden-1-one (1a).—The nmr spectra in chloroform-d and benzene-d_6 were identical with respect to integration. Chemical shifts for the vinyl hydrogen differed: nmr ($DCCl_3$) δ 3.54 (d, J = 5.5 Hz, H-7a), 5.98 (d, J = 5.5 Hz, H-7), 6.18 (s, H-4), 6.8–7.5 (m, 20 aromatic H and H-2); nmr (C_6D_6) δ 3.54 (d, J = 5.5 Hz, H-7a), 6.13 (d, J = 5.5 Hz, H-7), 6.40 (s, H-4), 6.8–7.5 ppm (m, 20 aromatic hydrogens and H-2); ir (Nujol) 1690 cm^{-1} (C=O).

Registry No.—**1a**, 16643-52-0; **2**, 16643-46-2; **3**, 16643-45-1.

(3) Melting points are not corrected. Infrared spectra were determined on a Perkin-Elmer Infracord and Model 421 and nmr spectra were obtained with a Varian A-60 spectrometer.

(4) On occasion the ketone from the pyrolysis was obtained in a crystalline form which melted at 153.5–155°. This sample upon standing in ethanol slowly changed into the 176° melting form. The ir spectra were identical. This behavior explains the range of melting points reported by Japp[5] for this compound.

(5) F. R. Japp and C. I. Burton, *J. Chem. Soc.*, **51**, 420 (1887).

Neighboring Carboxylate Groups and the Oxidation of Benzhydrol and Benzaldehyde by Permanganate[1]

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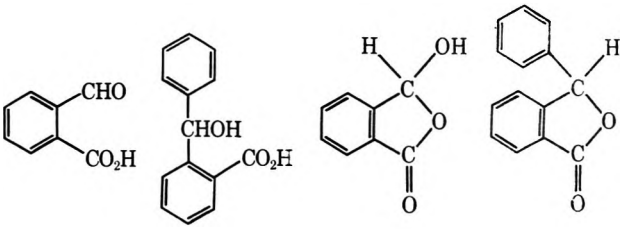
Received November 18, 1971

The permanganate oxidation of both benzhydrol and benzaldehyde is much faster in alkaline solution than at neutral pH. The activation of alcohols toward *external* base is due to formation of alkoxide ion.[2] We have investigated the effect of *internal* base (in the form of neighboring carboxylate) on the oxidation of alcohols and aldehydes and have reported elsewhere the existence of such catalysis in the case of *cis*-2-hydroxycyclohexanecarboxylic acid.[3] However, no such effect can be observed in the case of the anions of the ortho carboxy derivatives of benzaldehyde and benzhydrol, **1** and **2**, as will be seen from the subsequent discussion.



1 **2** **3** **4**

The present brief report is prompted by the appearance of a paper which reports the presence of such intramolecular catalysis in the oxidation of **1** by bromine.[4]

Comparison of the oxidation of the anions of **1** and **2** was made with the corresponding compounds lacking a carboxyl group and with those containing such a group in the para position. The results are summarized in Table I.

The effect of a carboxylate group on the oxidation of benzaldehyde in the neutral and mildly basic regions is small, whether the group is in the ortho or para position. As the medium is made more acidic than pH 5 the oxidation of all three compounds accelerates and becomes autocatalytic. The one striking effect of the ortho carboxyl group in phthalaldehydic acid is that at still higher acidities the oxidation rate for this compound decreases again and the autocatalysis vanishes. A clean second-order reaction is observed at pH 1.55 at a rate that is considerably less than that observed under neutral conditions. This is presumably due to **1** existing under these conditions almost completely in the ring-closed phthalide form, **3**,[5] a form whose oxidation behavior should resemble that of an alcohol rather than an aldehyde.

In the case of benzhydrol an ortho carboxy group has a pronounced *inhibiting* effect on the oxidation both in neutral and in basic solution. This effect cannot be due to the formation of the ring-closed phthalide compound, **4**,[6] since this form predominates only below pH 5, where, indeed, it precipitates from the reaction mixture and makes a study of its reaction with permanganate impossible. The inhibiting effect of adjacent carboxylate can be attributed to electrostatic repulsion between this group and permanganate ion. Evidently, a specific conformational relationship between alcoholic hydroxyl and neighboring carboxylate is required before intramolecular catalysis of the permanganate–alcohol reaction can be observed.[4]

Experimental Section

The rate measurements were made by both iodometric and spectrophotometric means, essentially as previously described.[2a,3]

(1) The financial support of the National Research Council of Canada is gratefully acknowledged.

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TABLE I

RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE PERMANGANATE OXIDATION OF VARIOUS COMPOUNDS IN WATER

Registry no.	Compd	k, l. mol^{-1} sec^{-1}, at 25°			$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
		pH 8.1	pH 10.3	pH 12.7		
	Benzaldehyde[a]	0.37	0.42		10.3[b]	−26.2[b]
119-67-5	Phthalaldehydic acid (1)	0.18	0.17		10.4[c]	−27.1[c]
619-66-9	Terephthalaldehydic acid	0.28	0.39		11.2[c]	−23.4[c]
91-01-0	Benzhydrol[d]	0.070	0.10	3.7	*e*	*e*
34737-60-5	Benzhydrol-2-carboxylic acid (2)	0.006	0.004	0.19	8.8[f]	−36.4[f]
579-52-2	Benzhydrol-4-carboxylic acid	0.057	0.060	6.0	8.9[f]	−32.4[f]

[a] K. B. Wiberg and R. Stewart, *J. Amer. Chem. Soc.*, 77, 1786 (1955). [b] At pH 6.5. [c] At pH 8.1. [d] Reference 2a. [e] $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ for this compound are 5.7 and −38.4, respectively, at pH 12.3, a pH at which the oxidation proceeds almost entirely by way of the alkoxide ion. [f] At pH 5.45, for which k at 25° is 0.0237 and 0.139 l. mol^{-1} sec^{-1} for the 2- and 4-substituted compounds, respectively.

The oxidations of 1 and terephthalaldehydic acid in water were allowed to proceed to completion and the organic products were isolated. The only products were phthalic and terephthalic acids, each being formed in near quantitative yield. In the case of benzhydrol-2-carboxylic acid the reaction was quenched, at the point where the kinetic experiments showed the reaction to be 60% complete, by the addition of sodium bisulfite and acid. The organic product was taken up in ether and this solution was extracted with aqueous bicarbonate. The two fractions yielded 3-phenylphthalide and 2-benzoylbenzoic acid in quantitative amount corresponding to 60% reaction. The physical properties of the phthalide,[6] 2-benzoylbenzoic acid, and 4-benzoylbenzoic acid (formed in 98% yield by oxidation of 4-benzhydrolcarboxylic acid) were identical with those of authentic samples.

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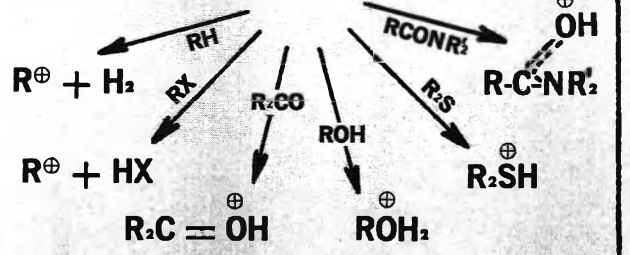

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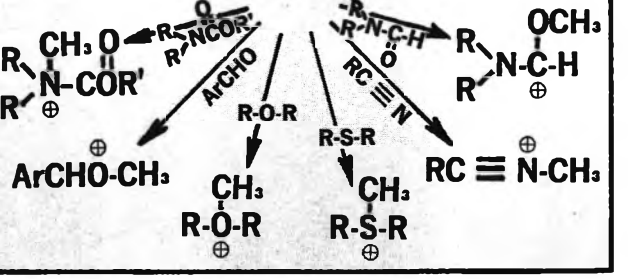

SUPERACIDS: The term 'superacid' was first used in 1927 by Hull and Conant[1] for perchloric acid which produced perchlorate salts with carbonyl compounds. Since then the field of superacids has been greatly extended,[2,4,6] particularly in the study of carbocations.[3] Fluorosulfuric acid has a higher acidity than sulfuric acid (H_o logarithmic Hammett acidity function value of −13.5 vs −12.0 for H_2SO_4) and also has a wider liquid range, from −89° to +161°C. These qualities permit the study of solutions of numerous protonated onium ions and carbocations over a wide range of temperatures by nmr spectroscopy.

The acidity of fluorosulfuric acid can be further enhanced[2,5] by the addition of SbF_5; so much so that 1:1 FSO_3H-SbF_5, **Magic Acid®**, is a million times stronger acid than 100% H_2SO_4. Thus **Magic Acid®** and **Fluoroantimonic Acid,** 1:1 HF-SbF_5, due to their exceptionally high acidity, can produce stable carbocations[3] by protonation and hydride or halide abstraction. Even methane[5] shows substantial reactivity in these superacids.

Superacids can be used to isomerize saturated hydrocarbons at lower temperatures than with conventional catalysts. This allows, for example, the formation of more highly branched hexane and heptane equilibrium mixtures needed as high octane gasoline components. A whole new era of chemistry is emerging in the superacidity range.

MAGIC METHYL✱ has been found to be a powerful alkylating agent,[7] though, of course, being a covalent ester, its reactivity cannot be compared to that of superalkylators such as $CH_3F \cdot SbF_5$.[12] These however are difficult to stabilize, while **Magic Methyl✱** is stable for many months. It can quaternize amines and readily alkylates amides and carbamates.[7,8] It forms nitrilium salts with nitriles which can be reduced with $NaBH_4$ to produce secondary amines like the reduction of N-ethylnitrilium fluoroborates reported by Borch.[9] Sulfides react with it to yield sulfonium salts[10] which can be used to form C-C bonds via Stevens Rearrangement.[11] Most ethers and carbonyl compounds form oxonium salts[7,10] with **Magic Methyl✱.**

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✱ Magic Methyl is a trademark of Aldrich Chemical Co.

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