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Reactions of Nitrilium Salts.[1,2] I. With Sodium and Dimethylammonium Azide

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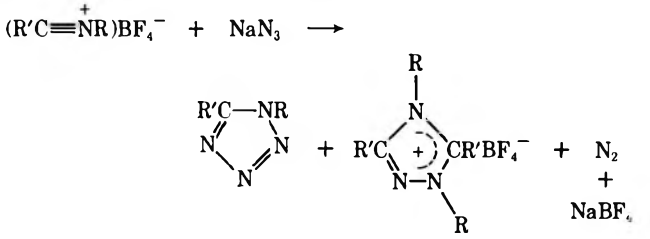
Received March 3, 1971

1-Methyl-5-vinyltetrazole (11), 1-ethyl-5-methyl- (1), 1,5-diethyl- (2), and 1-ethyl-5-phenyltetrazole (3) were synthesized by nucleophilic attack of azide ions on the corresponding nitrilium salts. The reaction of nitrilium salts with azide ions in toluene gives 1,3,4,5-tetrasubstituted 1,2,4-triazolium salts as well as 1,5-disubstituted tetrazoles. When acetonitrile was employed as the reaction solvent, good yields of tetrazoles and triazolium salts depended on the mode of addition of reactants.

In 1955 Klages[4] and Meerwein[5] described the first relatively stable nitrilium salts[6] and later developed general methods for their preparation. Nitrilium salts of the general formula $(R'C{\equiv}N^+R)BF_4^-$ may be prepared by the reaction of trialkyloxonium fluoroborate salts with nitriles. These salts react[7] with nucleophiles such as OH^-, H_2O, ROH, NH_3, and RNH_2 giving amides, imino ethers, and amidines.

As anticipated, nitrilium salts react with azide ion, an excellent nucleophile, to give 1,5-disubstituted tetrazoles.[8] Earlier it was reported[9] that *N*-ethylaceto- and *N*-ethylpropionitrilium fluoroborate react with sodium azide in toluene to give 1-ethyl-5-methyl- (1) and 1,5-diethyltetrazole (2), respectively. The major products



R′ = Me; R = Et	1	4
R′ = R = Et	2	5
R′ = Ph; R = Et	3	6

which were not characterized at that time have been identified as 1,3,4,5-tetrasubstituted 1,2,4-triazolium fluoroborates.[10]

In a typical experiment, an excess of sodium azide is added to a stirred suspension of nitrilium salt in toluene at ambient temperature. An exotherm occurs after a short induction period with evolution of nitrogen. The initial reaction and exotherm apparently occur until the unreacted sodium azide is completely coated with the toluene-insoluble triazolium salt. If, however, the reaction is stirred and heated to reflux, causing the triazolium salt to become an oil, the reaction continues. Analyses of the reaction mixtures immediately after the exotherm indicated 20% conversion to tetrazole and 90% conversion after 6 hr. The amount of nitrogen evolved during the exotherm is about 15% of the theoretical.

The summarized data in Table I show that the mode of addition of reactants in the reaction of *N*-ethylaceto-

TABLE I

REACTIONS OF NITRILIUM SALTS WITH SODIUM AZIDE IN TOLUENE

R	Mode of addition[a,b]	Reaction temp, °C	% yield[c] Tetrazole	% yield[c] Triazolium salt
Me	A	0–110	34	65[d,e]
Me	B	25–110	30	62[e]
Et	B	25–110	32	53[e]
Ph	B	25–30[f]	14	34
Ph	B	25–110	10	45

[a] A, $(RC{\equiv}N^+Et)BF_4^-$ to NaN_3; B, NaN_3 to $(RC{\equiv}N^+Et)BF_4^-$. [b] All additions of reagents, except the reaction at 0–110° (3 min), were effected in 35 min under an atmosphere of nitrogen. [c] Yields are based on nitrilium salts. [d] 87% of theory of nitrogen, based on crude triazolium salt, was evolved. [e] Crude yield. [f] 7 days at ambient temperature.

(1) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966.

(2) Taken from the dissertation of L. A. Lee in partial fulfillment of the requirements for the Ph.D. degree, Howard University, 1970.

(3) Author to whom correspondence should be addressed at Polaroid Corp., Cambridge, Mass. 02139.

(4) F. Klages and W. Grill, *Justus Liebigs Ann. Chem.*, **594**, 21 (1955).

(5) H. Meerwein, *Angew. Chem.*, **67**, 379 (1955).

(6) For a review on nitrilium salts involving heterocyclic syntheses, see F. Johnson and R. Madroñero, *Advan. Heterocycl. Chem.*, **6**, 95 (1966).

(7) H. Meerwein, P. Laasch, R. Mersch, and J. Spille, *Chem. Ber.*, **89**, 209 (1956).

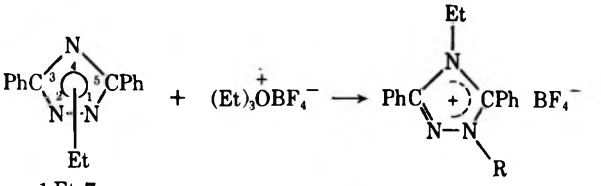
(8) For a review on tetrazoles, see (a) F. R. Benson, *Chem. Rev.*, **41**, 1 (1947); (b) F. R. Benson, *Heterocycl. Compounds*, **8**, 1 (1967).

(9) L. A. Lee, E. V. Crabtree, J. U. Lowe, Jr., M. J. Cziesla, and R. Evans, *Tetrahedron Lett.*, **No. 33**, 2885 (1965).

(10) L. A. Lee, J. W. Wheeler, Jr., M. J. Cziesla, and R. Evans, Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. S11.

nitrilium fluoroborate with sodium azide in toluene does not significantly affect the ratio of products, as expected for a heterogeneous reaction which is not instantaneous.

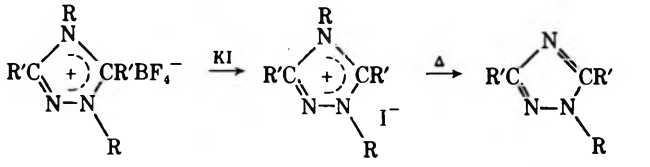
The 1,5-disubstituted tetrazoles were identified by their typically intense absorption in the 9–10-μ region of the infrared,[11a] proton magnetic resonance spectra,[11b] elemental analysis, or comparison with an authentic compound. The structure of 1,4-diethyl-3,5-diphenyl-1,2,4-triazolium fluoroborate (**6**) was confirmed by quaternization of either 1-ethyl-3,5-diphenyl-1,2,4-triazole (**7**) or 4-ethyl-3,5-diphenyl-1,2,4-triazole (**8**) with triethyloxonium fluoroborate.



1-Et, **7**
4-Et, **8**

6
+ Et_2O

1,4-Diethyl-3,5-dimethyl- (**4**) and 1,3,4,5-tetraethyl-1,2,4-triazolium fluoroborate (**5**) were identified by conversion of their crude and hygroscopic fluoroborates to the iodides with sodium iodide in acetone. Pyrolysis of the iodides at 250° *in vacuo* gave 1-ethyl-3,5-dimethyl- (**9**) and 1,3,5-triethyl-1,2,4-triazole (**10**), respectively. Symmetrical 3,4,5-trialkyl-1,2,4-triazoles were not isolated in either case.



4
5

9, R = Et; R′ = Me
10, R = R′ = Et

The infrared and proton magnetic resonance[11b] data of the isolated compounds were identical with those of authentic samples prepared by the procedure of Einhorn–Brunner.[12]

In an effort to increase the yield of tetrazole, acetonitrile was chosen as the reaction solvent. This polar aprotic media is capable of dissociating the nitrilium salts into solvent-separated ion pairs. When nitrilium salts dissolved in acetonitrile were added dropwise to suspensions of sodium azide or solutions of dimethylammonium azide *in situ* in acetonitrile, exotherms occurred with virtually no evolution of nitrogen. Good yields of tetrazoles and trace amounts of triazolium salts were isolated generally within 1 hr after the additions were complete. In reverse addition reactions, the azide was added to a solution of nitrilium salt in acetonitrile. During the addition, exotherms occur with evolution of nitrogen. Addition of *N*-ethylbenzonitrilium fluoroborate to sodium azide gave virtually no evolved nitrogen, a 73% yield of tetrazole, and only trace amounts of triazolium salt. Reverse addition of the same reagents at −20 to −25° produced practically no nitrogen gas. However, when the solution was warmed to −5°, evolution of nitrogen was observed.

(11) (a) E. Lieber, D. R. Levering, and L. J. Patterson, *Anal. Chem.*, **23**, 1594 (1951); (b) L. A. Lee and J. W. Wheeler, *J. Org. Chem.*, **37**, 348 (1972).
(12) M. R. Atkinson and J. B. Polya, *J. Chem. Soc.*, 141 (1954).

In general, the ratio of tetrazole to triazolium salt formed depends on the mode of addition of nitrilium salts and sodium azide in acetonitrile. During the normal addition, there is never an excess of unreacted nitrilium salt in the reaction mixture. However, in reverse addition, there is always an excess of nitrilium salt present and the major product afforded is tetrazole plus a significant amount of triazolium salt. Regardless of the mode of addition, excess nitrilium salt is also present in the heterogeneous reactions carried out in toluene. Because of the insoluble nature of the reactants, it is conceivable that sodium azide molecules could be surrounded by excess nitrilium salt. The reactions investigated are summarized in Table II.

TABLE II
REACTIONS OF NITRILIUM SALTS WITH SODIUM AND DIMETHYLAMMONIUM AZIDE IN ACETONITRILE

R	Mode of addition[a,b]	Reaction temp, °C	% yield[c] Tetrazole	% yield[c] Triazolium salt
Me	A	25–35	85	*d*
Et	A	25–35	80	*d*
Et	C	25–35	84	*e*
Et	B	25–35	52	36
Et	D	25–35	72	*e*
Et	B	60–70	29	64
Et	D	60–70	53	*e*
Ph	A	25–35	80	*d*
Ph	A	0–5	73	*d*
Ph	B	−20 to −25	40	8
Ph	B	25–35	55	13
Vinyl	A	25–35	13	*f*
Vinyl	C	25–35	80	*e*

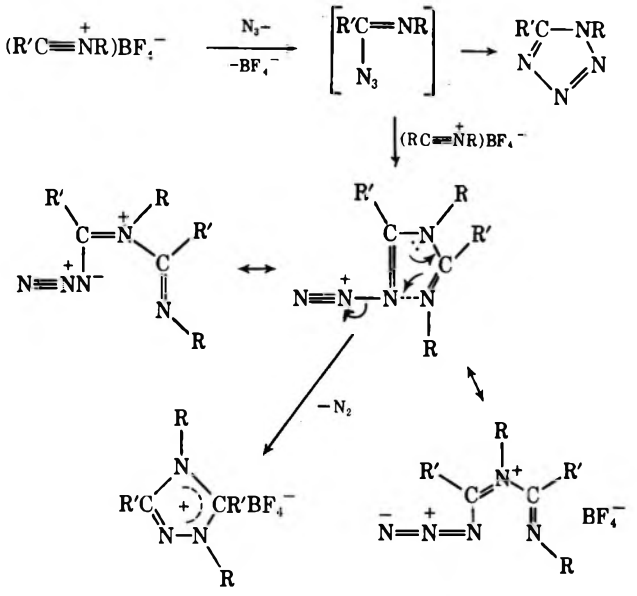
[a] A, $(RC{\equiv}N^+R')BF_4^-$ to NaN_3; B, NaN_3 to $(RC{\equiv}N^+R')BF_4^-$; C, $(RC{\equiv}N^+R')BF_4^-$ to dimethylammonium azide; D, dimethylammonium azide to $(RC{\equiv}N^+R')BF_4^-$. R′ = Et except where R = vinyl. [b] All additions of reagents were carried out within 35 min under an atmosphere of nitrogen. [c] Yields are based on nitrilium salts. [d] Yields are less than 1%. [e] Triazolium salts were not separated from unreacted azide and dimethylammonium fluoroborate. [f] Triazolium salt was not isolated from the mixture of polymeric nitrilium salt.

During the normal and reverse additions of dimethylammonium azide to *N*-ethylpropionitrilium fluoroborate in acetonitrile, the yield of 1,5-diethyltetrazole (**2**) is less dependent on the mode of addition of dimethylammonium azide than sodium azide. These results suggest that surface reactions play some role in the formation of tetrazoles and triazolium salts. When the addition of nitrilium salt to dimethylammonium azide in acetonitrile was carried out at 60–70° rather than at 25–35°, the yield of 1,5-diethyltetrazole (**2**) was decreased by 23% and that of 1,3,4,5-tetraethyl-1,2,4-triazolium fluoroborate (**5**) was increased by 28%. These results are consistent with enhanced decomposition of an azide intermediate at higher temperatures.

The low yield of 1-methyl-5-vinyltetrazole (**11**) afforded in the reaction of *N*-methylacrylonitrilium fluoroborate with sodium azide, inhibited with hydroquinone, may be a result of ionic polymerization of the nitrilium salt. Yields were improved when dimethylammonium azide was utilized as the azide source. *N*-Methylacrylonitrilium fluoroborate reacts with water to give *N*-methylacrylamide.

To ensure that tetrazoles formed in the presence of nitrilium salts did not decompose with liberation of nitrogen, tetrazoles and their corresponding nitrilium salts were refluxed in acetonitrile and toluene for 21 hr. In both cases no evolution of nitrogen was detected and virtually all of the starting tetrazoles were recovered.

A possible mechanism[13] for formation of triazolium salts and tetrazoles involves a cyclic transition state. A high degree of participation by nitrilium salts in the nitrogen elimination step may account for the mild conditions needed for decomposition of the imidoyl azide intermediates. A nitrilium salt–imidoyl azide complex appears to be formed at low temperatures which then undergoes elimination of nitrogen to form triazolium salts.



Concentrated solutions of nitrilium salts should enhance the formation of such complexes between imidoyl azides and nitrilium salts and should lead to higher yields of triazolium salts. This assumption is supported by several pieces of experimental evidence. A significant amount of triazolium salt is formed when sodium azide is added to a solution of the nitrilium salt in acetonitrile. Only trace amounts of triazolium salts are formed from addition of nitrilium salts in acetonitrile to sodium azide at ambient temperature.

The existence of a stable imidoyl azide–nitrilium salt complex is suggested by the following observations. Addition of sodium azide to a stirred solution of *N*-ethylbenzonitrilium fluoroborate in acetonitrile at −20 to −25° produced virtually no nitrogen gas. However, evolution of nitrogen was observed when the solution, after filtration to remove unreacted sodium azide and sodium fluoroborate, was allowed to warm to −5°.

Vapor phase chromatographic analysis of the solution of postulated azide complex before and after decomposition indicated no increase in tetrazole concentration. Attempts to isolate the imidoyl azide intermediate at −20 to −25° were unsuccessful. These results suggest that tetrazoles are not formed during the decomposition of the postulated complex and that tetrazoles are formed only by direct rearrangement of thir imidoyl azide intermediate.

It has been suggested[14] that nucleophilic additions to imidoyl chlorides proceed through a nitrilium ion intermediate. Taking into consideration the possibility of nitrilium ion formation, imidoyl chlorides were investigated to determine if the reaction with sodium azide was dependent on the mode of addition of reagents. The mode of addition in the reaction of *N*-ethylbenzimidoyl chloride with sodium azide in either toluene or acetonitrile was found to be unimportant since yields of tetrazole were essentially the same. During the normal and reverse addition, 1-ethyl-5-phenyltetrazole (**3**) was produced in 85–94% yield in acetonitrile and toluene. There was no evidence of gas evolution during these rapid and exothermic reactions. The purity of 1-ethyl-5-phenyltetrazole (**3**) prepared from *N*-ethylbenzimidoyl chloride was superior to that of **3** afforded from nitrilium salts during the normal addition reactions.

Experimental Section

All nitriles were rigorously dried by distillation from phosphorus pentoxide. Toluene was dried over sodium ribbons. Reagent grade cyclohexene was used without further purification. Finely divided sodium azide was prepared by a reported procedure.[15]

Infrared spectra (ir) were obtained with a Beckman IR-5 or IR-8 spectrophotometer with sodium chloride optics. Proton magnetic resonance (pmr) spectra were taken on a Varian Associates A-60 or HR-60 spectrometer. Positions are reported in parts per million from tetramethylsilane (δ). Mass spectra were taken on a Bendix Model 12-101 time-of-flight instrument at 70 eV.

Melting points of nitrilium salts were determined in sealed capillaries on a Büchi (capillary) melting point apparatus and, like the boiling points, are reported uncorrected. All other melting points reported were taken on a calibrated Kofler micro hot-stage apparatus.

For vapor phase chromatography (vpc) Perkin-Elmer vapor fractometer, Model 154D, and Beckman GC-100 units were used. The following columns were used, respectively: column A, 2 ft × 0.25 in., containing 20% GE-SF-96 silicon oil stationary phase on 35–80 mesh Chromosorb W support; column B, 6 ft × 0.625 in., containing 20% Paraplex on 40–60 mesh Chromosorb W support.

Gas evolution was measured with a Precision wet test meter or a gas burette. Microanalyses were performed by Mrs. P. P. Wheeler and Miss A. C. Richardson, Naval Ordnance Station, Indian Head, Md., and Galbraith Laboratories, Knoxville, Tenn.

Nitrilium Salts.[6,16]—*N*-Ethylaceto- (mp 75–77°), *N*-ethylpropio- (95–97°), and *N*-ethylbenzonitrilium fluoroborates (98–101°) were prepared from the corresponding nitriles and trialkyloxonium fluoroborates.

***N*-Methylacrylonitrilium Fluoroborate.**—Acrylonitrile (46.52 g, 0.876 mol), inhibited with hydroquinone (1.0 g), was slowly added to trimethyloxonium fluoroborate[17] (128.98 g, 0.876 mol). During the addition an exotherm (25–40°) occurred with evolution of dimethyl ether. After the addition was complete, the reaction mixture was allowed to stand at 25° for 18 hr. The reaction mixture was filtered and yellow needle-like crystals of *N*-methylacrylonitrilium fluoroborate (81.3 g, 60%) separated. The yellow crystals were washed with dry ethyl ether, dried under reduced pressure, and recrystallized several times from acrylonitrile. The light-yellow salt obtained melted at 132–137° and was very hygroscopic.

(13) Another possible mechanism involves decomposition of an imidoyl azide intermediate yielding a nitrene which could react with a nitrilium salt molecule and cyclize to form a triazolium salt. Attempts to trap the postulated nitrene intermediate with cyclohexene as an acceptor or isolate carbodiimides resulting from a 1,2 shift in the intermediates were unsuccessful.

(14) I. Ugi, F. Beck, and U. Fetzer, *Chem. Ber.*, **95**, 126 (1962).

(15) P. A. S. Smith, *Org. React.*, **3**, 382 (1946).

(16) R. F. Borch, *Chem. Commun.*, 442 (1968); *J. Org. Chem.*, **34**, 627 (1969).

(17) H. Meerwein, G. Hinz, P. Hoffman, E. Kronig, and E. Pfeil, *J. Prakt. Chem.*, **147**, 257 (1937).

Boron Trifluoride–Acetonitrile Complex.—The addition compound was prepared by the procedure of Coerver and Curran.[18]

Addition of *N*-Ethylacetonitrilium Fluoroborate to Sodium Azide in Toluene.—The following description of the reaction of *N*-ethylacetonitrilium fluoroborate with sodium azide in toluene is typical of the procedure employed for reactions mentioned in Table I. All reactions were carried out under nitrogen atmosphere and started at room temperature, rather than at 0°, except the following.

N-Ethylacetonitrilium fluoroborate (15.7 g, 0.10 mol) was was added to a stirred suspension of finely divided sodium azide (7.15 g, 0.11 mol) in toluene (250 ml) at 0°. After the addition was complete (3 min), the ice bath was removed and the reaction mixture was allowed to warm to room temperature. After a short induction period, an exotherm (40°) occurred with gas evolution, which was identified as nitrogen by mass spectrometry. After the ice bath had been removed (1 hr), the reaction temperature decreased to 25° and the evolution of nitrogen became negligible. During that time, 0.15 l. of nitrogen was liberated. The reaction mixture was finally heated and stirred at reflux temperature for 20 hr. A total of 0.63 l. of nitrogen (87% based on crude triazolium salt) was evolved in 21 hr. After the reaction mixture had cooled, suspended sodium fluoroborate and unreacted sodium azide were removed by filtration. The residue was washed with methylene chloride (400 ml) and the washings were combined with the filtrate. The solvents were removed at 60° under reduced pressure leaving a brown residue which was continuously extracted with ether for 72 hr. The ethereal extract was concentrated and distilled giving 3.81 g (34%) of hygroscopic 1-ethyl-5-methyltetrazole (**1**): bp 100–101° (1 mm); n^{25}D 1.4611; ir (neat) 2985 (m), 2941 (w), 1520 (s), 1404 (s), 1377 (m), 1253 (m), 1236 (m), 1178 (m), 1089 (s), 1050 (m), 1004 (m), 969 (m), 712 (m), 666 (m), 641 (m), and 1111–1000 cm^{-1} (tetrazole ring[11]).

Anal. Calcd for $C_4H_8N_4$: C, 42.84; H, 7.19; N, 49.97. Found: C, 42.61; H, 7.40; N, 49.74.

The ether-insoluble residue from the extraction was heated at 80–85° (1 μ) for 7 hr in an effort to dry the material assumed to be 1,4-diethyl-3,5-dimethyl-1,2,4-triazolium fluoroborate (**4**) (7.86 g, 65%), but this attempt was unsuccessful. Conversion of the salt to the iodide by treatment with sodium iodide in boiling acetone did not give a crystalline product either.

Pyrolysis of 1,4-Diethyl-3,5-dimethyl-1,2,4-triazolium Iodide.—Pyrolysis of the crude iodide (6.02 g, 0.021 mol) was carried out at 250° (5 μ) using a short-path distillation apparatus. The distillate (0.85 g) was redistilled affording 0.63 g (24%) of hygroscopic 1-ethyl-3,5-dimethyl-1,2,4-triazole (**9**): bp 82–84° (12 mm) [lit.[12] bp 80.5–81.5° (12 mm)]. The analytical and pmr samples were obtained by preparative vpc on column B (injector 225°; column 191°; flow 25 psi. R_t 3 min): ir (neat) 2976 (s), 2924 (s), 2874 (w), 1522 (s), 1408 (s), 1370 (s), 1333 (s), 1081 (m), 1033 (m), 1005 (m), 980 (m), and 778 cm^{-1} (m). The ir, pmr, boiling point, and R_t data of **9** were identical with those obtained from an authentic sample.[13]

Anal. Calcd for $C_6H_{11}N_3$: C, 57.57; H, 8.86; N, 33.57. Found: C, 56.45; H, 8.99; N, 32.73.

The hygroscopic nature of the substance no doubt accounts for the discrepancies in the analyses.

Addition of Sodium Azide to *N*-Ethylpropionitrilium Fluoroborate in Toluene.—Sodium azide (14.04 g, 0.22 mol) was added in small portions to a stirred suspension of *N*-ethylpropionitrilium fluoroborate (36.54 g, 0.21 mol) in 150 ml of toluene. The reaction temperature was maintained between 25 and 35° by controlling the rate of addition of azide (30 min). After a short induction period, gas evolution was observed. After the addition had been completed (1 hr), the reaction mixture was stirred and heated at reflux temperature for 20 hr. The isolation procedure was the same as previously described for **1**. Very hygroscopic 1,5-diethyltetrazole (**2**) (9.01 g, 32%), bp 104–105° (1 mm), mp 36–37° after recrystallization from hexane–ether, showed ir max (neat) at 3003 (s), 2950 (m), 2882 (w), 1513 (s), 1449 (s), 1374 (m), 1302 (m), 1252 (m), 1217 (m), 1174 (m), 1089 (s), 1064 (s), 971 (m), 800 (w), and 665 cm^{-1} (m).

Anal. Calcd for $C_5H_{10}N_4$: C, 47.60; H, 7.99; N, 44.41. Found: C, 47.60; H, 8.01; N, 44.61.

A crude hygroscopic compound assumed to be 1,3,4,5-tetraethyl-1,2,4-triazolium fluoroborate (**5**) (14.92 g, 53%) was also isolated.

(18) H. J. Coerver and C. Curran, *J. Amer. Chem. Soc.*, **80**, 3522 (1958).

Pyrolysis of 1,3,4,5-Tetraethyl-1,2,4-triazolium Iodide.—Preparation of the iodide from **5**, pyrolysis, and isolation of the product was the same as for **4**. Pyrolysis of the iodide (6.23 g, 0.02 mol) gave 0.5 g (16%) of 1,3,5-triethyl-1,2,4-triazole (**10**), bp 79–82° (8 mm). An analytical sample was obtained from preparative vpc (R_t 4.7 min column B, 225°; inlet 225°; flow 20 psi): n^{20}D 1.4765; ir (neat) 2985 (s), 2941 (m), 2882 (m), 1449 (m), 1372 (m), 1300 (m), 1269 (m), 1065 (s), 1044 (s), 962 (m), and 800 cm^{-1} (w). The ir, pmr, boiling point, and R_t data of **10** were identical with those obtained from an authentic sample prepared below.

Anal. Calcd for $C_8H_{15}N_3$: C, 62.71; H, 9.87; N, 27.43. Found: C, 61.99; H, 9.15; N, 27.55.

1,3,5-Triethyl-1,2,4-triazole (10).—A mixture of dipropioamide[19] (9.70 g, 0.075 mol) and ethylhydrazine oxalate (6.75 g, 0.045 mol) heated at 145° for 5 hr afforded 1.99 g (29%) of hygroscopic **10**, bp 84–85° (8 mm). Compound **10** was isolated and purified as previously described for **9**.

Anal. Calcd for $C_8H_{15}N_3$: C, 62.71; H, 9.87; N, 27.43. Found: C, 62.65; H, 9.80; N, 27.49.

Addition of Sodium Azide to *N*-Ethylbenzonitrilium Fluoroborate in Toluene.—Sodium azide (4.00 g, 0.06 mol) was slowly added to a stirred suspension of *N*-ethylbenzonitrilium fluoroborate (10.31 g, 0.047 mol) in 250 ml of toluene. An exotherm (25–50°) occurred with evolution of nitrogen. After the addition was complete, the reaction mixture was stirred and heated at reflux temperature for 20 hr. The toluene layer was decanted and the insoluble material was washed with toluene. The toluene washings and decanted solvent were combined and then removed on a rotary evaporator leaving 0.82 g (10%) of 1-ethyl-5-phenyltetrazole (**3**), mp 70–71° (lit.[20] mp 70–71°) after recrystallization from ethanol. The toluene-insoluble material was washed with chloroform and then filtered leaving chloroform-insoluble sodium fluoroborate and unreacted sodium azide. The solvent was removed from the filtrate affording 4.00 g (45%) of 1,4-diethyl-3,5-diphenyl-1,2,4-triazolium fluoroborate (**6**): mp 165–166° after recrystallization from ethanol; ir (solid film) 3077 (w), 3003 (w), 1608 (m), 1548 (m), 1449 (m), 1387 (w), 1000–1111 (s), 778 (m), 743 (m), and 696 cm^{-1} (s). A mixture melting point with an authentic sample prepared below was not depressed and the ir and pmr spectra were identical.

Anal. Calcd for $C_{18}H_{20}BF_4N_3$: C, 59.19; H, 5.52; N, 11.51. Found: C, 59.70; H, 5.59; N, 11.57.

4-Ethyl-3,5-diphenyl-1,2,4-triazole (8).—*N*-Ethylbenzamide (59.68 g, 0.4 mol) was treated with phosphorus pentachloride (83.30 g, 0.4 mol) and benzhydrazide (54.46 g, 0.4 mol) in 200 ml of chloroform by the method of Scheuing and Walach[21] to give 37.74 g (38%) of **8**: mp 163.5–164.5° after recrystallization from ethanol; ir (KBr) 3040 (w), 2941 (m), 2849 (w), 1471 (s), 1433 (m), 1342 (m), 1247 (m), 1075 (m), 1022 (m), 795 (m), 775 (s), 725 (s), 722 (s), and 699 cm^{-1} (s).

Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86. Found: C, 77.48; H, 6.24; N, 16.84.

1-Ethyl-3,5-diphenyl-1,2,4-triazole (7).—3,5-Diphenyl-1,2,4-triazole[22] (**20**) (14.00 g, 0.064 mol) was dissolved in a solution of sodium ethoxide (0.07 mol) in 15 ml of ethanol, then mixed with ethyl iodide (10.8 g, 0.07 mol), and heated in a Fischer-Porter tube (20 × 2.5 cm) at 120° for 15 hr. The product was slurried with 5% aqueous sodium carbonate and extracted with benzene. The extract was evaporated to dryness and the residue was recrystallized from petroleum ether–benzene (1:9) to give 6.45 g (39%) of **7**: mp 75–76°; ir (KBr) 3077 (w), 2976 (w), 1458 (m), 1433 (s), 1350 (s), 1126 (m), 1087 (w), 1064 (w), 1026 (w), 1015 (s), 786 (m), 769 (s), 741 (s), 724 (s), 698 (s), 687 (s), and 655 cm^{-1} (w).

Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86. Found: C, 77.11; H, 6.32; N, 16.81.

1,4-Diethyl-3,5-diphenyl-1,2,4-triazolium Fluoroborate (6).—A solution of 4-ethyl-3,5-diphenyl-1,2,4-triazole (**8**) (1.00 g, 3.8 mmol) and triethyloxonium fluoroborate (0.77 g, 4.0 mmol) in 25 ml of ethylene chloride was heated with stirring at 65° for 3 hr. The reaction mixture was concentrated *in vacuo* and the residue obtained was washed with ether and recrystallized from absolute ethanol affording 1.41 g (95%) of **6**, mp 165–166°.

(19) Q. E. Thompson, *ibid.*, **73**, 5841 (1951).

(20) E. K. Harvill, R. M. Herbst, E. C. Schreiner, and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(21) G. Scheuing and B. Walach, German Patent 543,026 [*Chem. Abstr.*, **26**, 3263 (1932)].

(22) K. T. Potts, *J. Chem. Soc.*, 3461 (1954).

A solution of 1-ethyl-3,5-diphenyl-1,2,4-triazole (**7**) (1.00 g, 3.8 mmol) in 25 ml of ethylene chloride gave 1.10 g (80%) of **6**, mp 165–166°. A mixture melting point with a sample from the synthesis above was not depressed and the ir and pmr spectra were identical.

Addition of Sodium Azide to *N*-Ethylbenzonitrilium Fluoroborate in Acetonitrile at −20 to −25°.—To a stirred solution of *N*-ethylbenzonitrilium fluoroborate (4.38 g, 0.02 mol) in acetonitrile (25 ml) was added in small portions sodium azide (1.96 g, 0.03 mol) at −20 to −25°. After the addition was complete (30 min), the reaction mixture was allowed to stir for 1 hr. During this time no nitrogen evolution was detected. After an aliquot was taken from the reaction mixture for vpc analysis, the reaction mixture was filtered quickly at −20 to −25° removing unreacted sodium azide and sodium fluoroborate. The filtrate was stirred vigorously with a magnetic stirring bar and was allowed to warm up to −5 ± 0.5° in a constant temperature flask (50 ml) fitted with an alcohol thermometer and gas outlet. The method used for determining the rate of decomposition was the measurement of the volume of nitrogen evolved *vs.* time. Because it is impossible to bring the flask containing the postulated 1:1 nitrilium salt–imidoyl azide complex to the required temperature instantaneously, nitrogen evolution was recorded 20 min after the desired temperature was obtained, allowing thermal equilibration and saturation of the solution with nitrogen. After 2 hr the reaction mixture was allowed to warm to room temperature and then another aliquot was taken from the reaction mixture for vpc analysis (column A at 170°). Vpc analyses of the solution before and after decomposition indicated no apparent increase in tetrazole concentration. The reaction mixture was filtered to remove unreacted sodium azide and sodium fluoroborate. The filtrate was concentrated under reduced pressure and the remaining residue was washed with methylene chloride and then filtered leaving sodium fluoroborate. The filtrate was concentrated and the residue was washed with benzene leaving a mixture of salts. The benzene washings were combined and concentrated giving 1.39 g (40%) of **3**. The benzene-insoluble material was treated with 25 ml of 10% aqueous sodium hydroxide and extracted with ether and methylene chloride. The respective extracts were combined and dried over anhydrous sodium sulfate. The ethereal solution was concentrated affording 0.20 g (7%) of *N*-ethylbenzamide. Removal of solvent from the methylene chloride solution gave 0.30 g (8%) of **6**.

Addition of *N*-Methylacrylonitrilium Fluoroborate to Sodium Azide in Acetonitrile.—*N*-Methylacrylonitrilium fluoroborate (15.4 g, 0.10 mol) dissolved in acetonitrile (25 ml) and inhibited with hydroquinone (0.1 g) was added dropwise to a stirred suspension of sodium azide (9.75 g, 0.15 mol) in 225 ml of acetonitrile under nitrogen. The reaction temperature was maintained at 25–35° by controlling the rate of addition. After the addition was complete, an immediate analysis of the reaction mixture by vpc indicated 5% yield of 1-methyl-5-vinyltetrazole (**11**). The reaction mixture was stirred an additional 2 hr and further analysis showed no increase in tetrazole concentration. Finally the reaction mixture was stirred and heated to reflux for 3 hr. The reaction mixture was cooled and filtered to remove suspended sodium fluoroborate and unreacted sodium azide (9.36 g). The filtrate was concentrated under reduced pressure at 40–50° and the remaining residue was extracted with ether. The ether-insoluble material was the major product (15.1 g) which appeared to be a polymer. The ethereal extract was concentrated under reduced pressure at 40° giving 0.52 g (5%) of crude 1-methyl-5-vinyltetrazole (**11**). The ir and pmr spectra and R_t and R_f values were identical with those of authentic[23] **11**.

Reaction of *N*-Methylacrylonitrilium Fluoroborate with Water.—*N*-Methylacrylonitrilium fluoroborate (3.10 g, 0.02 mol) was added slowly to distilled water (25 ml). The solution was then stirred at ambient temperature for 1 hr. The reaction mixture was made basic (pH 10) with 10% aqueous sodium hydroxide and extracted with ether. The ethereal extract was dried (Na_2SO_4), concentrated, and distilled giving 0.70 g (41%) of the monomer of *N*-methylacrylamide: bp 93–95° (7 mm) [lit.[24] bp 84° (3 mm)]; ir (neat) 3279 (NH), 2941 (CH_3–), 1890 (H_2C=CH), 981, 952, and 1645 cm^{-1} (amide II); pmr (CD_3CN) 7.54 (br, 1, NH), 5.53 (m, 1, H_2C=CH), 6.22 (m, 2, H_2C=CH).

Addition of Sodium Azide to *N*-Ethylbenzimidoyl Chloride in Toluene.—Sodium azide (0.98 g, 0.015 mol) was added to a stirred solution of *N*-ethylbenzimidoyl chloride[14] (1.68 g, 0.01 mol) in toluene (25 ml). The reaction temperature was maintained between 25 and 35° with an ice bath during the addition of imidoyl chloride. After the addition was complete, the reaction mixture was allowed to stir at ambient temperature (25°) for 2 hr. The reaction mixture was filtered, removing sodium chloride and unreacted sodium azide, and the solvent was removed from the filtrate under reduced pressure leaving 1.57 g (90%) of 1-ethyl-5-phenyltetrazole (**3**), mp 70–71° after recrystallization from ethanol.

Addition of *N*-Ethylbenzimidoyl Chloride to Sodium Azide in Toluene.—Dropwise addition of *N*-ethylbenzimidoyl chloride (1.68 g, 0.01 mol) to a stirred suspension of sodium azide (0.98 g, 0.015 mol) in 25 ml of toluene gave 1.64 g (94%) of **3**, mp 70–71° after recrystallization from ethanol.

Registry No.—**1**, 32675-38-0; **2**, 32675-39-1; **3**, 32675-43-7; **6**, 32675-53-9; **7**, 32675-48-2; **8**, 32675-51-7; **9**, 32675-46-0; **10**, 32675-47-1; sodium, 7440-23-5; dimethylammonium azide, 32649-51-7; *N*-methylacrylonitrilium fluoroborate, 32830-06-1; *N*-methylacrylamide, 1187-59-3.

Acknowledgment.—This work was supported by the Foundational Research Program of the Naval Air Systems Command.

(23) R. A. Henry, U. S. Patent 3,351,627 (1967); W. G. Finnegan, *et al.*, U. S. Patent 3,055,911 (1962); W. G. Finnegan, R. A. Henry, and S. Skolnik, U. S. Patent 3,004,959 (1961) [*Chem. Abstr.*, **56**, 15518*d* (1962)].

(24) B. F. Goodrich Co., British Patent 648,886 (1951) [*Chem. Abstr.*, **45**, 8032*b* (1951)].

Proton Magnetic Resonance Spectra of Some Tetrazoles, Triazoles, and Tetrazolium and Triazolium Salts[1]

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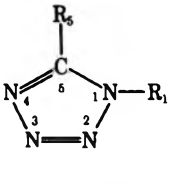
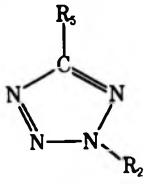
Structural assignments of 1,5- and 2,5-disubstituted tetrazoles and 1,3,5- and 3,4,5-trisubstituted 1,2,4-triazoles can be made on the basis of their proton magnetic resonance spectra. The 2-alkyl substituents in tetrazoles and the 1-alkyl substituents in triazoles are further downfield than the 1- and 4-alkyl substituents, respectively. Different isomers of phenyl-substituted triazole and tetrazole derivatives can be distinguished by the absence (or degree) of an anisotropic effect on the ortho protons.

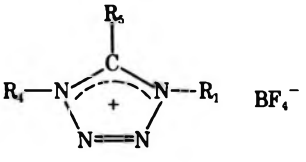
A previous paper[3] dealt with the synthesis of some 1,5- and 2,5-disubstituted tetrazoles and 1,3,5- and 3,4,5-trisubstituted 1,2,4-triazoles and their tetrazolium and triazolium salts. Pmr data obtained for compounds of Tables I and II allow a comparison of the triazole and tetrazole derivatives investigated and assignment of structure.



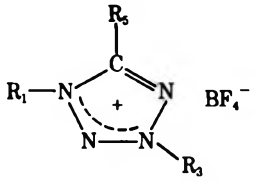
1, R_1 = Et; R_5 = Me
2, R_1 = R_5 = Et
3, R_1 = Me; R_5 = vinyl
4a, R_1 = H; R_5 = Ph
5, R_1 = Me; R_5 = Ph
6, R_1 = Et; R_5 = Ph



4b, R_2 = H; R_5 = Ph
7, R_2 = Et; R_5 = Ph



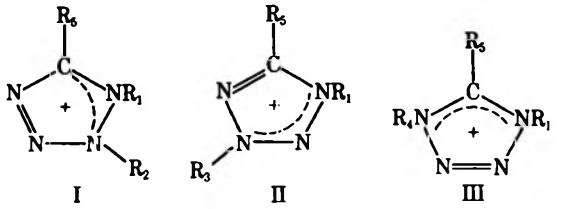
8, R_1 = R_4 = Et; R_5 = Me
9, R_1 = R_4 = Et; R_5 = Ph



10, R_1 = R_3 = Et; R_5 = Ph

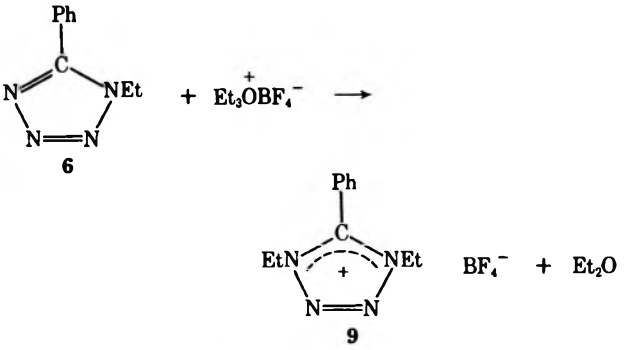
The pmr data of the tetrazoles and tetrazolium salts are reported in Table I. The observed chemical shift of the CCH_3 resonance at δ 2.53 in **1** agrees with the CCH_3 resonance at 2.58 reported for 1,5-dimethyltetrazole.[4] The pmr spectrum of **2** shows that the NCH_2 resonance at 4.32 and the NCH_2CH_3 at 1.47 are more deshielded than the CCH_2 resonance at 2.91 and the CCH_2CH_3 at 1.35. Phenyl protons ortho to the tetrazole ring of **4** and **7** are deshielded by 0.5–0.6 ppm relative to the meta and para protons. This deshielding effect was not observed in **6**, **9**, or **10**. Although there is no deshielding in **6**, **5** exhibits deshielding of 0.3 ppm. These results are consistent with greater deshielding for smaller groups ortho to the phenyl group on the tetrazole ring which allows a greater degree of coplanarity of tetrazole and phenyl rings. The difference in chemical shift between ortho and para–meta protons of **5** in deuteriochloroform (0.2 ppm) was smaller than that observed in deuterioacetonitrile (0.3 ppm). Fraser and Hague[5] have reported that the pmr spectrum of **5** in deuteriochloroform (TMS) showed a NCH_3 resonance at 4.16 and showed ortho, para, and meta protons on the phenyl ring at 7.64 with no deshielding effect.

Quaternization of 1,5-disubstituted tetrazoles with alkyl halides has been reported[6] to give 1,4,5-trisubstituted tetrazolium salts (III). Three possibilities exist: 1,2,5-trisubstituted (I), 1,3,5-trisubstituted (II), and 1,4,5-trisubstituted (III) tetrazolium salts. Alkaline degradation[6a] of the methiodide of 5-methyl-1-phenyltetrazole to phenyl azide and methylamine supports structure III.



I II III

It appeared that the structure of 1,4,5-trisubstituted tetrazolium salts might be elucidated by physical methods rather than by chemical degradation. The model compound selected was 1,4-diethyl-5-phenyltetrazolium fluoroborate (**9**), synthesized by quaternizing 1-ethyl-5-phenyltetrazole (**6**) with triethyloxonium fluoroborate. The only isomer isolated exhibited in its pmr spectrum a triplet at 1.53, a quartet at 4.47, and



6 **9**

a singlet at 7.72 with relative areas of 6:4:5 corresponding to six equivalent methyl protons at positions 1 and

(1) Taken from the dissertation of L. A. Lee in partial fulfillment of the requirements for the Ph.D. degree, Howard University, 1970.

(2) Author to whom correspondence should be addressed at Polaroid Corp., Cambridge, Mass. 02139.

(3) L. A. Lee, R. Evans, and J. W. Wheeler, *J. Org. Chem.*, **37**, 343 (1972).

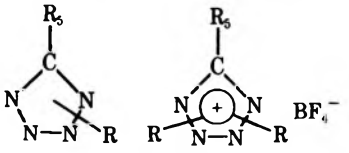
(4) J. H. Markgraf, W. T. Bachmann, and D. P. Hollis, *ibid.*, **30**, 3472 (1965).

(5) R. R. Fraser and K. E. Hague, *Can. J. Chem.*, **46**, 2855 (1968).

(6) (a) G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chem. Ind. (London)*, 1355 (1955); (b) F. R. Benson, L. W. Hartzel, and W. I. Savell, *J. Amer. Chem. Soc.*, **73**, 4457 (1951); (c) R. M. Herbst and K. G. Stone, *J. Org. Chem.*, **22**, 1139 (1957).

TABLE I

PMR DATA[a] OF TETRAZOLES AND TETRAZOLIUM SALTS

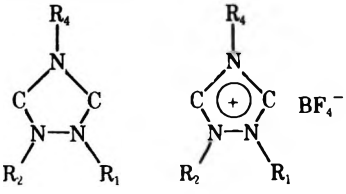


Compd	Solvent	Ph Ortho	Ph Meta–para	NCH_2	CCH_2	NCH_3	C_5CH_3
1	*b*			4.39 q, J = 7		1.47 t, J = 7	2.53 s
8	*b*			4.59 q, J = 7		1.62 t, J = 7	2.89 s
2	*b*			4.32 q, J = 7	2.91 q, J = 7	1.47 t, J = 7	1.35 t, J = 7
3	*b*				6.31 q[e]	4.18 s	
					5.86 q[f]		
4	*c*	7.68 m	7.14 m				
5	*d*	7.78 m	7.60 m			4.18 s	
	b	7.85 m	7.58 m			4.18 s	
6	*b*	7.64 m		4.49 q, J = 7		1.51 t, J = 7	
9	*b*	7.72 s		4.47 q, J = 7		1.53 t, J = 7	
7	*b*	8.15 m	7.55 m	4.72 q, J = 7		1.61 t, J = 7	
	c	7.65 m	7.15 m	4.54 q, J = 7		1.53 t, J = 7	
10	*b*	7.68 m		4.88 q, J = 7; 4.64 q, J = 7		1.72 t, J = 7; 1.61 t, J = 7	

[a] δ values are in ppm relative to TMS. J values in Hz. Abbreviations used are s, singlet; t, triplet; q, quartet; m, multiplet. [b] CD_3CN. [c] DMSO-d_6. [d] $CDCl_3$. [e] Pair of doublets, J_{AX} = 17, J_{AB} = 2.5 Hz. [f] Pair of doublets, J_{BX} = 10, in addition to H_X at 6.90 as a pair of doublets.

TABLE II

PMR DATA[a] OF TRIAZOLES AND TRIAZOLIUM SALTS



Compd	Solvent	Ph Ortho	Ph Meta–para	N_1CH_2	N_4CH_2	3 and 5 CCH_2	N_1CH_3	N_4CH_3	C_3CH_3	C_5CH_3
11	*b*			3.96 q, J = 7			1.32 t, J = 7		2.31 s	2.18 s
12	*b*			3.90 q, J = 7		2.60 m[e]	1.28 m[f]		1.28[f]	1.28[f]
14	*c*	8.27 m	7.56 m							
13	*b*	8.12 m	7.60 m	4.28 q, J = 7			1.48 t, J = 7			
18	*b*	7.74 m		4.13 q, J = 7	4.13 q, J = 7		1.47 t, J = 7	1.05 t, J = 7		
16	*d*	7.52 m			4.13 q, J = 7			1.05 t, J = 7		
15	*d*	7.60 m						3.70 s		
17	*b*	7.72 m		4.22 q, J = 7			1.47 t, J = 7	3.58 s		

[a] δ, J, and abbreviations as in Table I. [b] CD_3CN. [c] DMF-d_6. [d] $CDCl_3$. [e] Two overlapping quartets appearing as five lines. [f] Three overlapping triplets appearing as four lines.

4, four equivalent methylene protons at positions 1 and 4, and five phenyl protons at position 5. This pmr spectrum strongly suggests that quaternization occurred at position 4, affording the symmetrical 1,4,5-trisubstituted tetrazolium salt, in accord with chemical evidence.[6a] Analogous results were observed for **8** and have been reported for the methiodide of 1-methylimidazole,[7] protonated imidazoles, and benzimidazoles in sulfuric acid.[8]

The quaternization of 2,5-disubstituted tetrazoles has not been reported. When 2-ethyl-5-phenyltetrazole (**7**) was treated with triethyloxonium fluoroborate, only one isomer was isolated. Its pmr spectrum shows that the two ethyl groups are affected by a positive charge distributed between nitrogen atoms at positions 1, 2, and 3 within the tetrazole ring as are the ethyl groups in **8**, its methylene and methyl protons being deshielded by 0.20 and 0.15 ppm compared with the parent compound **1**. Deshielding of the ethyl groups in **9** appears to be negligible because most of the charge is localized in the phenyl ring through resonance in spite of steric hindrance.

The appearance of two quartets for the CH_2 groups and two triplets for the CH_3 groups eliminates the 2,3-substituted isomer as that compound is symmetrical and would have equivalent groups, leaving the only possibilities either the 1,3 or the 1,2 isomers. Although arguments can be made on the basis of chemical shifts, neither the pmr spectrum nor the mass spectrum allows an unequivocal assignment of this compound as either the 1,2- or 1,3-diethyl-5-phenyltetrazolium salt. Attempts to prove the structure by chemical reduction of the salt were unsuccessful.

Although two mass spectral studies have been published recently on the fragmentation pattern of tetra-

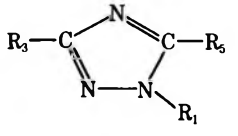
(7) C. G. Oberberger, J. C. Salamone, and S. Yaroslavsky, *J. Org. Chem.*, **30**, 3580 (1965).

(8) H. A. Staab and A. Mannschreck, *Tetrahedron Lett.*, **No. 20**, 913 (1962).

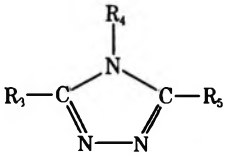
zoles,[5,9] tetrazolium salts have not been studied. Fraser and Hague[5] showed that the 1- and 2-methyltetrazoles could be differentiated by mass spectrometry. Similarly the 1- and 2-ethyl isomers (**6** and **7**) can be differentiated on the basis of their mass spectra. The 1-ethyl isomer shows a stronger parent ion and a peak at *m/e* 118 that is not observed for the 2-ethyl. Mass spectra of the tetrazolium salts **9** and **10** were essentially the same as those of the parent tetrazoles at 200° showing no peaks above *m/e* 175. The observation of an ion at *m/e* 118 in the mass spectrum of 1,2- (or 1,3-) diethyl-5-phenyltetrazolium fluoroborate (**10**) suggests the presence of 1-ethyl-5-phenyltetrazole. This evidence is in accord with pmr data which eliminates the 2,3-diethyl isomer as a possible product of quaternization as it would give only the 2-ethyl isomer.

Spectra of the tetrazolium salts **9** and **10** at 150° on an LKB-9000 instrument showed two peaks at higher *m/e* than the parent tetrazoles at 174. Both salts gave a peak at *m/e* 203, corresponding to the tetrazolium cation itself, as well as a peak at *m/e* 222, corresponding to that cation plus a fluorine or the original fluoroborate salt minus boron trifluoride.

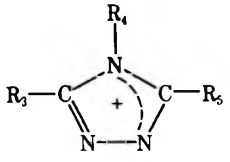
Nmr Correlations of *sym*-Triazoles and Triazolium Salts.—Pmr data of some triazoles and triazolium salts are reported in Table II. The pmr spectrum of **11**



11, $R_3 = R_5 = Me$; $R_1 = Et$
12, $R_1 = R_3 = R_5 = Et$
13, $R_1 = Et$; $R_3 = R_5 = Ph$
14a, $R_1 = H$; $R_3 = R_5 = Ph$



14b, $R_4 = H$; $R_3 = R_5 = Ph$
15, $R_4 = Me$; $R_3 = R_5 = Ph$
16, $R_4 = Et$; $R_3 = R_5 = Ph$



17, $R_4 = Me$; $R_1 = Et$; $R_3 = R_5 = Ph$
18, $R_1 = R_4 = Et$; $R_3 = R_5 = Ph$

shows a quartet at 3.96, triplet at 1.32 for the NCH_2CH_3 group, and two singlets at 2.31 and 2.18 for C_3CH_3 and C_5CH_3. Assignment of the peak at 2.18 to C_5CH_3 was made on the basis of the shielding effect of the adjacent ethyl group. Compound **12** shows a quartet at 3.90 for the NCH_2 protons and a multiplet (two quartets with almost identical chemical shifts) at 2.60 for CH_2 protons at C_3 and C_5 and a multiplet consisting of four peaks with additional splittings accounting for the three methyl groups at C_3, C_5, and N, at 1.28.

The phenyl proton resonances in 1,3,5-trisubstituted 1,2,4-triazoles and 1,3,4,5-tetrasubstituted 1,2,4-triazolium salts also exhibit an anisotropy effect of the heterocyclic ring on the ortho protons of the phenyl ring, as observed in the previously discussed tetrazole and tetrazolium salts. The phenyl protons ortho to the triazole ring of **14a** and **14b** and **13** are deshielded by 0.5–0.6 ppm relative to the meta and para protons. The pmr spectrum of **13** indicated that the C-5 phenyl ortho protons are less deshielded relative to the meta and para protons due to steric hindrance with the ethyl group, in contrast to the unhindered phenyl group at C-3. A study of the areas of phenyl protons resonances (1:4 rather than 2:3) suggests the presence of an anisotropic effect on the ortho protons of the phenyl group at C-3 and its decrease or absence at C-5. The pmr spectra of **15** and **16** and their triazolium salts exhibited multiplets at 7.60, 7.52, 7.72, and 7.74 with areas of five protons indicating that both phenyl groups at C-3 and C-5 are prevented from attaining coplanarity with the triazole ring. Similar observations of magnetic anisotropy have been observed in the pmr spectra of substituted phenyl pyrazoles.[10]

The ethyl group at position 1 with resonances at 4.28 (N_1CH_2) and 1.48 ($N_1CH_2CH_3$) in **13** is more deshielded than the ethyl group in position 4 of **16** (N_4CH_2 at 4.13 and $N_4CH_2CH_3$ at 1.05) by 0.15 and 0.43 ppm for the methylene and methyl resonances. This observation is reasonable since the 3-phenyl group in the 1 isomer can effectively conjugate with the triazole ring, thus deshielding the ethyl group *via* resonance and inductive effects. Partial deshielding is possible by the sterically hindered 5-phenyl group. Because of steric hindrance in **16**, there is a smaller deshielding effect due to the loss of coplanarity of both phenyl groups. The fact that the chemical shift difference for the methyl group is greater than the methylene group suggests that the methyl group positioned between the rings reflects ring current effects of the phenyl groups. Similar results are also observed in **18** whose pmr spectrum shows a multiplet for the phenyl protons at 7.74 and a quartet at 4.13 for CH_2 groups at 1 and 4 with no chemical shift difference and triplets at 1.47 and 1.05 for N_1CH_3 and N_4CH_3.

As the 1 substituent is changed from H (**4a**, **4b**) to Me (**5**) to Et (**6**) in 5-phenyltetrazole, the anisotropy effect is decreased. As expected, the anisotropy effect is greater in 2-ethyl-5-phenyltetrazole (**7**) than in 1-ethyl-5-phenyltetrazole (**6**) because of ideal resonance conjugation and the absence of steric hindrance between the phenyl and tetrazole ring. The loss of the anisotropy effect in 1,2- or 1,3-diethyl-5-phenyltetrazolium fluoroborate (**10**) indicates the presence of steric inhibition to resonance between the phenyl and tetrazole ring. Similar effects were observed for 1-ethyl-3,5-diphenyl-1,2,4-triazole (**13**) and 4-ethyl-3,5-diphenyl-1,2,4-triazole (**16**).

Experimental Section[11]

Proton magnetic resonance spectra were taken on a Varian Associates A-60 or HR-60 spectrometer. Positions are reported in parts per million from tetramethylsilane (δ). A Beckman IR-5 or IR-8 spectrophotometer with sodium chloride optics was used for all ir spectra. Mass spectra were recorded on a Bendix Model 12-101 time-of-flight mass spectrometer at 70 eV using a liquid or solid inlet system and an LKB-9000 instrument.

1- and 2-Ethyl-5-phenyltetrazole (6 and 7).—A solution of 5-phenyltetrazole[12] (50.0 g, 0.342 mol), sodium hydroxide (18.0 g, 0.45 mol), and diethyl sulfate (52.73 g, 0.342 mol) in 500 ml of distilled water was stirred at reflux temperature for 12 hr. The

(9) D. M. Forkey and W. R. Carpenter, *Org. Mass Spectrom.*, **2**, 433 (1969).

(10) L. G. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966); B. M. Lynch and Y. Y. Hung, *Can. J. Chem.*, **42**, 1605 (1964).

(11) All compounds listed in Tables I and II except **6**, **7**, **8**, **9**, **15**, and **17** are reported in ref 3.

(12) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Amer. Chem. Soc.*, **80**, 3908 (1958).

reaction mixture was then concentrated to one-third volume under reduced pressure at 65° and extracted with ether. The ether extract was washed with water, dried over sodium sulfate, concentrated, and distilled giving 19.90 g (30%) of 2-ethyl-5-phenyltetrazole (7): bp 77–78° (0.20 mm); ir (neat) 1575 (s), 1555 (s), 1374 (s), 1342 (s), 786 (s), 730 (s), 715 (s), 690 (s), and 653 cm^{-1} (w).

Anal. Calcd for $C_9H_{10}N_4$: C, 62.05; H, 5.79; N, 32.17; mol wt, 174. Found: C, 62.11; H, 5.72; N, 32.23; mol wt, 174 (mass spectrometry).

The still pot residue that solidified after cooling was recrystallized from ethanol affording 6.05 g (10%) of 1-ethyl-5-phenyltetrazole[13] (6): mp 70–71°; ir (KBr) 1451 (s), 1170 (s), 1114 (s), 1076 (s), 776 (s), 735 (s), 694 (s), and 650 cm^{-1} (s).

1,4-Diethyl-5-phenyltetrazolium Fluoroborate (9).—A solution of 1-ethyl-5-phenyltetrazole (6) (5.00 g, 0.03 mol) and triethyloxonium fluoroborate (5.46 g, 0.03 mol) in ethylene chloride (50 ml) was stirred at reflux temperature for 4 hr. The solvent was removed under reduced pressure and the remaining residue was washed with ether. Recrystallization from ethanol gave 4.15 g (59%) of 1,4-diethyl-5-phenyltetrazolium fluoroborate (9): mp 131–132°; ir (KBr) 1486 (s), 1449 (m), 1100–1000 (vs), 770 (s), 742 (s), 717 (s), and 691 cm^{-1} (s).

Anal. Calcd for $C_{11}H_{15}BF_4N_4$: C, 45.54; H, 5.21; N, 19.32. Found: C, 45.93; H, 5.43; N, 19.41.

1,2- or 1,3-Diethyl-5-phenyltetrazolium Fluoroborate (10).—A solution of 2-ethyl-5-phenyltetrazole (7) (5.00 g, 0.03 mol) and triethyloxonium fluoroborate (5.46 g, 0.03 mol) in ethylene chloride (50 ml) was stirred at reflux temperature for 4 hr. The product was isolated in the same manner as the tetrazolium salt described above. Compound **10** (5.5 g, 78%) was recrystallized from ethanol to give a white crystalline solid which had a melting point of 71–72°: ir (KBr) 1605 (m), 1477 (s), 1449 (s), 1100–1000 (vs), 802 (m), 781 (s), 773 (s), 747 (s), 728 (s), and 694 cm^{-1} (s).

Anal. Calcd for $C_{11}H_{15}BF_4N_4$: C, 45.54; H, 5.21; N, 19.32. Found: C, 45.37; H, 5.30; N, 19.26.

1,4-Diethyl-5-methyltetrazolium Fluoroborate (8).—1-Ethyl-5-methyltetrazole (5.00 g, 0.045 mol) was added dropwise to a magnetically stirred solution of triethyloxonium fluoroborate (8.47 g, 0.045 mol) in ethylene chloride (50 ml). The reaction temperature was maintained at 25–35° by means of a cooling bath. After the addition was complete, the reaction mixture was stirred at 25° for 4 hr. The solvent was then removed under pressure at 40° leaving a 4.50 g (88%) of hygroscopic **8**: mp 129–130° after recrystallization from ethanol; ir (solid film) 1575 (m), 1445 (s), 1111–1000 (s), 722 (m), 689 (w), and 665 cm^{-1} (m).

Anal. Calcd for $C_6H_{13}BF_4N_4$: C, 31.67; H, 5.76; N, 24.63. Found: C, 31.48; H, 5.25; N, 24.25.

4-Methyl-3,5-diphenyl-1,2,4-triazole (15).—*N*-Methylbenzamide (54.05 g, 0.40 mol) was treated with phosphorus pentachloride (83.30 g, 0.40 mol) and benzhydrazide (54.46 g, 0.40 mol) in chloroform (200 ml) by the method of Scheuing and Walach[14] yielding 59.20 g (63%) of 4-methyl-3,5-diphenyl-1,2,4-triazole (15): mp 242–243° (lit.[14] mp 243°) after recrystallization from ethanol; ir (KBr) 1464 (s), 1064 (m), 1020 (w), 1005 (m), 769 (s), 727 (s), and 687 cm^{-1} (s).

4-Methyl-1-ethyl-3,5-diphenyl-1,2,4-triazolium Fluoroborate (17).—A stirred solution of 4-methyl-3,5-diphenyl-1,2,4-triazole (2.35 g, 0.01 mol) and triethyloxonium fluoroborate (1.90 g, 0.01 mol) in ethylene chloride (50 ml) at reflux temperature for 2 hr gave 3.30 g (94%) of **17**: mp 148–149°; ir (solid film) 1608 (m), 1100–1000 (vs), 794 (m), 733 (m), and 697 cm^{-1} (s). The isolation procedure used was described previously for compound **8**.

Anal. Calcd for $C_{17}H_{18}BF_4N_3$: C, 58.15; H, 5.17; N, 11.97. Found: C, 58.20; H, 5.26; N, 11.90.

Registry No.—**1**, 3641-05-2; **2**, 3641-06-3; **3**, 15284-40-9; **4a**, 3999-10-8; **5**, 20743-50-4; **6**, 24433-71-4; **7**, 31818-94-7; **8**, 32827-41-1; **9**, 32675-44-8; **10**, 32675-45-9; **11**, 32675-46-0; **12**, 32675-47-1; **13**, 32675-48-2; **14a**, 2039-06-7; **15**, 32272-86-9; **16**, 32675-51-7; **17**, 32675-52-8; **18**, 32675-53-9.

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(13) E. K. Harvill, R. M. Herbst, E. C. Schreiner, and C. W. Roberts, *J. Org. Chem.*, **15**, 662 (1950).

(14) G. Scheuing and B. Walach, German Patent 543,026 [*Chem. Abstr.*, **26**, 3263 (1932)].

Reactions of Pyrrole with Isocyanates. Preparation and Reactions of *N*-Ethoxycarbonylpyrrole-2-carboxamide and Pyrrole-1,2-dicarboximide

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Treatment of pyrrole with ethoxycarbonyl isocyanate in toluene yields *N*-ethoxycarbonylpyrrole-2-carboxamide (**1**), which is readily hydrolyzed to either pyrrole-2-carboxamide or pyrrole-2-carboxylic acid and cyclized to pyrrole-1,2-dicarboximide (**8**). Reaction of **8** with ammonia gives *N*-carbamoylpyrrole-2-carboxamide (**10**) and its N-tosylation followed by hydrolysis affords *N*-tosylpyrrole-2-carboxamide (**13**), which is found to be identical with the compound formed from pyrrole and tosyl isocyanate in dioxane. Pyrrolylpotassium reacts with ethoxycarbonyl isocyanate in tetrahydrofuran to form, after acidification, *N*-ethoxycarbonylpyrrole-1-carboxamide (**2**).

The reactions of pyrrole with phenyl isocyanate[1] and trichloroacetyl isocyanate[2] are known to yield the corresponding derivatives of pyrrole-2-carboxamide. Of these, *N*-phenylpyrrole-2-carboxamide has been shown to react further with phenyl isocyanate, in the presence of triethylamine, to form *N*-phenylpyrrole-1,2-dicarboximide (**7**).[3] Unexpectedly, in view of the higher reactivity of the 2 position of pyrrole toward electrophilic reagents,[4] treatment of pyrrole with tosyl isocyanate in dioxane has been reported to lead to *N*-tosylpyrrole-3-carboxamide.[5]

In analogous reactions of enamines with ethoxycarbonyl isocyanate, the initial products have been shown

(1) A. Treibs and W. Ott, *Justus Liebigs Ann. Chem.*, **577**, 119 (1952).

(2) L. R. Smith, A. J. Speziale, and J. E. Fedder, *J. Org. Chem.*, **34**, 633 (1969).

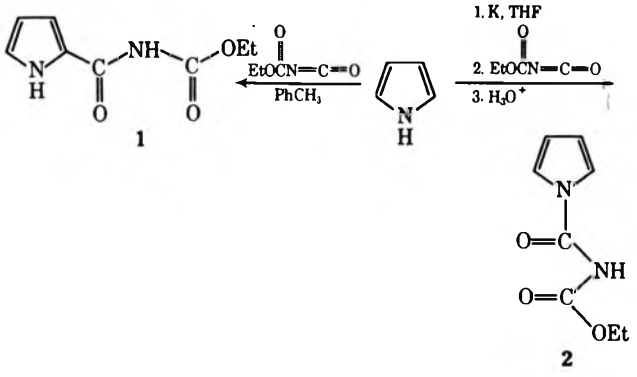
(3) E. P. Papadopoulos and H. S. Habiby, *ibid.*, **31**, 327 (1966).

(4) K. Schofield, "Hetero-Aromatic Nitrogen Compounds," Butterworths, London, 1967, pp 90, 91.

(5) M. Seefelder, *Chem. Ber.*, **96**, 3243 (1963).

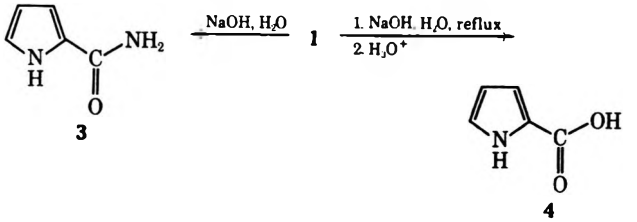
to undergo cyclization to form heterocyclic systems.[6] It was of interest to investigate the reaction of pyrrole with this isocyanate, because cyclization of the expected product (1) would yield pyrrole-1,2-dicarboximide (8). Availability of this compound would allow an unambiguous synthesis of *N*-tosylpyrrole-2-carboxamide (13) for comparison with the product of the reaction of pyrrole with tosyl isocyanate.

Pyrrole reacts readily with ethoxycarbonyl isocyanate to form *N*-ethoxycarbonylpyrrole-2-carboxamide (1). The reaction must be run in solution, because the neat reagents react violently and resinification of their mixture cannot be prevented. Structure 1 is

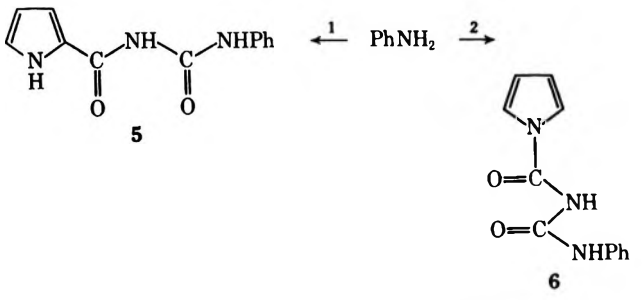


consistent with the infrared spectrum of the product, which contains strong NH absorption bands at 3450 and 3320 cm^{-1}, as well as carbonyl bands at 1770 and 1680 cm^{-1}. The relatively low frequency of the second carbonyl band indicates attachment of the side chain to a carbon atom of the ring.[3] This is confirmed by the nmr spectrum which, in addition to singlets at δ 11.8 (pyrrole NH) and 10.5 (imide NH), displays three multiplets centered at δ 7.3, 7.1, and 6.3, characteristic of the CH protons of a pyrrole ring with a carbonyl substituent at the 2 position.[2] For the sake of comparison of spectral data, *N*-ethoxycarbonylpyrrole-1-carboxamide (2) was prepared by the reaction of pyrrolylpotassium with ethoxycarbonyl isocyanate in tetrahydrofuran followed by acidification. The infrared spectrum of 2 shows relatively weak NH absorption at 3450 and 3300 cm^{-1} [7] and contains carbonyl bands at 1800 and 1730 cm^{-1}. Its nmr spectrum displays a singlet at δ 10.9 for the imide proton, and two triplets centered at δ 7.6 and 6.3 for the pyrrole CH protons.

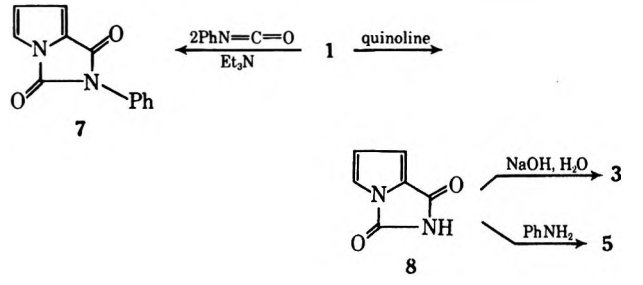
Treatment with warm, aqueous sodium hydroxide hydrolyzes and decarboxylates 1 with formation of pyrrole-2-carboxamide (3). More drastic hydrolysis of 1 yields pyrrole-2-carboxylic acid (4). These reactions provide convenient methods of preparation of 3 and 4 in two steps from pyrrole. As would be expected,[3] the carbonyl group attached to the pyrrole ring in 2 is considerably more reactive toward nucleophilic reagents than the corresponding group in 1 and alkaline hydrolysis of 2 results in formation of pyrrole.



Upon brief heating with aniline, both 1 and 2 undergo substitution at the ester carbonyl to form *N*-phenylcarbamoylpyrrole-2-carboxamide (5) and *N*-phenylcarbamoylpyrrole-1-carboxamide (6), respectively. In support of the above structures, the infrared spectrum (Nujol) of 5 displays NH absorption bands at 3320 and 3230 cm^{-1}, and carbonyl bands at 1700 and 1650 cm^{-1}. Its nmr spectrum contains singlets at δ 12.0, 11.1, and 10.7 for the three NH protons. Correspondingly, the infrared spectrum (Nujol) of 6 shows NH stretching at 3250 and carbonyl stretching at 1720 and 1690 cm^{-1}, while its nmr spectrum contains only two NH singlets at δ 10.8 and 10.3.



When 1 is treated with phenyl isocyanate, in the presence of triethylamine, *N*-phenylpyrrole-1,2-dicarboximide (7) is formed in a reaction completely analogous to that involving formation of 7 from *N*-phenylpyrrole-2-carboxamide.[3] On the other hand, the anticipated cyclization to pyrrole-1,2-dicarboximide (8) occurs readily when 1 is heated with quinoline. The infrared spectrum of 8 exhibits absorption at 3440 cm^{-1}, due to the cyclic imide NH,[8,10] and carbonyl bands at 1795 and 1745 cm^{-1}, consistent with the hydantoin ring.[3,10] Its nmr spectrum confirms the structure by displaying a broad singlet at δ 11.2 for the imide proton,[9,10] and three multiplets centered at δ 7.5, 6.9, and 6.6, corresponding to pyrrole ring protons. Treatment of 8 with aqueous alkali opens the hydantoin ring to yield 3 with loss of carbon dioxide. Hydantoin ring opening is observed also when 8 is heated with aniline to form 5. The results of the last two reactions, together with the nmr data, exclude the alternate structure of pyrrole-2,3-dicarboximide for the cyclization product of 1.



(6) (a) R. W. Lamon, *J. Heterocycl. Chem.*, **6**, 261 (1969); (b) R. Niess and R. K. Robins, *ibid.*, **7**, 243 (1970).

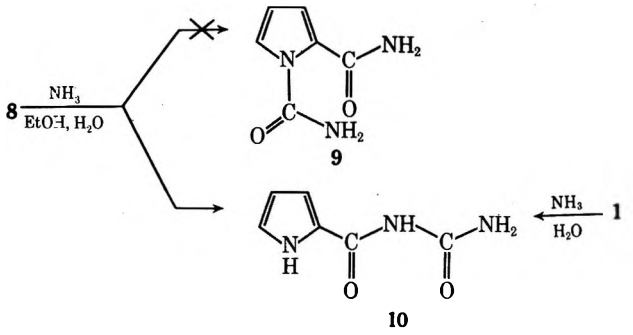
(7) In this and other similar cases, pyrrole and imide NH absorption bands appear at nearly the same frequency in solution spectra. In spectra of mulled samples, however, pyrrole NH stretching appears at a frequency 50–100 cm^{-1} higher than that of imide NH.

(8) Broad band at 3250–3120 cm^{-1} in spectrum of mulled sample.[9]

(9) E. E. Smissman, P. L. Chien, and R. A. Robinson, *J. Org. Chem.*, **35**, 3818 (1970).

(10) Compare with corresponding spectral values of phthalimide: ν_{NH} 3430 cm^{-1}; $\nu_{C=O}$ 1780, 1740 cm^{-1}; δ_{NH} 11.4.

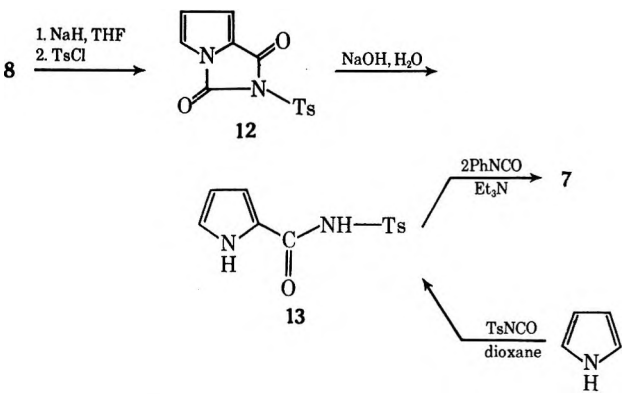
In a communication on the isolation of **8** from the urine of patients with rheumatoid arthritis,[11] this compound is reported to melt at 180–183°, in a sealed capillary, as it sublimes at 130–140°, and to yield pyrrole-1,2-dicarboxamide (**9**), mp 237°, upon treatment with aqueous alcoholic ammonia. In the present study, **8** has been found to melt at 210–212°, in an open capillary. Because conversion of **8** into **9** would involve a hydantoin ring opening different from that observed in the cases of its hydrolysis and reaction with aniline, the action of ammonia on **8** was reinvestigated.



When treated with a mixture of ethanol and concentrated aqueous ammonia (1:1), or the latter reagent alone, **8** goes into solution and a new solid (mp 240–241°) precipitates in a few moments. Instead of **9**, spectroscopic data strongly support the structure of *N*-carbamoylpyrrole-2-carboxamide (**10**) for this product. A compound of structure **9** would be expected to show carbonyl absorption below 1700 cm^{-1} in its infrared spectrum (Nujol)[12] and no signal corresponding to either pyrrole or imide NH proton in its nmr spectrum. In contrast, the infrared spectrum (Nujol) of the compound in question displays carbonyl bands at 1710 and 1670 cm^{-1},[12] and its nmr spectrum displays singlets for both pyrrole (δ 11.8) and imide (δ 10.2) NH protons.[13] Finally, the formation of **10** from **1** by treatment with aqueous ammonia at room temperature, or much faster at 100° under pressure, adds further support to its assigned structure.

As in the case of hydrolysis, the reaction of **2** with aqueous or alcoholic ammonia follows a different pattern and leads to formation of pyrrole-1-carboxamide (**11**).

The identity of the product of the reaction of pyrrole with tosyl isocyanate[5] has been established in the following manner. Treatment of the sodium salt of **8** with tosyl chloride in tetrahydrofuran yields *N*-tosylpyrrole-1,2-dicarboximide (**12**), as evidenced by the absence of NH absorption in the infrared spectrum of the product and the presence in it of strong bands at 1290 and 1180 cm^{-1}, indicative of *N*,*N*-disubstituted sulfonamide.[14] Furthermore, structure **12** is entirely consistent with the nmr spectrum of the product. Warm aqueous sodium hydroxide hydrolyzes **12** rapidly to yield a compound identical in all respects (ir and nmr spectrum, mixture melting point) with the product of the reaction of pyrrole with tosyl isocyanate in dioxane.[5] In the light of the ring opening observed in the hydrolysis of **7**,[3] **8**, and other condensed hydantoins,[9] it can be concluded that the above compound is *N*-tosylpyrrole-2-carboxamide (**13**). The nmr spectrum confirms this structure by displaying singlets at δ 12.0 and 11.8 for the NH protons, and three multiplets centered at δ 7.3, 7.1, and 6.2, characteristic of 2-substituted pyrrole derivatives of this type.[2] Attachment of the side chain at the 2 position of the pyrrole ring in the adduct of pyrrole and tosyl isocyanate is further indicated by the formation of *N*-phenylpyrrole-1,2-dicarboximide (**7**) upon treatment of the adduct with phenyl isocyanate and triethylamine.



Experimental Section[15]

***N*-Ethoxycarbonylpyrrole-2-carboxamide** (**1**).—To a stirred solution of 16.7 g (0.25 mol) of pyrrole in 50 ml of toluene was added 28.7 g (0.25 mol) of ethoxycarbonyl isocyanate[6a] dissolved in 50 ml of toluene, dropwise, over 1 hr. The reaction mixture was kept under nitrogen and its temperature was held at 30–40° by intermittent cooling. After completion of the addition, the solution was stirred at room temperature for a further 22 hr, then it was filtered and the precipitate was washed with five 25-ml portions of dichloromethane. The yield was 37.0 g (81%) of crude **1**, mp 137–139°. Recrystallization from dichloromethane yielded the pure compound: mp 140–141°;[16] ir 3450, 3320, 1770, 1680, 1540, 1480, 1300, 1280, 1155, 1110, 1090, 1045, 1030, 905, and 570 cm^{-1}; nmr δ 11.8 (s, 1, pyrrolyl NH), 10.5 (s, 1, imide NH), 7.3 (m, 1, pyrrolyl CH), 7.1 (m, 1, pyrrolyl CH), 6.3 (m, 1, pyrrolyl CH), 4.2 (q, 2, J = 7 Hz, $-CH_2-$), and 1.3 (t, 3, J = 7 Hz, $-CH_3$).

Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.87; H, 5.40; N, 15.36.

***N*-Ethoxycarbonylpyrrole-1-carboxamde** (**2**).—Pyrrolylpotassium was prepared in a nitrogen atmosphere by refluxing a stirred solution of 16.1 g (0.24 mol) of pyrrole in 50 ml of tetrahydrofuran with 7.8 g (0.20 g-atom) of potassium until all of the metal had reacted. Following dilution with 150 ml of solvent and cooling of the slurry to about 5° there was added 20.7 g (0.18 mol) of ethoxycarbonyl isocyanate dissolved in 100 ml of tetrahydrofuran, dropwise, over 0.5 hr. Throughout the addition and for a further 15 min the temperature of the reaction mixture was held below 15°. After it had been stirred at room temperature for an additional 5 hr, the mixture was diluted with an excess of anhydrous ethyl ether and filtered. The precipitate, washed with anhydrous ether, dried, and crushed into a fine powder, was mixed thoroughly with cold, dilute hydrochloric acid. There

(11) M. Yamaguchi, Y. Mori, and N. Nishimura, *Wakayama Med. Rep.*, **11**, 119 (1966); *Chem. Abstr.*, **68**, 11169s (1968).

(12) Consider $\nu_{C=O}^{cm^{-1}}$ (Nujol) values: **3**, 1650; **11**, 1680; phthalamide, 1670; benzoylurea, 1710, 1670; acetylurea, 1710, 1640.

(13) Compare with δ values for NH_2 protons of **3**, 7.3; **11**, 7.6; NH (imide) proton of benzoylurea, 10.5; acetylurea, 10.2.

(14) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 363.

(15) Melting points were determined in a Thomas-Hoover apparatus with use of a calibrated thermometer. A Perkin-Elmer Model 337 infrared spectrophotometer was used to take infrared spectra (in chloroform solution, unless otherwise indicated). Nmr spectra were obtained on a Varian A-60A spectrophotometer using solutions in hexadeuteriodimethyl sulfoxide, unless otherwise specified, with tetramethylsilane as internal standard. Spectral data of model compounds were determined experimentally.

(16) Some variation of melting point was observed depending on solvent of recrystallization, size of crystals, and rate of heating.

resulted 27.9 g (85%) of crude **2**, mp 117–119°, an analytical sample of which (recrystallized from ethanol) melted at 121.5–123°: ir 3450, 1800, 1730, 1495, 1325, 1275, 1155, 1095, 1075, 1020, 960, 900, and 590 cm^{-1}; nmr δ 10.9 (s, 1, NH), 7.6 (t, 2, J = 2 Hz, pyrrolyl CH), 6.3 (t, 2, J = 2 Hz, pyrrolyl CH), 4.3 (q, 2, J = 7 Hz, $-CH_2-$), and 1.3 (t, 3, J = 7 Hz, $-CH_3$).

Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.84; H, 5.29; N, 15.10.

Pyrrole-2-carboxamide (3). A. By Hydrolysis of 1.—A mixture of 2.0 g of **1**, 1.0 g of sodium hydroxide, and 10 ml of water was heated on the steam bath until a clear solution had been obtained (about 5 min). Upon cooling, there precipitated 0.80 g (66%) of **3**: mp 174–175°, raised to 175–177° by recrystallization from aqueous ethanol (lit.[17] mp 176.5°); ir 3545, 3460, 3425, 1660, 1590, 1420, 1360, 1190, 1115, 1080, and 1040 cm^{-1}; nmr δ 11.5 (s, 1, pyrrolyl NH), 7.3 (s, 2, NH_2), 6.9 (m, 2, CH), and 6.2 (m, 1, CH).

B. By Hydrolysis of 8.—A solution of 0.50 g of **8** in 5 ml of 10% aqueous sodium hydroxide was heated on the steam bath for 15 min. Cooling, followed by filtration, yielded 0.25 g of a solid, mp 172–174°, the ir and nmr spectra of which were identical with those of the product of the previous reaction. Recrystallization from aqueous ethanol raised the melting point to 173.5–175°, and a mixture of the two products melted at 174–175°.

Pyrrole-2-carboxylic Acid (4).—A mixture of 2.0 g of crude **1**, 4.0 g of sodium hydroxide, and 20 ml of water was refluxed for 2 hr and the resulting solution was cooled and washed with ether. Following acidification with cold, dilute hydrochloric acid, the solution was extracted with ether and the extract was treated with charcoal, dried ($MgSO_4$), and evaporated to dryness to yield 0.90 g (74%) of pyrrole-2-carboxylic acid: mp 206–208° dec (lit.[18] mp 207–208°); ir (Nujol) 3370, 1650, 1550, 1320, 1190, 1120, 1035, 950, 885, 755, 690, 600, and 555 cm^{-1}; nmr δ 11.7 (s, 2, NH and COOH) 7.0 (m, 1, CH), 6.9 (m, 1, CH), and 6.3 (m, 1, CH).

Hydrolysis of 2.—A mixture of 2 g of **2**, 4 g of sodium hydroxide, and 20 ml of water was refluxed for 1 hr. Removal of the solvent from an ethereal extract of the resulting solution yielded pyrrole, recognized from its ir spectrum. Careful acidification of the chilled aqueous solution with ice-cold, dilute hydrochloric acid followed by extraction and the usual isolation procedure did not give any other product.

***N*-Phenylcarbamoylpyrrole-2-carboxamide (5). A. From 1.**—A mixture of 1 g of **1** and 5 ml of aniline was boiled for about 1 min. Cooling, then filtration and washing of the precipitate with carbon tetrachloride, yielded 1.1 g (87%) of **5**: mp 254–255°, raised to 257–257.5° by recrystallization from ethanol; ir (Nujol) 3320, 3230, 1700, 1650, 1600, 1550, 1325, 1305, 1250, 1225, 1170, 1125, 890, 835, 760, 740, 690, 595, 575, and 505 cm^{-1}; nmr δ 12.0 (s, 1, pyrrolyl NH), 11.1 (s, 1, NH), 10.7 (s, 1, NH), 7.7–7.2 (m, 7, phenyl and pyrrolyl CH), 6.3 (m, 1, pyrrolyl CH).

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 63.17; H, 4.67; N, 18.44.

B. From 8.—Run as above, a reaction of 1 g of **8** with aniline yielded 1.3 g of product, mp 254.5–255°, raised to 257° after recrystallization from ethanol. Comparison of the ir and nmr spectra, as well as a mixture melting point (256.5–257.5°), showed that this compound was the same as the product of the previous reaction.

***N*-Phenylcarbamoylpyrrole-1-carboxamide (6).**—Run as for **5**, a reaction of 1 g of **2** with aniline afforded 1.2 g (95%) of **6**: mp 224–225°, raised to 229–230° by recrystallization from isopropyl alcohol; ir (Nujol) 3250, 1720, 1690, 1600, 1560, 1550, 1500, 1325, 1300, 1250, 1230, 1175, 1070, 960, 885, 750, 735, 690, 585, 575 and 505 cm^{-1}; nmr δ 10.8 (s, 1, NH), 10.3 (s, 1, NH), 7.7–7.2 (m, 7, phenyl and pyrrolyl CH), and 6.4 (m, 2, pyrrolyl CH).

Anal. Calcd for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.97; H, 4.69; N, 18.36.

***N*-Phenylpyrrole-1,2-dicarboximide (7). A. From 1.**—To 1.8 g (0.010 mol) of finely powdered **1** mixed with 2.4 g (0.020 mol) of phenyl isocyanate was added 3 ml of triethylamine and the resulting mixture was allowed to stand at room temperature for 5 min and on the steam bath for another 5 min, under a calcium chloride tube. Washing of the cooled product with two 25-ml portions of ethanol yielded 1.6 g (76%) of **7**: mp 225–226° (lit.[3] mp 226–227°); ir 1800, 1770, 1750, 1725, 1560, 1495, 1440, 1410, 1370, 1315, 1275, 1145, 1090, 1050, 1005, 835, 630, and 585 cm^{-1}; nmr (CF_3COOH) δ 7.6 (m, 6, phenyl and pyrrolyl CH), 7.1 (d, 1, J = 3 Hz, pyrrolyl CH), and 6.7 (t, 1, J = 3 Hz, pyrrolyl CH).

B. From 13.—A mixture of 1.3 g (0.005 mol) of **13**, 1.2 g (0.010 mol) of phenyl isocyanate, and 2 ml of triethylamine was heated on the steam bath for 22 hr, under a calcium chloride tube, and the product was washed with an excess of ethanol to yield 0.8 g (76%) of **7**, mp 225–227°.

Pyrrole-1,2-dicarboximide (8).—A mixture of 10 g of **1** and 20 ml of dry quinoline was heated in a 125-ml Erlenmeyer flask until the temperature of the escaping vapor reached 170–180°. Treatment of the cooled product with cold, dilute hydrochloric acid, followed by filtration, yielded a solid which was added to an ether extract of the filtrate. The resulting ethereal solution was washed with saturated aqueous sodium chloride, treated with charcoal, dried ($MgSO_4$), and evaporated under reduced pressure to yield 5.4 g (72%) of **8**, mp 206–209°, and 1 g of less pure material, mp 190–200°. Sublimation under vacuum raised the melting point to 209–211° and subsequent recrystallization from ethanol gave pure **8**, pale yellow crystals: mp 210.5–212°; ir 3440, 1795, 1745, 1560, 1445, 1410, 1310, 1150, 1050, 1005, 995, 640, and 585 cm^{-1}; nmr δ 11.2 (s, 1, NH), 7.5 (m, 1, CH), 6.9 (m, 1, CH), and 6.6 (m, 1, CH).

Anal. Calcd for $C_6H_4N_2O_2$: C, 52.94; H, 2.96; N, 20.59. Found: C, 53.21; H, 2.80; N, 20.50.

***N*-Carbamoylpyrrole-2-carboxamide (10). A. From 8.**—A solution of 0.40 g of **8** in a mixture of 1.0 ml of concentrated aqueous ammonia and 1.0 ml of ethanol was allowed to stand at room temperature for 3 hr. Filtration yielded 0.30 g (67%) of **10**, mp 236–237°.

Similarly, from 0.50 g of **8** and 5 ml of concentrated aqueous ammonia, there was obtained 0.40 g (71%) of **10**, mp 237–238°.

Recrystallization from ethyl alcohol gave the pure compound: mp 240–241°; ir (Nujol) 3390, 3345, 3200, 1710, 1660, 1580, 1550, 1320, 1170, 1140, 1085, 1050, 1045, 890, 850, 785, 750, 610, 575, 540, and 445 cm^{-1}; nmr δ 11.8 (s, 1, pyrrolyl NH), 10.2 (s, 1, imide NH), 8.1–7.1 (broad, ill-formed doublet, partly overlapping with two multiplets, 4, NH_2 and CH), and 6.2 (m, 1, CH).

Anal. Calcd for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 47.03; H, 4.83; N, 27.38.

B. From 1.—A solution of 0.50 g of **1** in 10 ml of concentrated aqueous ammonia was allowed to stand at room temperature for 8 hr. Dilution with water and filtration yielded 0.25 g of a solid, mp 237–238°, raised to 240–241° by recrystallization from ethanol. Examination of the ir and nmr spectra and a mixture melting point determination showed that this compound was **10**.

Similarly, 0.6 g of **10** was obtained upon cooling of the solution formed when a mixture of 1 g of **1** and 10 ml of concentrated aqueous ammonia, contained in a pressure bottle, was heated on the steam bath for a few minutes.

Pyrrole-1-carboxamide (11).—A mixture of 2 g of **2** and 10 ml of concentrated aqueous ammonia was placed in a pressure bottle and heated on the steam bath for 1 hr. Upon cooling, there precipitated 0.8 g of crude **11**: mp 148–156°, raised to 163–165° by recrystallization from aqueous ethanol (lit.[19] mp 165–166); ir 3540, 3430, 1720, 1585, 1470, 1410, 1375, 1200, 1100, 1080, 1070, and 940 cm^{-1}; nmr δ 7.6 (s, 2, NH_2), 7.4 (t, 2, J = 2 Hz, CH), and 6.3 (t, 2, J = 2 Hz, CH).

***N*-Tosylpyrrole-1,2-dicarboximide (12),**—To a solution of 2.7 g (0.020 mol) of **8** in 25 ml of tetrahydrofuran was added 0.9 g of sodium hydride emulsion in mineral oil (57%) and the resulting mixture was stirred under nitrogen, at room temperature, for 2 hr. After dilution with 15 ml of solvent and dropwise addition (30 min) of 3.4 g (0.018 mol) of tosyl chloride dissolved in 50 ml of tetrahydrofuran, the reaction mixture was stirred at room temperature for a further 21 hr. Addition of 300 ml of dry ether followed by filtration yielded a solution which was washed with cold water, treated with charcoal, dried ($MgSO_4$), and evaporated to small volume under reduced pressure. Upon chilling, the residual solution yielded 2.4 g of **12**, mp 182–183°. Evaporation of the mother liquor to dryness and recrystallization of the residue from toluene afforded an additional 0.30 g (total yield 52%), mp 178–182°. An analytical sample of **12** (from toluene) melted at 183.5–184.5°: ir 1820, 1800, 1770, 1600, 1560, 1450,

(17) E. Fischer and D. D. Van Slyke, *Ber.*, **44**, 3166 (1911).

(18) P. Hodge and R. W. Rickards, *J. Chem. Soc.*, 2543 (1963).

(19) D. A. Shirley, B. H. Gross, and P. A. Roussel, *J. Org. Chem.*, **20**, 225 (1955).

1400, 1290, 1180, 1145, 1095, 1030, 1005, 920, 585, 565, and 545 cm^{-1}; nmr δ 8.0 (d, 2, J = 8 Hz, phenyl CH), 7.8 (d, 1, J = 3 Hz, pyrrolyl CH), 7.6 (d, 2, J = 8 Hz, phenyl CH), 7.2 (d, 1, J = 3 Hz, pyrrolyl CH), 6.7 (t, 1, J = 3 Hz, pyrrolyl CH), and 2.5 (s, 3, $-CH_3$).

Anal. Calcd for $C_{13}H_{10}N_2O_4S$: C, 53.78; H, 3.47; N, 9.65. Found: C, 53.62; H, 3.52; N, 9.50.

***N*-Tosylpyrrole-2-carboxamide (13).**—Brief (2–3 min) heating on the steam bath of a mixture of 1 g of 12 with 10 ml of 10% aqueous sodium hydroxide yielded a solution which was filtered cooled, and acidified with dilute hydrochloric acid. There precipitated 0.85 g of **13**: mp 214–218, raised to 224–225° by recrystallization from ethanol; ir (Nujol) 3300, 3275, 1675, 1590, 1550, 1350, 1300, 1190, 1175, 1145, 1120, 1090, 1070, 950, 875, 810, 740, 660, 605, 570, and 540 cm^{-1}; nmr δ 12.0 (s, 1, NH), 11.8 (s, 1, NH), 8.0 (d, 2, J = 8 Hz, phenyl CH), 7.5 (d, 2, J = 8 Hz, phenyl CH), 7.3 (m, 1, pyrrolyl CH), 7.1 (m, 1, pyrrolyl CH), 6.2 (m, 1, pyrrolyl CH), and 2.4 (s, 3, $-CH_3$). The above spectra were identical with the corresponding spectra of the product of the reaction of pyrrole with tosyl isocyanate in dioxane [mp 224–225° (lit.[5] mp 222–224°), mmp 224–226°].

Registry No.—**1**, 32846-52-9; **2**, 32846-53-0; **3**, 4551-72-8; **4**, 634-97-9; **5**, 32846-56-3; **6**, 32846-57-4; **7**, 4778-77-2; **8**, 13939-91-8; **10**, 32846-60-9; **11**, 21972-99-6; **12**, 32846-62-1; **13**, 32846-63-2.

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6,11-Dihydroacridizinium Derivatives Having a 6,11-Etheno Bridge[1]

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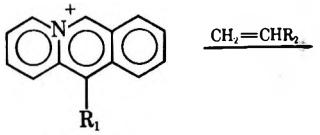
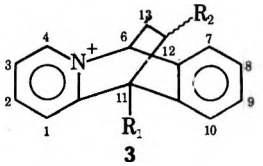
Ethano-bridged derivatives may be made by addition of vinyl alcohol or amine derivatives to the acridizinium ion, but no means has been found for converting these to etheno-bridged derivatives. Etheno-bridged derivatives may be prepared by addition of acetylenic compounds to 11-substituted acridizinium ions, but if no substituent is present at position 11 rearrangement occurs, affording derivatives of 1-(2-pyridyl)naphthalene.

Cycloaddition Reactions Using Vinyl Derivatives.—The synthesis of 6,11-dihydroacridizinium compounds having a 6,11-etheno bridge would provide a means for the study of the inductive effect of an adjacent but unconjugated positive charge on the addition reactions of a double bond, as well as an intermediate for the possible synthesis of an azoniajanusene.[2] Our initial plan was to prepare an ethano-bridged compound having a hydroxyl group (or suitable derivative) on the bridge, and to convert this to an etheno-bridged derivative *via* an elimination reaction.

It was found that ethyl vinyl ether, butyl vinyl ether, and vinyl acetate all added to the acridizinium ion in good yield (Table I). As would be expected from the strong polarization of such vinyl derivatives, the orientation in each case was that with the oxy function at position 12. Acid-catalyzed cleavage of the ether or ester linkages gave the same alcohol (**3**, R_1 = H; R_2 = OH). Acetylation of this hydroxyl derivative gave the acetate **7**, identical with that obtained in the cycloaddition reaction with vinyl acetate. It was also possible to convert the hydroxyl compound (**3**, R_1 = H; R_2 = OH) to the tosylate (**3**, R = H; R_2 = Tos) by action of tosyl chloride and pyridine.



1, R_1 = H
2, R_1 = Ph



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4, R_1 = H; R_2 = OEt
5, R_1 = Ph; R_2 = OEt
6, R_1 = H; R_2 = OBu
7, R_1 = H; R_2 = OAc
8, R_1 = H; R_2 = *N*-carbazyl
9, R_1 = H; R_2 = 1-pyrrolidin-2-one

The alcohol (**3**, R_1 = H; R_2 = OH) was not dehydrated when allowed to stand in concentrated sulfuric acid for 24 hr. The acetate **7** survived heating in a sealed tube at 210°, refluxing for 10 hr in dimethylformamide, or refluxing for 24 hr in pyridine. The tosylate was recovered (95%) after refluxing for 20 hr in pyridine and after refluxing in diglyme (162°) for 11 hr. It also resisted for 86 hr solvolysis in refluxing acetic acid containing sodium acetate.[3]

The addition of *trans*-1,2-dichloroethylene to acridizinium fluoroborate at 130° gave the expected 12,13-dichloro-6,11-dihydro-6,11-ethanoacridizinium fluoroborate. An attempt to remove the chlorine by the action of a zinc–copper couple[4] yielded a substance which was not a quaternary salt.

The addition of *N*-vinylcarbazole and *N*-vinyl-2-pyrrolidone to the acridizinium nucleus occurs quite readily but neither of the resulting bases (**8** or **9**) was suitable for a Cope elimination reaction.

Cycloaddition Reactions Using Acetylenic Derivatives.—Due to the lack of promise shown by these indirect approaches to the synthesis of etheno-bridged compounds, the addition of acetylenic derivatives to the acridizinium nucleus (Table II) was reexamined.

(1) This research was supported by Public Health Service Research Grant No. HE-02170 of the National Heart Institute of the National Institutes of Health.

(2) *Cf.* S. J. Cristol, and D. C. Lewis, *J. Amer. Chem. Soc.*, **89**, 1476 (1967).

(3) On the basis of subsequent experiments (*vide infra*) it would seem probable that decomposition products obtained in these and more drastic elimination attempts may have contained some salts of 1-(2-pyridyl)naphthalene.

(4) *Cf.* S. J. Cristol and W. Y. Lim, *J. Org. Chem.*, **34**, 1 (1969).

TABLE I

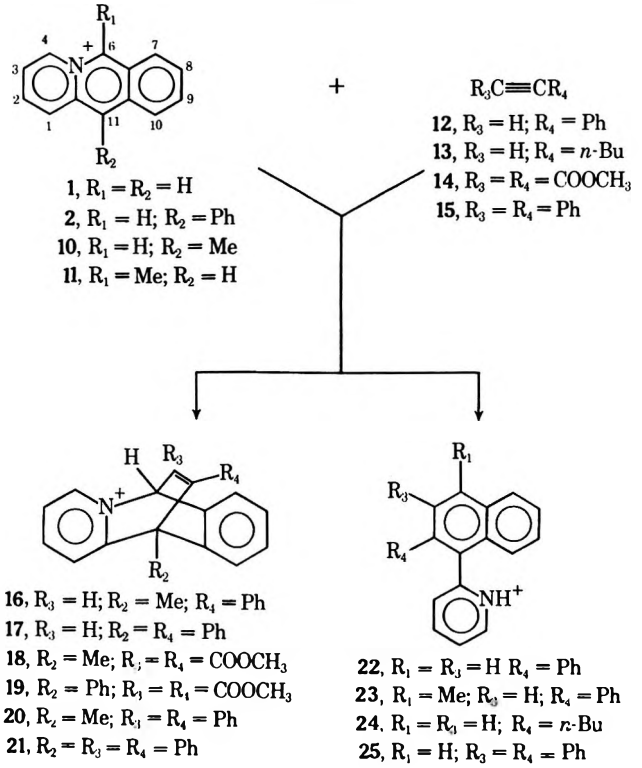
ADDITION OF VINYL DERIVATIVES TO ACRIDIZINIUM BROMIDE SALTS

Vinyl derivative	Acridizinium[a]	Temp, °C	Time, hr	Product	Method[b]	Mp, °C	Yield, %	Formula[c]
OEt	1	20	72	4	A	206–206.5[d]	91	$C_{17}H_{18}ClNO_5$
OEt	2	20	72	5	A	138–144[e]	33	$C_{23}H_{22}ClNO_6$
OBu	1	82	12	6	B	90–94[f,g]	64	$C_{19}H_{22}BrNO\cdot 0.5H_2O$
OAc	1[h]	65	72	7	A	215–217[e]	89	$C_{17}H_{16}ClNO_6$
N-Carbazyl	1[i,g]	20	15	8	B	227–230[d]	68	$C_{27}H_{21}ClN_2O_4$
1-Pyrr[j]	1[k,l]	20	12	9	B	214–216.5[f]	50	$C_{19}H_{19}ClN_2O_5$

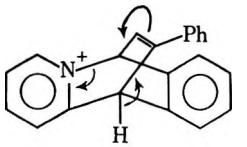
[a] Except as noted the starting material was the bromide salt. [b] See Experimental Section. Note that all products except **6** were isolated as perchlorate salts. [c] Satisfactory analytical data (C, H, N) were presented for all compounds in this table: Ed. [d] Recrystallized from MeCN–Et_2O; nmr (CF_3CO_2H, aliphatic protons only) δ 6.48 (broad s, 1, C-6 H), 5.53 (d, 1, J = 3 Hz, C-11 H), 4.4–4.7 (m, 1, C-12 H), 3.7–4.4 (m, CH_2CH_3), 2.8–3.3 (m, 1, C-13 H), 1.32 (t, 3, CH_3). [e] Recrystallized from MeOH. [f] Recrystallized from MeOH–Et_2O. [g] Note that this product is the bromide salt. [h] Cycloaddition carried out in methanol. [i] Reaction carried out in MeCN–MeOH (1:2). [j] 1-Pyrrolidin-2-one. [k] Acridizinium perchlorate was the starting material. [l] Reaction carried out in MeCN–$MeNO_2$ (1:1).

Fields, *et al.*,[5] had reported that they had been unable to effect the addition of dimethyl acetylenedicarboxylate to the acridizinium ion. It appeared possible, however, that such an addition could be made to succeed by use of higher temperatures and of less electron-deficient acetylene derivatives.

As expected, phenylacetylene reacted with the acridizinium ion much more slowly than did styrene and the reaction was best accomplished in a sealed tube at 135–140°. At this temperature acridizinium perchlorate would occasionally explode and the tetra-



fluoroborate anion was found more satisfactory. The reaction product proved not to be the simple cycloaddition product **26**, since nmr showed no bridgehead hydrogens, but is without doubt 1-(2-pyridyl)-2-phenylnaphthalene (**22**) as the tetrafluoroboric acid salt. This rearrangement of **26** is readily understandable if it is recalled that scission of a carbon–nitrogen bond could lead to the formation of a cinnamyl-type carbonium ion which could aromatize by elimination of a proton. A parallel aromatization leading to 2-morpholino-1-(2-pyridyl)naphthalene was observed by Fields, *et al.*,[5] when an attempted addition of 1,1-dimorpholinoethylene to the acridizinium ion occurred with elimination. Such elimination–rearrangements have been made the subject of a recent study.[6]



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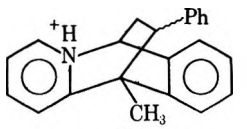

27

Rearrangement was also observed when the acridizinium ion was allowed to react with 1-hexyne or diphenylacetylene.

When phenylacetylene (**12**) was allowed to react with 11-methylacridizinium ion (**10**), no rearrangement occurred and the adduct **16** could be hydrogenated to a derivative **27** in which both the ethylene bridge and the pyridinium ring had been saturated. The identical derivative **27** could be prepared by addition of styrene to 11-methylacridizinium ion followed by catalytic reduction. This demonstrates that phenylacetylene adds to the 11-methylacridizinium ion with the same *regiospecificity*[7] as does styrene. Unrearranged addition products of 11-methyl- (**10**) and 11-phenylacridizinium ions with phenylacetylene (**12**), dicarbomethoxyacetylene (**14**), and diphenylacetylene (**15**) are recorded in Table II.

Experimental Section

Melting points were taken in capillaries using a Thomas–Hoover apparatus and are uncorrected. All nmr data were obtained using 60-megacycle instruments. Elemental analyses were by Janssen Pharmaceutica Research Laboratories, Beerse, Belgium, or by N-H-W Laboratories, Garden City, Mich. Mass spectra were taken at low resolution at the Research Triangle Center for Mass Spectrometry using the MS 902 spectrometer.

Fluoroborate Salts.—The fluoroborate salts were prepared either by (A) addition of fluoroboric acid to the known[8] bromide or (B) by substitution of 48% fluoroboric acid for perchloric acid in the isolation of the cation from polyphosphoric acid cyclization mixtures.[9–11] Results are summarized in Table III.

(5) D. L. Fields, T. H. Regan, and J. Dignan, *J. Org. Chem.*, **33**, 390 (1968).

(6) D. L. Fields and T. H. Regan, *ibid.*, **35**, 1870 (1970).

(7) *Cf.* A. Hassner, *J. Amer. Chem. Soc.*, **90**, 216 (1968).

(8) C. K. Bradsher and L. E. Beavers, *ibid.*, **77**, 4812 (1955).

(9) C. K. Bradsher and J. C. Parham, *J. Heterocycl. Chem.*, **1**, 121 (1964).

(10) C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83 (1963).

(11) C. K. Bradsher and T. W. G. Solomons, *J. Amer. Chem. Soc.*, **81**, 2550 (1959).

Table II

Products of the Reaction of Some Acridizinium Fluoroborates with Derivatives of Acetylene at 135–140°

Substituents						
Acetylene	Acridizinium	Time, hr	Yield, %	Mp, °C[a,b]	Formula	Product[c]
Ph		3	70	191–193	$C_{21}H_{16}NBF_4$	R 22[d]
Ph	6-Me	8	80	156–157[e]	$C_{22}H_{17}N$	R 23
Ph	11-Me	0.75	62	229–230[f]	$C_{22}H_{18}NBF_4$	U 16[g]
Ph	11-Ph	0.75[i]	50	240[f,h]	$C_{27}H_{20}NBF_4$	U 17
n-Bu		12	78	164.5–165.5[j]	$C_{25}H_{22}N_4O_7$	R 24
$(COOCH_3)_2$	11-Me	0.10	93	230.5–231[f]	$C_{20}H_{18}BF_4NO_4$	U 18
$(COOCH_3)_2$	11-Ph	1.75[i]	30	198–199[f]	$C_{25}H_{20}BF_4NO_4$	U 19
Ph_2		250[k]	30	265–270[f]	$C_{27}H_{20}BF_4N$	R 25
Ph_2	11-Me	40	85	269–269.5	$C_{28}H_{22}BF_4N$	U 20
Ph_2	11-Ph	239	40	264[f,l]	$C_{33}H_{24}BF_4N$	U 21

[a] Satisfactory analyses (±0.4% for C, H, N) were submitted for all products in this table: Ed. [b] All salts are tetrafluoroborates. [c] R = rearranged, U = unrearranged. [d] The free base, mp 106.5–107.5°, crystallized from ethanol–water, mass spectrum parent peak at *m/e* 281. *Anal.* Calcd for $C_{21}H_{15}N$: C, 89.65; H, 5.37; N, 4.98. Found: C, 89.83; H, 5.26; N, 4.93. [e] The yield and melting point reported are those of the free base; nmr (CD_3CN) δ 2.90 (s, 3, $ArCH_3$), 7.1–8.7 (m, 15, ArH). [f] With decomposition. [g] Nmr (CD_3CN) δ 2.20 (s, 3, CH_3), 6.9–9.2 (m, 15, ArH). [h] C, calcd 72.83; found, 73.25. [i] It is important that the reaction time not be extended and that the temperature be kept at almost exactly 140°. [j] The yield and melting point are of the picrate, obtained by the action of ethanolic picric acid solution on the free base; recrystallized from ethyl acetate. [k] A second 0.5-g portion of phenylacetylene was added after 80 hr. [l] C, calcd 76.02; found, 76.45.

Table III

Acridizinium Tetrafluoroborates

No.	Substituent	Method[a] of prepn	Mp, °C	Recrystn solvent	Formula[b]
1		A	184.5–185	MeOH	$C_{13}H_{10}BF_4N$
11	6-Me	B	200–201	HOH	$C_{14}H_{12}BF_4N$
10	11-Me	B	219–220	MeOH–EtOAc	$C_{14}H_{12}BF_4N$
2	11-Ph	B	234–235	MeOH	$C_{19}H_{14}BF_4N$

[a] Methods A and B refer to methods in paragraph on fluoroborate salts. [b] Data indicating satisfactory carbon, hydrogen, and nitrogen analyses for these compounds were submitted: Ed.

Addition of Vinyl Derivatives to Acridizinium Salts (Table I).—Unless otherwise indicated, the acridizinium derivative (**1** or **2**) as the bromide salt was dissolved or suspended in acetonitrile which had been dried by distilling it from phosphorus pentoxide. The volume of solvent varied from 25 to 100 ml per 1 g of salt. The vinyl derivative was added in 3–10 molar excess and the reaction was followed by disappearance of the long-wavelength absorptions characteristic of the acridizinium uv spectrum. The volume of solution was reduced to about one-third in a rotary evaporator and the product was isolated by (A) addition of water and sodium perchlorate to precipitate the perchlorate salt or (B) by addition of anhydrous ether to precipitate the salt without change in anion. Recrystallization solvents are indicated in the footnotes to Table I.

12-Hydroxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorate (3, R_1 = H; R_2 = OH). A. By Hydrolysis of the 12-Ethoxy Adduct (4).—The cleavage of the ethoxy linkage could be accomplished by the use of hydriodic hydrobromic, or hydrochloric acid, all yielding the same perchlorate salt on addition of sodium perchlorate. Five grams of the adduct 4 as the bromide salt was refluxed for 5 hr with a mixture of 50 ml of 47% hydrobromic acid and 10 ml of concentrated sulfuric acid. The hydrobromic acid was evaporated under reduced pressure, then 30 ml of water followed by an excess of sodium perchlorate was added. The resulting precipitate, mp 157–162.5°, yield 4.3 g (93%), was quite pure.

B. By Hydrolysis of the 12-Butoxy Adduct (6).—This could be effected by heating 0.5 g of the adduct 6 for 22 hr at 110° with 10 ml of 57% hydriodic acid. The product which separated appeared from its brown color to be a triiodide salt and addition of iodine caused precipitation of additional product. The combined precipitates (0.8 g) were stirred with silver chloride. The resulting chloride was, in turn, converted to the perchlorate identical with the product obtained by procedure A.

C. By Hydrolysis of the 12-Acetoxy Adduct (7).—Two grams of the perchlorate of vinyl acetate adduct **7** was refluxed for 2 hr in 50 ml of 1% hydrobromic acid solution. On cooling and collecting, 1.6 g (93%) of the product, mp 163.5–167.5°, was obtained. Preparation A, B, and C gave identical ir and nmr spectra.

The analytical sample, mp 159–162°, was crystallized from methanol as colorless needles.

Anal. Calcd for $C_{15}H_{14}ClNO_5$: C, 55.65; H, 4.36; N, 4.33. Found: C, 55.99; H, 4.49; N, 4.38.

The corresponding iodide, mp 196–199°, was crystallized from ethanol–ether as fine pale yellow needles.

Anal. Calcd for $C_{15}H_{14}INO$: C, 51.30; H, 4.02; N, 3.99. Found C, 51.01; H, 3.96; N, 4.02.

Acetylation of 12-Hydroxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorate (3, R_1 = H; R_2 = OH).—A small portion of the named salt was acetylated with a mixture of equal parts of acetic anhydride and acetyl chloride by heating the mixture at 50° for 3 hr. The liquid was evaporated under a stream of air and the residue was recrystallized from methanol. The product, mp 215–217°, was identical (ir) with the vinyl acetate adduct (7).

Tosylate of 12-Hydroxy-6,11-dihydro-6,11-ethanoacridizinium Perchlorate (3, R_1 = H; R_2 = *p*-$CH_3C_6H_4SO_2O$).—One gram of the perchlorate salt of the 12-hydroxy derivative (3, R_1 = H, R_2 = OH) was ground together in a mortar with 1.2 g of purified *p*-toluenesulfonyl chloride. The mixture was placed in 10 ml of purified pyridine and after 1 min the mixture was cooled and placed in a refrigerator for 24 hr. The product obtained by pouring the mixture on ice was recrystallized from methanol, affording 0.9 g (61%) of colorless needle clusters of analytical purity, mp 185–187°.

Anal. Calcd for $C_{22}H_{20}ClNO_7S$: C, 55.29; H, 4.21; N, 2.93. Found: C, 55.30; H, 4.10; N, 3.02.

12,13-Dichloro-6,11-dihydro-6,11-ethanoacridizinium Tetrafluoroborate.—In each of ten 16 × 125 mm ignition tubes, 0.3 g of acridizinium tetrafluoroborate, 5 ml of dry acetonitrile, and 1.5 g of *trans*-dichloroethylene were placed and the tubes were sealed under nitrogen. The sealed tubes were heated at 130° for 90 hr. After cooling, the contents of all tubes were poured into 1 l. of anhydrous ether to which 100 ml of petroleum ether (bp 30–60°) had been added. The ether mixture was decanted from the precipitate, which was crystallized from methanol–ether (Norit) as pale yellow aggregates, yield 1.9 g (46%), mp 221–226°.

Anal. Calcd for $C_{15}H_{12}BCl_2F_4N$: C, 49.50; H, 3.32; N, 3.85. Found: C, 50.04; H, 3.05; N, 3.76.

Addition of Acetylene Derivatives to Acridizinium Derivatives (Table II).—The technique was essentially the same as that used in making 12,13-dichloro-6,11-dihydro-6,11-ethanoacridizinium tetrafluoroborate except that 0.5 g of the appropriate acetylenic compound was substituted for the *trans*-dichloroethylene. Progress of the reaction was followed by opening a tube and measuring, by means of uv spectroscopy, the amount of the unreacted acridizinium ion remaining. When the reaction was complete, the mixture was poured into ether–hexane (2:1) and the resulting precipitate was recrystallized from acetonitrile–ether.

11-Methyl-12-phenyl-6,11-dihydro-6,11-ethanoacridizinium Fluoroborate.—The named salt was prepared essentially as was the previously reported[12] perchlorate salt, yield 90% of colorless microcrystals, mp 227–230°.

Anal. Calcd for $C_{22}H_{20}BF_4N$: C, 68.59; H, 5.23; N, 3.64. Found: C, 68.84; H, 5.26; N, 3.66.

11-Methyl-12-phenyl-1,2,3,4,5,6,11,11a-octahydroacridizinium Fluoroborate (27). A. By Hydrogenation of Adduct 16 from Phenylacetylene and 11-Methylacridizinium Fluoroborate.—To a suspension of 0.5 g of finely powdered 16 in 50 ml of ethanol, 0.1 g of platinum oxide was added and the mixture was hydrogenated at atmospheric pressure until slightly more than the theoretical quantity of hydrogen had been absorbed. After the catalyst had been removed by filtration the solution was concentrated and the residue was crystallized from acetonitrile–ether and then from pure acetonitrile, yield 0.25 g (50%) of colorless prisms, mp 198–199°.

B. By Reduction of 11-Methyl-12-phenyl-6,11-dihydro-6,11-ethanoacridizinium Fluoroborate.—Hydrogenation of 0.25 g of the named compound in 25 ml of ethanol using 0.1 g of platinum oxide catalyst afforded 0.15 g (60%) of colorless crystals, mp 198–199°. The ir spectra of the two preparations are identical.

Anal. Calcd for $C_{22}H_{26}BF_4N$: C, 67.53; H, 6.70; N, 3.58. Found: C, 67.45; H, 6.54; N, 3.24.

(12) C. K. Bradsher and J. A. Stone, *J. Org. Chem.*, **34**, 1700 (1969).

Registry No.—**1**, 32865-43-3; **2**, 32865-44-4; **3** (R_1 = H; R_2 = OH), 32861-29-3, 32861-30-6 (iodide); **3** (R_1 = H; R_2 = *p*-$CH_3C_6H_4SO_2O$), 32861-31-7; **4**, 32861-32-8; **5**, 32861-33-9; **6**, 32861-34-0; **7**, 32861-35-1; **8**, 32958-81-9; **9**, 32861-36-2; **10**, 32846-42-7; **11**, 32846-43-8; **16**, 32846-44-9; **17**, 32981-43-4; **18**, 32865-45-5; **19**, 32865-46-6, **20**, 32865-47-7; **21**, 32865-48-8; **22**, 32839-09-1; **22** free amine, 32861-37-3; **23** free amine, 32861-38-4; **24**, 32861-39-5; **25**, 32839-10-4; **27**, 32839-11-5; 12,13-dichloro-6,-11-dihydro-6,11-ethanoacridizinium tetrafluoroborate, 32846-45-0; 11-methyl-12-phenyl-6,11-dihydro-6,11-ethanoacridizinium fluoroborate, 32846-46-1.

The Cycloaddition of the Acridizinium Ion with Norbornene Derivatives[1]

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The adducts obtained by cycloaddition of norbornene derivatives with the acridizinium ion are exo and have one strongly shielded methylene proton that appears in the nmr at higher fields than δ 0. Norbornene derivatives which had an endo ring attached at positions 5 and 6 gave predominantly syn addition with respect to the benzenoid ring, the yields being highest when a heteroatom was in the ring. The acridizinium ion added twice to norbornadiene giving what is believed to be a syn,syn product.

Aromatic quaternary salts are electrophiles and in some instances[2-4] are capable of undergoing cycloaddition with appropriate alkenes. Since the products of the classical Diels–Alder reaction are cyclohexene derivatives, it seemed quite possible that such products might undergo a second cycloaddition reaction with a suitable aromatic quaternary salt. Such successive cycloaddition reactions would permit the easy synthesis of some relatively complex systems.

Although it was found that cyclohexene under sealed tube conditions can be made to add to the acridizinium ion (1) (Scheme I), it appeared more promising to carry out the proposed study with the more reactive norbornene and its derivatives (2). A great many norbornene derivatives of known stereochemistry are available by the use of the Diels–Alder reaction and many more can be derived from Diels–Alder products.

Addition of the acridizinium ion to norbornene (2, R = H_2) yields a mixture which, on the basis of nmr evidence, appears to contain only exo addition products. In the spectra of both components (**3** and **4**) of the mixture, signals arising from one proton (H_A-18)[5] of the methylene bridge appear at a magnetic field so high (above δ 0.0) as to be explicable only if the proton were strongly shielded by diamagnetic ring currents of an aromatic ring.

The addition of cyclopentadiene to norbornene is also reported[6] to occur exo. The H_A-18 signal at the *highest* field was a doublet at δ −0.85[7] which had approximately two-thirds the area of the other H_A-18 doublet at δ −0.42. The assignment of the higher field doublet as anti (with respect to the benzenoid ring) was made by reducing the mixture of syn and anti (**3** and **4**, R = H_2) catalytically. It is known[2,8] that the pyridinium ring is reduced in preference to the benzenoid ring; so it would be expected that the strong shielding effect due to the ring currents of the pyridinium ring would disappear while that due to the benzenoid ring would remain. The crude reduction product from the mixture had lost the resonance at δ −0.85 (**4** H_A-18) as well as another at δ 0.87 (**4**, H_B-18) while those at δ −0.42 (**3**, H_A-18) and 0.60 (**3**, H_B-18) remained. This made it possible to assign the isomer giving the signal at the highest field as the anti (**3**, R = H_2). Recrystallization of the mixture of isomers resulted in the isolation of the pure syn isomer (**3**, R = H_2). The residue from the mother liquors, when subjected to column chromatography using the gradient elution technique,[9] afforded a small quantity of the pure anti isomer (**4**, R = H_2). Nmr with pure samples afforded further evidence for the

(1) This research was supported in part by Public Health Service Research Grant No. HE-2170 of the National Heart Institute.

(2) C. K. Bradsher and T. W. G. Solomons, *J. Amer. Chem. Soc.*, **80**, 933 (1958).

(3) D. L. Fields, T. H. Regan, and J. C. Dignan, *J. Org. Chem.*, **33**, 390 (1968).

(4) C. K. Bradsher and F. H. Day, *Tetrahedron Lett.*, 409 (1971).

(5) The numbering for **3** is that recommended by Dr. Kurt L. Loening of *Chemical Abstracts* for the 6,11-*o*-benzene-7,10-methanobenzo[*b*]quinolizinium system. Our decision to use the same numbering system for adducts obtained from all norbornene derivatives was made to facilitate tabulation of the nmr data.

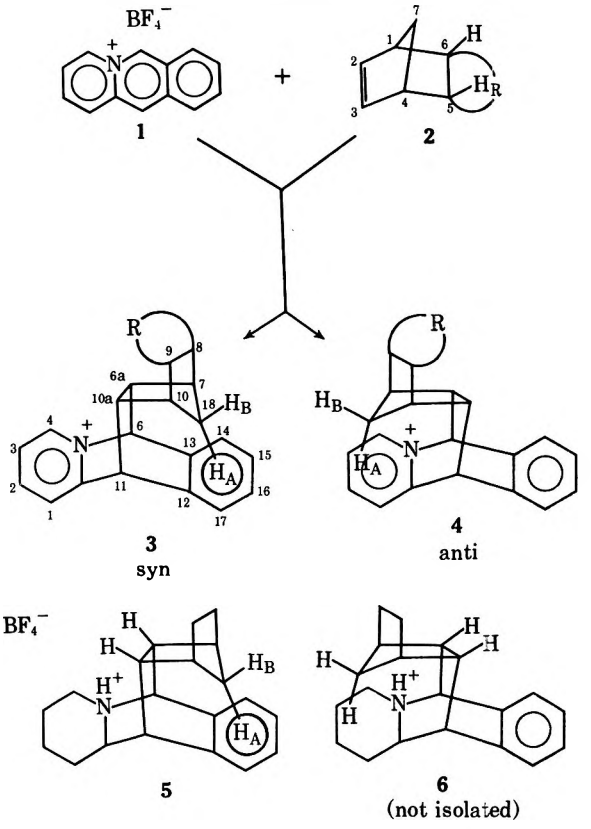
(6) S. B. Soloway, *J. Amer. Chem. Soc.*, **74**, 1027 (1942).

(7) Since some of the signals from the products of norbornene derivatives fell into the region of a tetramethylsilane signal, the primary internal standard for our measurements was the chloroform signal. This signal was set at δ 7.30 to put our results on approximately the usual TMS scale.

(8) C. K. Bradsher and L. E. Beavers, *J. Amer. Chem. Soc.*, **77**, 4812 (1955).

(9) The gradient device used was type E as described in Erich Heftmann, "Chromatography," 2nd ed, Reinhold, New York, N. Y., 1967, p 104.

SCHEME I
ADDITION OF ENDO 5,6-SUBSTITUTED NORBORNENES



correctness of the structural assignments (Table I). In the syn isomer (**3**, R = H_2), protons on carbons 7 and 10 over the uncharged benzene ring are so similar in their environment that they have the same resonance and because of the lack of coupling with protons 6 and 11 and with each other, appear to be magnetically equivalent. On the other hand the bridgehead protons at 6a and 10a project toward the pyridinium ring and appear as quartets with different resonances because of the different distances of the two protons from the positive charge.

The anti isomer (**4**, R = H_2) has bridgehead protons H-10 and H-7 over, and at different distances from, the quaternary nitrogen, and hence have resonances at different fields. On the other hand, the protons at the 10a and 6a bridgehead positions are directed over the uncharged benzene ring and appear as a single singlet.

Definite assignment of the resonances and the nature of the coupling was made possible by means of decoupling experiments. Using the pure syn isomer, when the doublet at δ −0.42 was irradiated, the doublet at δ 0.60 collapsed to a singlet. A similar collapse of the δ −0.42 doublet was observed when the signal at δ 0.60 was irradiated, indicating geminal coupling (J_{AB} = 12 Hz) of the 18A and 18B protons of the methylene group. The bridgehead proton (H-6) adjacent to nitrogen is easily identified because it is so strongly deshielded. With the syn isomer, irradiation of the signal at δ 6.30 due to H-6 caused the collapse of the quartet at δ 2.30 to a doublet, identifying the signal for the proton at 6a. Irradiation of the other easily identifiable protons at position 11 caused a collapse of the quartet at δ 2.18 to a doublet and identified the signal due to the proton at 10a.

TABLE I
ADDITION OF ENDO 5,6-SUBSTITUTED NORBORNENES (2) TO ACRIDIZINIUM FLUOROBORATES (1)

Substituent ring R	Time, hr	Temp, °C	Analytical sample, mp, °C	Formula[a]	Syn (3): anti (4)[b]	Yield,[c] %	Nmr, δ (multiplicity)[d] H-18A	H-18B	H-10	H-7	H-10a	H-6a	H-11	H-6
None	24	82[e]	Syn, 282–284	$C_{20}H_{20}BF_4N$	60:40	82	−0.42 (d)[f]	0.60 (d)[f]	2.27 (s)	2.27 (s)	2.18 (q)[g,h]	2.30 (q)[h,i]	5.05 (d)[g]	6.30 (d)[i]
			Anti, 270–271				−0.85 (d)[f]	0.87 (d)[f]	2.35 (s)	2.47 (s)	2.35 (s)	2.35 (s)	5.10 (s)	6.30 (s)
$(CH_2)_3$	48	82[e]	Mixture, 265–267	$C_{23}H_{24}BF_4N$	85:15	42	−0.32 (d)[f]	0.78 (d)[f]	*j*	*j*	*j*	*j*	5.03 (d)[k]	6.30 (d)[i]
CONHCO	72	82[e]	Syn, 400 dec	$C_{22}H_{19}BF_4N_4O_2$	100:0	62	−0.16 (d)[m]	1.10 (d)[m]	3.0 (m)	3.0 (m)	2.50 (q)[n,o]	2.83 (q)[i,o]	5.20 (d)[n]	6.43 (d)[i]
$CON(CH_3)CO$	120	82[e]	Syn, 375–377 dec	$C_{23}H_{21}BF_4N_2O_2$	100:0	99	−0.10 (d)[f]	1.09 (d)[f]	*j*	*j*	2.27 (q)[g,h]	2.62 (q)[i,h]	5.20 (d)[g]	6.43 (d)[i]
COOCO	96	120[p]	Syn, 300 dec	$C_{22}H_{18}BF_4NO_3$	100:0	25	−0.05 (d)[f]	1.08 (d)[f]	2.97 (s)	2.97 (s)	2.30 (q)[q,r]	2.80 (q)[i,r]	5.20 (d)[q]	6.67 (d)[i]
CH_2OCH_2	24	82[e]	Syn, 298–299	$C_{22}H_{22}BF_4NO$	100:0	53	−0.12 (d)[f]	0.94 (d)[f]	*s*	*s*	*s*	*s*	5.05 (d)[k]	6.30 (d)[i]
							−0.07 (d)[f,w]	1.10 (d)[f]	*s*	*s*	*s*	*s*	5.10 (d)[v]	6.37 (d)[x]
$CH_2NH_2{}^+CH_2{}^u$	96	120[p]	Mixture, 325–330[y]	$C_{24}H_{24}B_2F_8N_2$	70:30	22								
							−0.53 (d)[f,z]	1.30 (d)[f]	*s*	*s*	*s*	*s*	5.10 (d)[v]	6.37 (d)[x]

[a] Satisfactory analyses were submitted for all analytical samples described in this table: Ed. [b] Ratio of syn to anti as determined by nmr on first product isolated. [c] Unless otherwise indicated yields are of total cycloaddition product. [d] For numbering see Scheme I. All signals showed expected integration. [e] Refluxing acetonitrile. [f] J_{AB} = 12 Hz. [g] $J_{10a,11}$ = 3 Hz. [h] $J_{6a,10a}$ = 10 Hz. [i] $J_{6,6a}$ = 4 Hz. [j] Not clearly resolved. [k] $J_{10a,11}$ = 2 Hz. [l] $J_{6,6a}$ = 3 Hz. [m] J_{AB} = 12 Hz. [n] $J_{10a,11}$ = 3 Hz. [o] $J_{6a,10a}$ = 8 Hz. [p] Sealed tube. [q] $J_{10a,11}$ = 4 Hz. [r] $J_{6a,10a}$ = 9 Hz. [s] Not definitely assigned. [t] $J_{6,6a}$ = 2 Hz. [u] Both anions were fluoroborate. [v] This mixture was not separated. The nmr results have been assigned by analogy to the unsubstituted compound. [w] All data on this line assigned to syn isomer. [x] All data on this line assigned to anti isomer. [y] $J_{10a,11}$ = 1 Hz. [z] $J_{6,6a}$ = 1 Hz.

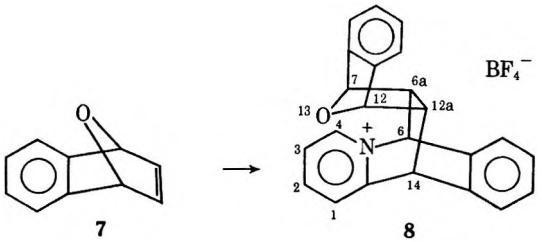
Similar irradiation experiments with the anti isomer (**4**, R = H_2) revealed signals from H-6A and H-10A as one singlet and those from H-7 and H-10 as singlets. It is significant that protons H-6 and H-11 are not coupled.

Hydrogenation of a pure sample of the syn isomer (**3**, R = H_2) afforded **5**, in which the resonances due to the methylene protons appeared at almost the same fields (H_{18A}, δ −0.33, H_B, δ 0.60) as in the starting materials. While there was not enough of the pure anti isomer (**4**, R = H_2) available to permit a similar reduction, reduction of the mixture of syn and anti products had shown the disappearance of signals at δ −0.85 and 0.87.

The remaining compounds in Table I were prepared to study the effect on the stereochemistry of the cycloaddition exerted by rings attached endo at positions 5 and 6 of the norbornene structure (**2**). Only when the ring consisted solely of methylene groups [**2**, R = $(CH_2)_3$] or when there was a positive charge on the ring (**2**, R = $CH_2N^+H_2CH_2$) was there evidence for the formation of any but the syn isomer. While in every case except that affording a 99% yield [**2**, R = $CON(CH_3)_2CO$] it might be presumed that significant quantities of the anti isomer were present, routine observation of the filtrate gave no evidence of the existence of anti isomer, and it is believed that the reaction in these cases does occur exclusively syn.

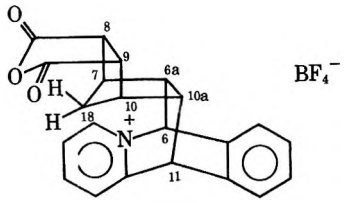
A plausible explanation for this stereoselectivity is that, when unshared electrons are available on the central atom of the endo ring, attraction to the positive charge of the acridizinium nitrogen is a controlling factor. The fact that even without an endo bridge (**2**, R = H_2) more syn then anti addition occurs, suggests that repulsion of the methylene hydrogens by the pyridinium ring may be greater than that by the benzenoid ring.

As a test of the attraction of unshared electrons toward the positive nitrogen, the addition of 1,4-dihydronaphthalene 14-*endo*-oxide (**7**) to the acridizinium nucleus was carried out. The expected product, the anti stereoisomer (**8**), was the only one obtained. Structural assignment was based on the observation that the protons at 6a and 12a are equivalent (hence over the benzenoid ring) while those at C-7 and C-12 were not, indicating that one of the two was significantly closer to the positive charge on nitrogen and hence more deshielded than the other.



7 **8**

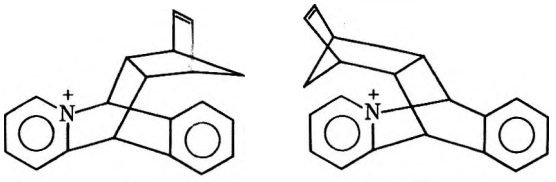
The only cycloaddition with an exo derivative of norbornene used the readily available[10] norbornene-*exo*-5,6-dicarboxylic anhydride. It was found that cycloaddition occurred more readily than with the endo isomer and that the product was a mixture. Interestingly, a single crystallization gave the pure anti adduct (**9**) in an overall yield of 15%. Assignment of



9

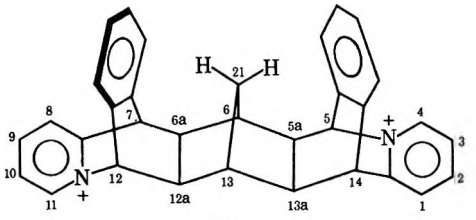
the structure rests on the effect of the positive nitrogen on the bridgehead proton signals in the nmr.

The addition of 2 mol of acridizinium ion to norbornadiene was carried out with the hope of creating an adduct in which both of the methylene protons would appear at negative values on the TMS scale. The reaction was carried out stepwise, the first addition taking place in refluxing acetonitrile and yielding a mixture consisting of approximately 73% syn (**10**) and 27% anti (**11**) isomers. Fractional crystallization of the mixture did not result in a useful change in isomer ratio, so the final step in the synthesis was carried out using the mixture. When heated with acridizinium fluoroborate in a sealed tube at 120°, the mixture reacted to afford the diadduct **12** in 51% yield.



10 **11**

(not separated)



12

The problem of regioisomerism in the second cycloaddition seems more difficult to resolve than problems of stereoisomerism. The formulation of the second azonia group as being at 11a rather than 7a rests only on the principle of maximum separation of like charges. Despite this uncertainty it is still possible to draw some interesting conclusions with regard to the stereochemistry of the system. Even if one assumes that there is no deviation from the usual preference for exo addition, there remain three possibilities for the structure: syn,syn; syn,anti; and anti,anti. It is easy to eliminate the possibility of endo addition and/or that the structure is syn,anti, for the data in Table I make it quite clear that under those circumstances the methylene protons should give rise to two distinct sets of doublets. Actually the product shows a singlet at δ −0.80 corresponding to two protons, evidence that the methylene protons have a symmetrical environment, eliminating every possibility except an exo,exo-syn,syn or exo,exo-anti,anti configuration. The possibility that the product is anti,anti is appealing, be-

(10) D. Craig, *J. Amer. Chem. Soc.*, **73**, 4889 (1951).

cause the field at which the two-proton singlet appears is matched in Table I only by the H_A proton of an anti derivative, but this line of reasoning does not take into account the effect of overlapping fields which arises from the aromatic ring facing the *vicinal* proton of the methylene group. Decisive in our assignment of the diadduct as syn,syn was the yield (51%) of diadduct observed, for, barring rearrangements or dissociation–recombination, such a yield of anti,anti product would be impossible with a starting material that was only 27% anti. In addition, decoupling experiments indicate that protons 6 and 13 occur as a singlet as do H-7 and H-10 in syn isomer **3**. Likewise protons at 5 and 12 and 7 and 14 are split by protons at 5a and 6a and 12a and 13a, respectively, again corresponding with the pattern observed in syn isomer **3**.

Experimental Section

Methods.—All nmr data were obtained by use of a Varian T-60 spectrometer and, unless otherwise specified, using trifluoroacetic acid as solvent and chloroform (δ 7.30) as an internal standard. The melting points were determined in capillaries using a Thomas-Hoover apparatus. All analyses were by Janssen Pharmaceutica Research Laboratories, Beerse, Belgium, or M-H-W Laboratories, Garden City, Mich.

Materials.—*endo*-1,2-Dihydrodicyclopentadiene,[11] *endo*-*N*-methylbicyclo[2.2.1]hept-5-ene-2,3-dicarboximide,[12] 2-oxa-1,2-dihydro-*endo*-dicyclopentadiene,[13] and *endo*-2-aza-1,2-dihydrodicyclopentadiene[13] were prepared according to published directions. A quantity of *endo*-5-norbornene-2,3-dicarboximide was obtained from Professor Pelham Wilder, Jr. Except as noted, other norbornene derivatives were purchased.

6,11[1′,2′]Cyclohexeno-6,11-dihydroacridizinium.—A solution of 0.95 g of freshly distilled cyclohexene and 0.3 g of acridizinium tetrafluoroborate[14] in 3 ml of dry acetonitrile was heated for 2 days at 120° in a sealed tube. The reaction mixture was poured into ether, affording 0.35 g (94%) of a colorless powder, mp 261–262°. Recrystallization from methanol gave yellowish crystals, mp 267°.

Anal. Calcd for $C_{19}H_{20}BF_4N$: C, 65.35; H, 5.77; N, 4.01. Found: C, 65.59; H, 5.79; N, 3.85.

Cycloaddition of Acridizinium Fluoroborate (1) with Norbornene Derivatives (2). A. In Refluxing Acetonitrile.—To the acridizinium fluoroborate suspended in anhydrous acetonitrile (7 ml/g 1) 2 or 3 equiv of the norbornene derivative was added and the mixture was refluxed until the uv absorption of a sample showed that absorption in the 399-mμ region was absent. The recovery of the product was made either by pouring the mixture into dry ether or by evaporating the solvent and triturating the residue with acetone or methanol. In every case the product was recrystallized from acetonitrile.

B. In a Sealed Tube.—The sealed tube reactions were carried out similarly except that the solutions were more concentrated (1.5 ml CH_3CN/g 1) and the tubes were heated at 120°. The adduct (**3** and **4**, R = $CH_2N^+H_2CH_2$) obtained from *endo*-2-aza-1,2-dihydrodicyclopentadiene was crystallized from acetonitrile–ethyl acetate to which a few drops of fluoroboric acid had been added.

Separation of *syn*- and *anti*-Norbornene Adducts (3 and 4, R = H_2).—From 13 g of the 60:40 mixed product in two recrystallizations from acetonitrile, 1.7 g of pure syn isomer was obtained. The mother liquors from the crystallization were concentrated, 5 g of alumina was added, and the solvent was removed under reduced pressure. This material was placed at the top of an alumina column (4 × 100 cm) of Merck 80–200 mesh alumina packed by the slurry method using methylene chloride. Elution was by the gradient method[9] with 33% acetonitrile–67% methylene chloride as the polar solvent and methylene chloride as the nonpolar solvent. Progress of the elution could be followed by fluorescence under uv light. Only a partial separation was obtained but the first fractions contained 0.08 g of pure anti isomer.

1,2,3,4,5,6,6a,7,8,9,10,10a,11,11a-Tetradecahydro-6,11-*o*-benzeno-7,10-methanoacridizinium Fluoroborate (5).—A suspension of 0.9 g of pure *syn*-6,6a,7,8,9,10,10a,11-octahydro-6,11-benzeno-7,10-methanoacridizinium fluoroborate (**3**, R = H_2) was suspended in 100 ml of ethanol and 0.1 g of platinum oxide catalyst was added. The mixture was hydrogenated at atmospheric pressure until slightly more than the theoretical quantity of hydrogen had been absorbed. The tan product (0.9 g) was recrystallized from acetonitrile affording colorless crystals: mp 292°; nmr δ −0.33 (d, 1, J_{AB} = 12 Hz, H_A-18), 0.60 (d, 1, J_{AB} = 12 Hz, H_B-18), 4.57 (d, 1, $J_{6,6a}$ = 3 Hz, H-6).

Anal. Calcd for $C_{20}H_{26}BF_4N$: C, 65.41; H, 6.86; N, 3.81. Found: C, 65.24; H, 6.93; N, 3.78.

6,7,12,14-Tetrahydro-6,14-*o*-benzenobenz[*i*]acridizinium 7,12-Oxide Fluoroborate (8).—The addition of 1,4-dihydronaphthalene 1,4-*endo*-oxide (**7**)[15] to acridizinium fluoroborate was carried out in acetonitrile by heating at 50° for 12–14 hr. After removal of the solvent, ether trituration of the residue afforded crystals which were recrystallized from acetone and then from methanol: yield 1 g (43%); mp 230° dec; nmr δ 2.80 (s, 2, H-6a,12a), 5.40 (s, 1, H-14), 5.60 (s, 1, H-12), 5.77 (s, 1, H-7), 6.66 (s, 1, H-6).

Anal. Calcd for $C_{23}H_{18}BF_4NO$: C, 67.18; H, 4.41; N, 3.41. Found: C, 67.21; H, 4.57; N, 3.41.

***anti*-6,6a,7,8,9,10,10a,11-octahydro-6,11-*o*-benzeno-7,10-methanoacridizinium-*exo*-8,9-carboxylic Acid Anhydride Fluoroborate (9).**—The refluxing acetonitrile procedure was used with *exo*-5,6-norbornenedicarboxylic acid anhydride[10] as in procedure A, the reaction taking 4 days. The product crystallized from acetonitrile, affording the pure anti adduct in 15% yield: mp >360 nmr δ −0.60 (d, 1, J_{AB} = 12 Hz, H_A-18), 0.94 (d, 1, J_{AB} = 12 Hz, H_B-18), 2.65 (s, 2, H-6a,10a), 3.16 (s, 1, H-10), 3.28 (s, 1, H-7), 3.33 (s, 2, H-8,9), 5.26 (s, 1, H-11), 6.50 (s, 1, H-6).

Anal. Calcd for $C_{22}H_{18}BF_4NO_3$: C, 61.28; H, 4.21; N, 3.25. Found: C, 61.36; H, 3.98; N, 3.16.

6,6a,7,10,10a,11-Hexahydro-6,11-*o*-benzeno-7,10-methanoacridizinium Fluoroborate (10 and 11).—In refluxing acetonitrile 1 reacted with excess norbornadiene in 24 hr to afford a 90% yield of a mixture of syn (**10**) and anti (**11**) isomers, mp *ca.* 280°. Although it was not practicable to effect separation by recrystallization, the presence of 73% *syn*-**10** and 27% *anti*-**11** was evidenced by nmr: syn, δ −0.23 (d, 1, J_{AB} = 12 Hz, H-18$_A$), 0.85 (d, 1, J_{AB} = 12 Hz, H-18$_B$); anti, −0.73 (d, 1, J_{AB} = 12 Hz, H-18$_A$), 1.25 (d, 1, J_{AB} = 12 Hz, H-18$_B$); syn and anti, 5.06 (d, 1, $J_{11,10a}$ = 3 Hz, H-11), 6.37 (m, 3, H-6,8,9).

Anal. Calcd for $C_{20}H_{18}BF_4N$: C, 66.88; H, 5.05; N, 3.90. Found: C, 66.95; H, 5.13; N, 3.75.

***syn,syn*-5,5a,6,6a,7,12,12a,13,13a,14-Decahydro-5,14;7,12-bis-*o*-benzeno-6,13-methano-4a,11a-diazonia Fluoroborate (12).**—A solution of 0.67 g of the monoadduct (**10** + **11**) and 0.5 g of acridizinium fluoroborate (**1**) was heated at 120° for 4 days in a sealed tube. The highly insoluble product crystallized on the walls of the tube and the solvent containing any unreacted material was decanted, yield 0.6 g (51%). The product was crystallized, mp >360°, from a large quantity of acetonitrile: nmr δ −0.30 (s, 2, CH_2), 2.4–2.6 (m, 6, H-5a,6,6a,12a,13,13a), 5.13 (d, 2, $J_{6a,7} = J_{13a,14}$ = 2Hz, H-7,14), 6.38(d, 2, $J_{5,5a} = J_{12,12a}$ = 3 Hz, H-5,12).

Anal. Calcd for $C_{33}H_{28}B_2F_8N_2$: C, 63.29; H, 4.51; N, 4.47. Found: C, 63.52; H, 4.42; N, 4.36.

Registry No.—**1**, 32865-43-3; **3** (R = H), 32958-93-3; **3** [R = $(CH_2)_3$], 32865-49-9; **3** (R = CONHCO), 32865-50-2; **3** [R = CON(CH_3)CO], 32865-51-3; **3** (R = COOCO), 32865-52-4; **3** (R = CH_2OCH_2), 32865-53-5; **3** (R = $CH_2NH_2^+CH_2$), 32839-12-6; **4** (R = H), 32865-54-6; **4** [R = $(CH_2)_3$], 32865-55-7; **4** (R = $CH_2NH_2^+CH_2$), 32839-13-7; **5**, 32839-14-8; **8**, 32865-56-8; **9**, 32958-94-4; **10**, 32865-57-9; **11**, 32865-58-0; **12**, 32981-44-5; 6,11[1′,2′]cyclohexeno-6,11-dihydroacridizinium, 32865-60-4.

(11) H. G. Bruson and T. W. Riener, *J. Amer. Chem. Soc.*, **67** 723 (1945); *cf.* P. Wilder, Jr., C. F. Culberson, and G. T. Youngblood, *ibid.*, **81**, 656 (1959).

(12) C. F. Culberson and P. Wilder, Jr., *J. Org. Chem.*, **25**, 1358 (1960).

(13) C. F. Culberson, J. H. Seward, and P. Wilder, Jr., *J. Amer. Chem. Soc.*, **82**, 2541 (1960).

(14) W. S. Burnham and C. K. Bradsher, *J. Org. Chem.*, **36**, 355 (1971).

(15) L. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, **43**, 1599 (1965).

Acknowledgment.—We are indebted to Professor Pelham Wilder, Jr., for samples of certain norbornene derivatives as well as for advice on the synthesis of such derivatives. We would also like to thank Professor J. R. Wiseman of the University of Michigan for helpful suggestions concerning the structure proof.

Bromohydrin Formation in Dimethyl Sulfoxide. V.[1] The Reaction of Norbornene

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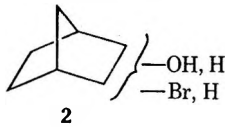
The reaction of bicyclo[2.1.1]heptene (norbornene) with *N*-bromosuccinimide (NBS) in moist dimethyl sulfoxide (DMSO) has been examined in detail. The structures of the products have been elucidated and it has been shown (contrary to an earlier report) that no 2,3-bromohydrin products are obtained. In addition, bromohydrins which were not obtained, but which might have been, *a priori*, expected, were synthesized and shown to be stable to the reaction conditions. The products which were obtained, also stable to the reaction conditions, are accounted for on the basis of ionic and free-radical processes.

We have demonstrated[1,5] that a wide variety of olefins react with *N*-bromosuccinimide (NBS) in moist dimethyl sulfoxide (DMSO) to generate, without rearrangement, stereo- and regiospecifically, the corresponding bromohydrins. Unique among all olefins we have examined, in that rearrangement occurs, is bicyclo[2.2.1]heptene (norbornene) (**1**).

In our initial report[5] concerning the results of the reaction of norbornene (**1**) with NBS in moist DMSO we indicated that 3-bromobicyclo[2.2.1]heptan-2-ol (geometry unspecified) (**2**), *syn*-7-bromobicyclo[2.2.1]-



2

heptan-2-*exo*-ol (**3**), and nortricyclene bromide (**4**) were formed in the ratio 3:3:1. This result was based solely upon gas–liquid partition chromatography (glpc) comparison of the products obtained in the NBS–DMSO system with those obtained in *tert*-butyl alcohol–water–sulfuric acid by earlier workers.[6]

Since positive halogen reagents usually do not provide unrearranged material in large amounts when permitted to react with norbornene,[7] and since the geometry of the 2,3 product could potentially provide insight into the reason for the lack of rearrangement, we felt that a thorough investigation of this system merited our attention.

Results and Discussion

When norbornene (**1**) is permitted to react with NBS in moist DMSO six products (99.2%) are, in fact, formed. These products and the relative per cent yields in which they were obtained are shown in Table I

TABLE I

Product	Yield, %
Nortricyclene bromide (**4**)	61.8
syn-7-Bromobicyclo[2.2.1]heptan-2-*exo*-ol (**3**)	21.7
exo-syn-2,7-Dibromobicyclo[2.2.1]heptane (**11**)	8.3
anti-7-Bromobicyclo[2.2.1]heptan-2-*exo*-ol (**8**)	4.4
syn-7-Bromobicyclo[2.2.1]heptan-2-one (**7**)	2.2
endo-exo-2,3-Dibromobicyclo[2.2.1]heptene (**10**)	1.6

and can be accounted for by the species shown in Scheme I.

Thus, **1** is converted (perhaps after initial complexation)[8] into a bromocation which can be represented as the α-bromocarbonium ion A, the bromonium ion B, or some other positive species for which these structures (Scheme I) represent idealized constructions.[9] In either ion A or B the bulk of the bromine atom would presumably preclude exo attack by DMSO[7b,10] but not endo attack by this nucleophilic reagent.

Indeed, formation of the ultimate product of endo attack [*i.e.*, *exo*-3-bromobicyclo[2.2.1]heptan-2-*endo*-ol (**5**)] would be expected either from attack on the first ion or a rearrangement product of this ion resulting from 6,1-hydride migration in the nonclassical ion C (Scheme I).[11] Nevertheless, this product, although sought, is not found and we attribute its absence to the bulky nature of the solvated nucleophile and the requirement that it attack the endo face of the system. Thus, the major product (nortricyclene bromide) (**4**) derives simply from loss of a proton, presumably to succinimide anion.

Transformation of the first ion A or B into C, through σ bond delocalization, or D by a Wagner–Meerwein rearrangement, followed by attack of solvent at C_1 (norbornene numbering) in C or at the positive charge in D from the exo direction results in formation of *syn*-7-

(1) For paper IV in this series, see D. R. Dalton and V. P. Dutta, *J. Chem. Soc. B*, 85 (1971).

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(3) Taken in part from the doctoral dissertation submitted by R. K. R. to the Graduate School of Temple University, June 1971, in partial fulfillment of the requirements for the Ph.D. degree.

(4) Université de Genève, Ecole de Chimie, Genève, Switzerland.

(5) D. R. Dalton, V. P. Dutta, and D. G. Jones, *J. Amer. Chem. Soc.*, **90**, 5498 (1968).

(6) L. H. Zalkow and A. C. Oehlschlager, *J. Org. Chem.*, **29**, 1625 (1964).

(7) (a) L. Kaplan, H. Kwart, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **82**, 2341 (1960), and references cited therein; (b) D. R. Marshall, P. Reynolds-Warnhoff, and E. W. Warnhoff, *Can. J. Chem.*, **49**, 885 (1971).

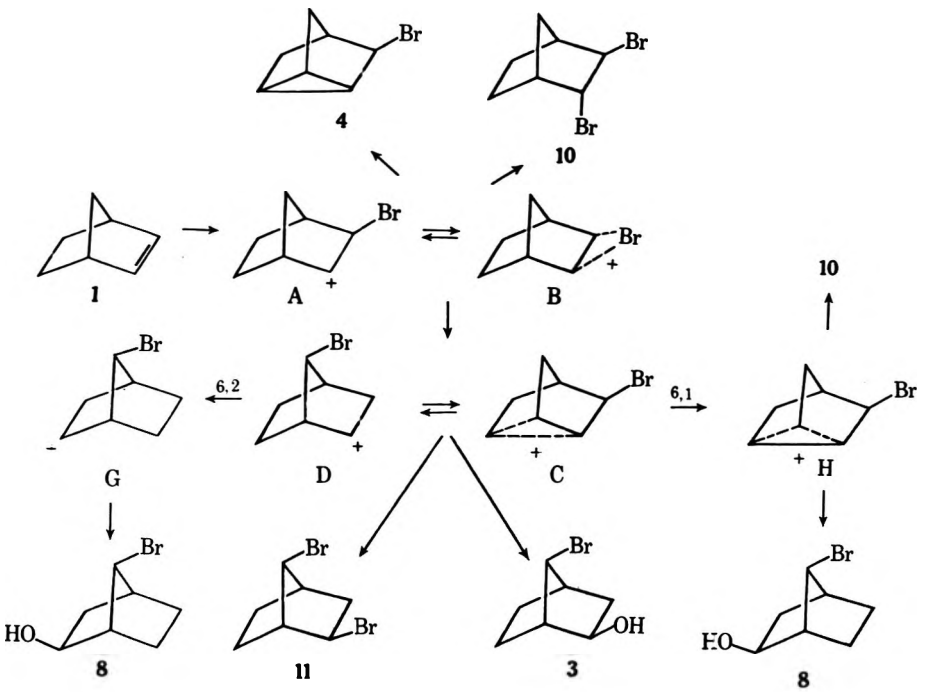
(8) J. E. Dubois and F. Gerner, *Tetrahedron Lett.*, 3961 (1968).

(9) R. D. Bach and H. F. Henneike, *J. Amer. Chem. Soc.*, **92**, 5589 (1970).

(10) J. A. Berson, A. W. McRowe, and R. G. Bergman, *ibid.*, **89**, 2573 (1967).

(11) J. A. Berson, "Molecular Rearrangements," Part 1, P. deMayo, Ed., Wiley-Interscience, New York, N. Y., 1963, pp 162, 163.

SCHEME I



bromobicyclo[2.2.1]heptan-2-*exo*-ol (**3**), the second major product. Presumably, endo attack on D is precluded for the same reasons given above (*vide supra*), while the delocalized bond in C shields that face which would also yield *syn*-7-bromobicyclo[2.2.1]heptan-2-*endo*-ol (**6**) as this material, too, is not found.

It is interesting to speculate, nevertheless, that the small amount of *syn*-7-bromobicyclo[2.2.1]heptan-2-one (**7**) isolated in the reaction mixture (Table I) might have come from endo rather than exo addition of DMSO to a species such as D. We suggest this may be a possibility since precedent does exist, in nonbicyclic systems, for the presumed dimethylsulfoxonium intermediate (E or F, Scheme II) to undergo oxidation by the path shown;[12] and proton loss in E (from the exo face) should certainly be more facile than from the endo face in F. Indeed, relief of steric strain in the crowded intermediate E would aid the process and further help to explain this unusual product.[13]

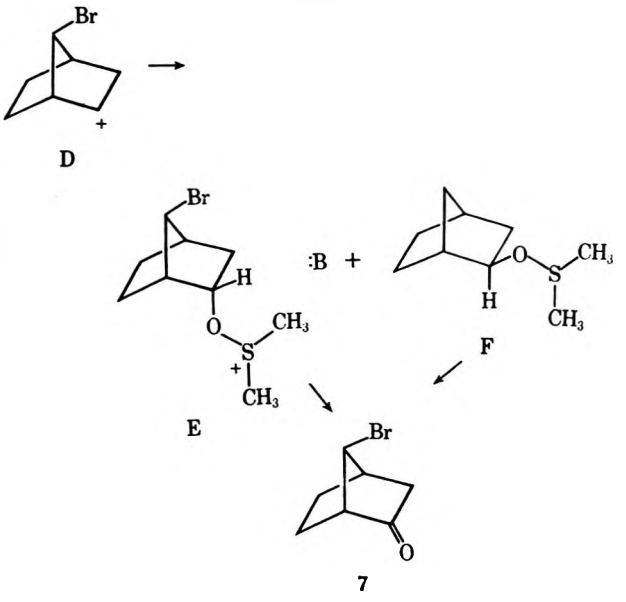
Now, a 6,2-hydride migration in D or a 6,1-hydride migration in C generates new ions G and H, respectively (Scheme I). Ion G, suffering attack from the exo direction by DMSO, would, on hydrolysis, afford *anti*-7-bromobicyclo[2.2.1]heptan-2-*exo*-ol (**8**) as would attack at C_6 (norbornene numbering) in H. Although ion G should certainly be subject to endo attack, product which might arise from this process was not detected. Indeed, product arising from exo attack, which should predominate in any case, was only present to the extent of *ca.* 4% (Table I) so that *anti*-7-bromobicyclo[2.2.1]heptan-2-*endo*-ol (**9**), had it been formed, might have gone undetected.

The final two products observed, *i.e.*, *endo-exo*-2,3-dibromobicyclo[2.2.1]heptane (**10**) and *exo-syn*-2,7-dibromobicyclo[2.2.1]heptane (**11**), are worthy of special comment.

(12) K. Torssell, *Acta Chem. Scand.*, **21**, 1 (1967).

(13) Despite the fact that we have now run this reaction on more than 30 olefins, we have been unable to detect ketonic or aldehydic materials in any other case.

SCHEME II



It is generally true[5] that dibromide products are not observed in reactions of olefins with NBS in DMSO unless the olefin is sterically (*e.g.*, 2,3,3-trimethyl-1-butene) or electronically (*e.g.*, *p*-nitrostyrene) inhibited from rapid reaction with NBS and DMSO, presumably because initial ion formation is difficult and there is time for bromine itself to form and react.[14] In addition, olefins (*e.g.*, 1-phenylpropene) which might form specially stabilized ions and do often[15] appear to react as α-bromocarbonium as well as bromonium ions do not, in the NBS–DMSO system, generate dibromide products, presumably because they react rapidly. In this case, however, we suggest that it is

(14) Small quantities of bromine are generated in this reaction by the oxidation of DMSO by Br^+. See, *e.g.*, (a) S. Iriuchijima and G. Tsuchihashi, *Synthesis*, 588 (1970); (b) v. D. Martin, A. Berger, and R. Peachel, *J. Prakt. Chem.*, **312**, 683 (1970).

(15) (a) J. H. Rolston and K. Yates, *J. Amer. Chem. Soc.*, **91**, 1469, 1477, 1483 (1969); (b) R. C. Fahey and H.-J. Schneider, *ibid.*, **90**, 4429 (1968).

the inability of the solvent to rapidly attack the initial ion rather than slow initial ion formation which accounts for the dibromide product.

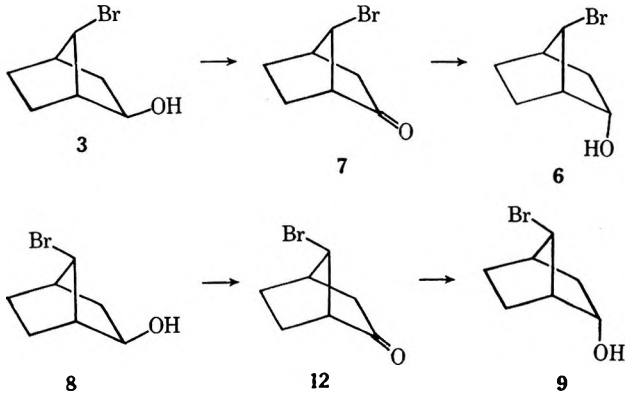
Thus, **10**[16] can arise by attack on the first formed ion from the endo direction by bromide anion or on the rearranged ion H (Scheme I) at C_2 (norbornene numbering) while attack on ions C or D would account for **11**. However, as has been recently pointed out,[7b] **10**, in another system, is also formed *via* radical addition to norbornene. We suggest that the radical pathway to **10** may be important here too, since if bromide anion were attacking the first formed ion (A or B) or the rearranged ion (H) to form this product some competition from DMSO and formation of the corresponding bromohydrin **5** would have been expected.

The complete lack of 2,3-bromohydrins, considered in light of the usual stereo- and regiospecificity of the NBS–DMSO system and the known penchant for rearrangement in the bicyclo[2.2.1]heptane system, led us to question the stability of the products found and the potential, but not obtained, bromohydrins to the reaction conditions.

To answer this question, each of the products (Table I) was resubjected to the reaction conditions (except that norbornene was excluded) and work-up, and reisolated. In addition, the bromohydrins which might have been formed were prepared and subjected to the reaction conditions.

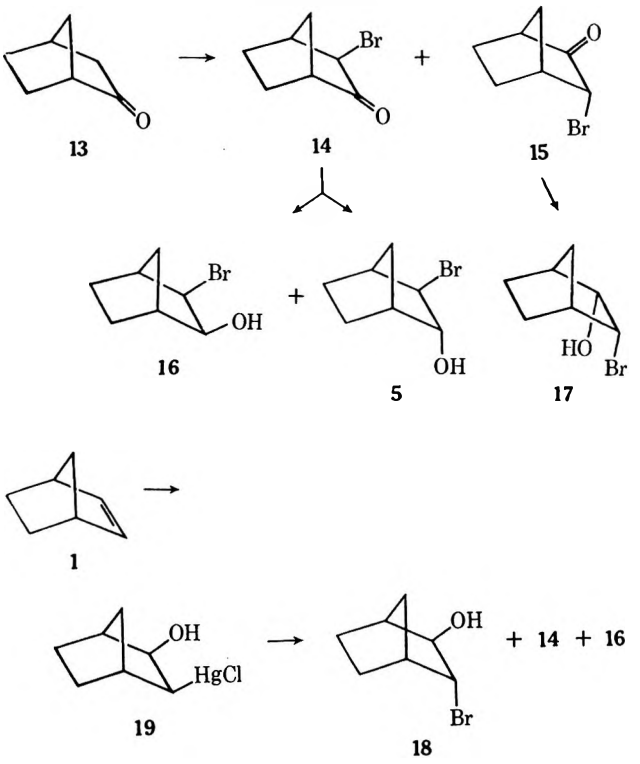
Thus, *syn*-7-bromobicyclo[2.2.1]heptan-2-one (**7**) was prepared in larger quantity by the oxidation of **3** with Jones reagent.[17] Reduction of **7** with diborane[18,19] generated a mixture of **3** and **6** in the ratio 5:3 (pmr integration), from which **6** was separated by distillation followed by column chromatography. Similarly, oxidation of **8** under the same conditions yielded *anti*-7-bromobicyclo[2.2.1]heptan-2-one (**12**) which, on reduction with sodium borohydride generated **9** exclusively (Scheme III).

SCHEME III



The 2,3-bromohydrins were prepared in a similar fashion[20] (Scheme IV). Thus, bicyclo[2.2.1]heptan-2-one (**13**) was brominated with pyridinium bromide perbromide[21] to yield a mixture (95:5 by pmr integration) of *exo*-3-bromobicyclo[2.2.1]heptan-2-one (**14**) and *endo*-3-bromobicyclo[2.2.1]heptan-2-one (**15**). The major isomer was freed from the minor one by several low-temperature crystallizations from ether. The minor isomer (**15**) could be obtained from the mother liquors by preparative gas–liquid partition chromatography (glpc) or, what was more convenient, the crude reaction mixture could be isomerized to a *ca.* 50:50 mixture of isomers with potassium *tert*-butoxide in *tert*-butyl alcohol and the separation effected.

SCHEME IV



Reduction of **14** with diborane[18,19] yielded a mixture of *exo*-3-bromobicyclo[2.2.1]heptan-2-*exo*-ol (**16**) and *exo*-3-bromobicyclo[2.2.1]heptan-2-*endo*-ol (**5**) in a 1:1 ratio from which, through repeated fractional distillation, the known **5** was isolated.

Although **16** could also be isolated from this reaction mixture, we found it more convenient to prepare it by the sodium borohydride reduction of **14**, from which a 78% yield resulted. The preferential addition of hydride to the endo face of the system presumably is accounted for by the steric effect of the bromine at the adjacent carbon.[19]

Thus, *endo*-3-bromobicyclo[2.2.1]heptan-2-one (**15**) on reduction with sodium borohydride generated, exclusively, *endo*-3-bromobicyclo[2.2.1]heptan-2-*endo*-ol (**17**) as would be expected.

The final compound required, *endo*-3-bromobicyclo[2.2.1]heptan-2-*exo*-ol (**18**), had not previously been reported. We found that it could be prepared conveniently, but in low yield, by the bromination of the known *exo*-3-mercurichloride bicyclo[2.2.1]heptan-2-*exo*-ol (**19**)[22] which also yielded, in somewhat larger quantity, **14** and **16**.

(16) Despite the small amount of dibromide **10** which is formed, we are currently attempting to determine, through the use of radical inhibitors, whether or not this material comes solely from radical sources.

(17) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 255 (1953).

(18) Diborane was obtained, as used as received, as a 1 *M* solution in THF from the Ventron Corp., Beverly, Mass.

(19) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 201 (1970).

(20) Compounds **5**, **14**, **15**, **16**, and **17** have been reported. The synthetic sequence which we used was similar to that employed by H. Krieger, *Suom. Kemistilehti A*, **31**, 340, 348 (1958); *B*, **31**, 112, 320 (1958).

(21) L. F. Fieser, "Organic Experiments," 3rd ed, D. C. Heath, Boston, Mass., 1964, p 68.

(22) T. G. Taylor and A. W. Baker, *J. Amer. Chem. Soc.*, **85**, 2746 (1963).

Each of the isolated bromohydrins was characterized and submitted, along with the compounds obtained in the initial reaction, to the conditions of the NBS–DMSO reaction. In no case could evidence for isomerization be found and the material was, in each case, recovered unchanged and in high yield (>90%).

Conclusions

The reaction of norbornene with NBS in moist DMSO leads, contrary to an earlier report, to a complicated mixture of products. It is suggested that the products arise through rearrangements characteristic of the bicyclo[2.2.1]heptane system and that the simple addition product expected is not observed because the initial bromonium or α-bromocarbonium ion experiences difficulty in being attacked by DMSO. Despite these results, however, we remain intrigued by the possibility of a solvent of sufficient nucleophilicity to carry out the desired trapping of the bromo cation before rearrangement is possible.

Experimental Section[23]

Reaction of Bicyclo[2.2.1]heptene (1) with NBS in DMSO.—The olefin 1 (37.0 g, 0.34 mol) was dissolved, with slight warming, in DMSO (300 ml). With stirring, water (14.4 g, 0.80 mol) was added and the solution was placed in an ice bath. The addition of NBS (113.2 g, 0.64 mol) was commenced and regulated so that the heat evolved was sufficient to keep the olefin in solution (5 min was required for complete addition). After the reaction mixture stirred at room temperature for 0.5 hr it was poured, with stirring, into a saturated aqueous solution (900 ml) of sodium carbonate which had been precooled by standing in an ice bath during the course of the reaction. After warming to room temperature, the aqueous solution was extracted with six portions (250 ml each) of ether and the combined ether extracts were washed with water.

The ether extract was dried over anhydrous magnesium sulfate and the solvent was removed at reduced pressure.[27] The pmr spectrum obtained on the crude residue proved to be a composite of the materials subsequently isolated. No evidence, as demonstrated by subsequent synthesis (*vide infra*), could be found for products other than those isolated.

Analysis of the Reaction Mixture. A. Glpc.—The crude ether extract was injected directly onto an XE-60 (10% on firebrick) glass column held at 155° (detector, 200°; collector, 190°; injector port, 170°; He flow rate 102 cc/min) and the products were collected in receivers cooled in Dry Ice–acetone. The analysis of the effluent is shown below (Table II).

TABLE II

Peak no.	Retention time, min	Per cent of reaction mixture	Compd[a]
1	9.69	60.75	4
2	30.47	1.66	10
3	39.90	0.95	...[b]
4	49.50	21.74	3
5	74.42	6.61	7, 8
6	98.03	8.27	11

[a] Each material isolated was reinjected under the conditions of its isolation and reisolated unchanged. In addition, collection of the *total* effluent generated a mixture whose pmr spectrum possessed all of the signals (and lacked none) found in the mixture initially placed on the column although some differences in intensities were observed. [b] Insufficient quantities of this material could be isolated. However, the retention time under the conditions specified was different from that for the bromohydrins subsequently synthesized.

B. Column Chromatography.—The crude reaction mixture, after removal of the solvent[27] (30.135 g), was placed on a column (5 cm i.d., 1000 g) equipped with an automatic fraction collector, and eluted with chloroform; 10 ml fractions were taken.

Fractions 101–137 (5.201 g) consisted of one material (tlc) which was identical with the sample collected as peak 1 from glpc and by comparison to an authentic sample (ir, pmr) was identified as nortricyclene bromide (4),[27,28] n^{20}D 1.5290 (lit.[29] n^{20}D 1.5290).

Fractions 138–189 (1.688 g) were combined and subjected to bulb-to-bulb distillation (82°, 0.3 mm) to yield a material identical with peak 6 collected from glpc. The ir and pmr spectra of this material were superimposable upon that of an authentic sample of 11,[25] n^{20}D 1.5709 (lit.[26] n^{20}D 1.5710). *Anal.* Calcd for $C_7H_{10}Br_2$: C, 33.09; H, 3.97; Br, 62.95. Found: C, 33.01; H, 3.86; Br, 62.99.

Fractions 850–1050 (4.613 g) were combined and found (tlc) to be a mixture of two compounds (3 and 7). Oxidation of the mixture with Jones reagent[17] produced a single compound (92% weight recovery) which was identified as 7 (ir, C=O, 5.69): n^{20}D 1.5552; 2,4-DNPH mp 198–199.5° (lit.[6] 201.5–202.5°). *Anal.* Calcd for $C_{13}H_{13}N_4O_4Br$: C, 42.27; H, 3.52; N, 15.13. Found: C, 42.69; H, 3.54; N, 15.13. Examination of the integrated pmr spectrum of collected glpc peak 5 indicated that this ketone constituted 33 ± 2% of that fraction.

Fractions 1051–1150 (4.723 g) were combined and the residue, on removal of the solvent, crystallized. Sublimation of this pale yellow material yielded a white, waxy solid, mp 44.5–46.0°, which proved to be identical with glpc peak 4. This material was identified as 3 by (a) elemental analysis (*Anal.* Calcd for $C_7H_{11}OBr$: C, 43.98; H, 5.75; Br, 41.88. Found: C, 43.82; H, 5.88; Br, 41.93); (b) high yield (93%) conversion to the bromo ketone 7 on treatment with Jones reagent[17] in acetone at 0° for 5 min, and (c) its spectra [ir, –OH, 2.81 (sharp) and 2.90 μ (broad); pmr (100 MHz) δ 3.88 (1 H, $W_{1/2}$ = 3.9 Hz), 3.70 (t of d, $J_{2,3\text{-cis}}$ = 6.0 Hz, $J_{2,3\text{-trans}}$ = 5.5 Hz, $J_{2,7}$ = 1.6 Hz)].

Fractions 1151–1250 (7.086 g) were a mixture (tlc) of two compounds (3 and 8). A portion of this mixture (4.0 g) was rechromatographed (2 cm i.d., 250 g) and the column was eluted with 4:1 (v/v) cyclohexane–ether (10-ml fractions were taken). In this chromatography, fractions 151–200 contained material identical with 3, while fractions 250–499 contained a new material which produced a white waxy solid (0.522 g) on sublimation. This material (mp 53–55°) was identical with the second component of glpc peak 5 by pmr and examination of the integrated pmr spectrum of glpc peak 5 indicated that this material constituted 66 ± 2% of that fraction. This material was identified as 8 by (a) elemental analyses (*Anal.* Calcd for $C_7H_{11}OBr$: C, 43.98; H, 5.75; Br, 41.88. Found: C, 43.98; H, 5.76; Br, 42.04) and (b) high yield (89%) conversion to the corresponding bromo ketone 12 on treatment with Jones reagent as outlined above [The 2,4-DNPH had double mp 119.5–120.5 and 156.5–157.2° (lit.[30] 116.5–117.5 and 151.5–152.5°). *Anal.*

(23) DMSO, Fisher Certified Reagent, was dried over molecular sieve prior to use. NBS was obtained from Arapahoe Chemical Co., Boulder, Colo., and used as received. Bicyclo[2.2.1]heptene (norbornene) was obtained from the Aldrich Chemical Co., Milwaukee, Wis., and distilled from sodium wire prior to use. Gas–liquid partition chromatography (glpc) was carried out on an Aerograph A90-P3 instrument under the conditions specified. Woelm activity grade I columns and thin layer plates of silica gel were used throughout. Infrared spectra were taken as neat oils or KBr pellets on a Beckman IR-5A spectrophotometer.[24] Proton magnetic resonance (pmr) spectra were taken on Varian A-60, A-60A, XL-100-15, and HR-220[25] spectrometers and values are expressed in parts per million (δ) relative to TMS = 0.00.[26] Melting points were obtained on a Thomas–Hoover melting point apparatus in sealed capillaries and are uncorrected. Analyses were performed by Schwartzkopf Microanalytical Laboratories, Woodside, N. Y.

(24) The spectrophotometer was purchased from funds provided by a grant (CA 08841) from the National Cancer Institute, National Institutes of Health.

(25) These spectra were graciously provided by Professor A. Lewin, Department of Chemistry, Brooklyn Polytechnic Institute, Brooklyn, N. Y. We gratefully acknowledge her interest and constructive comments.

(26) The complete details of the pmr spectra of the compounds reported here will be the subject of a future communication. Copies of the spectra are available from the senior author on request.

(27) Subsequent analysis indicated that significant (30–50%) quantities of nortricyclene bromide as well as smaller amounts of the other products may be lost on the solvent is removed.

(28) These spectra were provided by Professor N. LeBel, Department of Chemistry, Wayne State University, to whom we are grateful.

(29) H. Kwart and L. Kaplan, *J. Amer. Chem. Soc.*, **76**, 4072 (1954).

(30) A. C. Oehlschlager, C. D. Kennedy, and L. H. Zalkow, *J. Org. Chem.*, **31**, 1628 (1966).

Calcd for $C_{13}H_{13}N_4O_4Br$: C, 42.27; H, 3.52. Found: C, 42.18; H, 3.55]; and (c) spectra [ir –OH, 2.74 (sharp) and 3.00 μ (broad); pmr (100 MHz) δ 4.20 (1 H) unresolved multiplet ($W_{1/2}$ = 4.5 Hz), 3.78 (1 H) d of d ($J_{2,3\text{-cis}}$ = 7.2 Hz, $J_{2,3\text{-trans}}$ = 2.6 Hz)].

Compound **10** was not found on column chromatography. Collection of glpc peak 2 and examination of its pmr spectrum (100 MHz) led us to the conclusion (by comparison to the spectrum of an authentic sample)[7b,25] that it was *endo-exo*-2,3-dibromobicyclo[2.2.1]heptane (**10**).

***syn*-7-Bromobicyclo[2.2.1]heptan-2-*exo*-ol (3) and *syn*-7-Bromobicyclo[2.2.1]heptan-2-*endo*-ol (6).**—The bromo ketone **7** (73.2 g, 0.495 mol) was placed in THF (1 l.) and treated with diborane (550 ml of a 1 *M* solution)[18] added dropwise, with stirring, through an addition funnel. After the addition was complete, the reaction mixture was permitted to stir at room temperature for 3 hr and the resulting solution was extracted with ether (three 300-ml portions). The combined ether extracts were washed with water and dried over magnesium sulfate. Removal of the solvent yielded an orange oil (93.9 g, 99%). Analysis (pmr integration) indicated a 5:3 mixture of **3** and what was presumed to be **6**. A portion of the reaction mixture (78.8 g) was fractionated as follows (0.1 mm): fraction 1 (6.0 g), 76–78°; fraction 2, 18.0 g, 80–85°; fraction 3, 29.2 g, 85–88°; fraction 4, 11.9 g, 88–90°. In fraction 4, by pmr integration, the ratio of **3** to presumed **6** was *ca.* 3:5. The earlier fractions were recombined and distilled to yield 37.7 g of material of fraction 4 quality. This material was redistilled to yield a mixture in which the ratio of **3** to presumed **6** was 1:2.5. Chromatography (2.5 cm i.d., 500 g) utilizing 1:1 (v/v) heptane–ether as eluent (250 ml fractions) yielded presumed **6** (fractions 18–30, 3.86 g). This material crystallized from heptane–ether (4:1 v/v) yielding needles, mp 55.5–57.0°, and was characterized as **6** by (a) elemental analysis (*Anal.* Calcd for $C_7H_{11}OBr$: C, 43.98; H, 5.75; Br, 41.88. Found: C, 44.16; H, 5.77; Br, 41.66); (b) high yield (93.5%) conversion under Jones oxidation conditions (*vide supra*) to **7**; and (c) spectra [ir –OH, 2.77 (sharp), 2.98 μ (broad); pmr δ 4.47 (1 H) complex multiplet (d of t), $J_{2,3\text{-cis}}$ = 10.5 Hz, $J_{2,3\text{-trans}}$ = $J_{1,2}$ = 3.0 Hz; 4.12 (1 H), narrow multiplet].

***anti*-7-Bromobicyclo[2.2.1]heptan-2-*endo*-ol (9).**—*anti*-7-Bromobicyclo[2.2.1]heptan-2-one (**12**) (9.481 g, 0.05 mol) was dissolved in absolute methyl alcohol (200 ml) and, with stirring, sodium borohydride (1.805 g, 0.05 mol) was added over several minutes. After the addition was complete, the mixture was stirred for 0.5 hr and poured, with stirring, into water (500 ml). The aqueous solution was neutralized with dilute (6 *N*) HCl and extracted with ether (six 250-ml portions). The combined ether extracts were washed with water and dried over magnesium sulfate, and the solvent was removed to yield essentially pure **9** (8.769 g, 91.5%). Crystallization from heptane–ether (4:1 v/v) followed by several sublimations (0.03 mm) yielded material, mp 67.5–69°, which was identified as **9** by (a) elemental analysis (*Anal.* Calcd for $C_7H_{11}OBr$: C, 43.98; H, 5.75; Br, 41.88. Found: C, 43.82; H, 5.88; Br, 41.93); (b) high yield conversion (96.5%) to **12** under conditions of the Jones oxidation (*vide supra*); and (c) spectra [ir –OH 2.78 (sharp), 2.99 μ (broad); pmr δ 4.25 (1 H) d of t, $J_{2,3\text{-cis}}$ = 10.0 Hz, $J_{2,3\text{-trans}}$ = $J_{1,2}$ = 3.8 Hz].

***exo*-3-Bromobicyclo[2.2.1]heptan-2-one (14).**—Bicyclo[2.2.1]-heptan-2-one (**13**) (50.0 g, 0.453 mol) in glacial acetic acid (500 ml) was treated with pyridinium bromide perbromide[21] and the mixture was warmed on the steam bath until solution was complete (0.5 hr.). The reaction mixture was transferred to a large beaker and aqueous sodium hydroxide (12 *N*) solution was added to neutralize the acetic acid [the final stages of neutralization being completed through addition of sodium carbonate solution (10%)]. The aqueous solution was extracted with ether (five 200-ml portions) and the combined ether extract was washed with water, 10% aqueous sodium carbonate, and water and then dried over magnesium sulfate. Removal of the solvent yielded an orange acrid oil (75.1 g, 89.5%) which was, by pmr integration, predominantly (*ca.* 95%) **14** although about 5% of **15** was clearly present. The oil was dissolved in ether and crystallization was induced by cooling (−78°) and scratching. The crystals of **14** liquefied on warming to room temperature: $n^{20}D$ 1.5295 (lit.[20] $n^{20}D$ 1.5298); ir C=O, 5.80 μ; pmr δ 3.76 (1 H), d, $J_{2,7\text{-anti}}$ = 3.0 Hz; 2,4-DNPH mp 148.5–150°. *Anal.* Calcd for $C_{13}H_{13}N_4O_4Br$: C, 42.27; H, 3.52; N, 15.13. Found C, 42.53; H, 3.76; N, 15.06.

***endo*-3-Bromobicyclo[2.2.1]heptan-2-one (15).**—The concentrate from successive crystallizations of **14** was separated into two components on a 20 ft × 0.375 in. preparative glass glpc column of XE-60 (10% on firebrick) (He flow rate 110 cc/min, column temperature 160°, injector 175°, detector 170°, collector 165°). Component 1 (**14**) had retention time 27.6 min, and component 2 had retention time 35.5 min. The latter was identified as **15**: $n^{20}D$ 1.5319; ir C=O, 5.80 μ; pmr δ 4.30 (1 H), d, $J_{3,4}$ = 4.5 Hz; 2,4-DNPH mp 146.5–147.5°. *Anal.* Calcd for $C_{13}H_{13}N_4O_4Br$: C, 42.27; H, 3.52; N, 15.13. Found: C, 42.48; H, 3.32; N, 14.88. The 2,4-DNPH derivatives of **14** and **15** showed significant (*ca.* 30°) depression on admixture.

Isomerization of 14 to 15.—*exo*-3-Bromobicyclo[2.2.1]heptan-2-one (**14**) (1.58 g, 8 mmol) was dissolved in *tert*-butyl alcohol (50 ml) and treated with potassium *tert*-butoxide (896 mg, 8 mmol). After standing overnight at room temperature, the sample was diluted with water, neutralized, and extracted with ether. The ether extract was dried, the solvent was removed, and the residue was examined by pmr. The spectrum was that of a 1:1 mixture of **14** and **15**.

***exo*-3-Bromobicyclo[2.2.1]heptan-2-*exo*-ol (16) and *exo*-3-Bromobicyclo[2.2.1]heptan-2-*endo*-ol (5).**—*exo*-3-Bromobicyclo-[2.2.1]heptan-2-one (**14**) (9.361 g, 0.049 mol) was dissolved in THF (100 ml) and diborane (58 ml of a 1 *M* solution)[18] was added dropwise with stirring. The reaction mixture was allowed to stir at room temperature for 2 hr after the addition was complete. The resulting mixture was poured, with stirring, into ice–water and worked up as indicated above to yield a colorless oil (9.257 g, 91%) which was a mixture of two compounds (*ca.* 1:1 by pmr integration). A portion of this mixture (4.0 g) was fractionally distilled at 0.02 mm through an 8 in. Vigreux column to yield fraction 1, 35–40° (1.154 g), fraction 2, 40–45° (0.814 g), fraction 3, 50–53° (0.796 g), and fraction 4, 53–55° (1.118 g). In fractions 3 and 4 the ratio of the two compounds was 10:1. Combination and redistillation of fractions 3 and 4 yielded a single compound, identified as **5**: $n^{20}D$ 1.5367 (lit.[20] $n^{20}D$ 1.5375); ir, –OH, 2.78 (sharp) and 2.98 μ (broad); pmr δ 4.49 (1 H), d of d, $J_{2,3\text{-trans}}$ = 2.6 Hz, $J_{1,2}$ = 4.5 Hz, $J_{2,6\text{-exo}}$ = 1.2 Hz; 3.52 (1 H), t, $J_{2,3\text{-trans}}$ = $J_{3,7\text{-anti}}$ = 2.6 Hz. The *p*-nitrobenzoate ester was prepared, mp 129.5–130.5°. *Anal.* Calcd for $C_{14}H_{14}NO_4Br$: C, 49.43; H, 4.15; Br, 23.49; N, 4.12. Found: C, 49.38; H, 3.99; Br, 23.47; N, 4.46. This ester was hydrolyzed with methanolic aqueous sodium hydroxide to the same bromohydrin from which it was formed (84.8%) and the latter was reoxidized, under the usual conditions with Jones reagent (*vide supra*) to yield the bromo ketone **14** in 93% yield. The remainder of the reaction mixture was enriched in the other isomer and was identical with **16** as indicated below.

***exo*-3-Bromobicyclo[2.2.1]heptan-2-*exo*-ol (16). The Sodium Borohydride Reduction of 14.**—*exo*-3-Bromobicyclo[2.2.1]heptan-2-one (**14**) (15.8 g, 0.083 mol) was dissolved in absolute methanol (250 ml) and sodium borohydride (3.403 g, 0.07 mol) was added during 1–2 min. The reaction was permitted to stir at room temperature for 1 hr and was then poured into 500 ml of water, with stirring. The reaction was worked up in the usual fashion to yield a colorless oil (12.1 g, 87.6%). The oil, in heptane–ether (4:1 v/v) crystallized at −10° and the crystals were filtered off at −20°. These crystals reverted to an oil at room temperature and the latter was characterized as **16**, identical with the second component in the diborane reduction of **14** by (a) elemental analysis (*Anal.* Calcd for $C_7H_{11}OBr$: C, 43.98; H, 5.75; Br, 41.88. Found: C, 43.86; H, 5.85; Br, 42.32); (b) $n^{20}D$ 1.5376 (lit.[20] $n^{20}D$ 1.5377); (c) spectra [ir, –OH, 2.83 (sharp) and 2.90 μ (broad); pmr δ 4.06 (1 H) d of d, $J_{2,3\text{-cis}}$ = $J_{3,7\text{-anti}}$ = 2.0 Hz; 3.56 (1 H) d of d, $J_{2,3\text{-cis}}$ = 6.0 Hz, $J_{2,7\text{-anti}}$ = 1.4 Hz].

***endo*-3-Bromobicyclo[2.2.1]heptan-2-*endo*-ol (17).**—*endo*-3-Bromobicyclo[2.2.1]heptan-2-one (**15**) (1.136 g, 6.1 mmol) was dissolved in absolute methanol (25 ml) and sodium borohydride (240.5 mg, 6.4 mmol) was added during about 1 min. The reaction was stirred at room temperature and worked up in the usual fashion (*vide supra*) to yield 17 (970 mg), $n^{20}D$ 1.5426 (lit.[20] $n^{20}D$ 1.5433). *Anal.* Calcd for $C_7H_{11}OBr$: C, 43.98; H, 5.64; Br, 41.88. Found: C, 43.97; H, 5.60; Br, 42.04. Spectra follow: ir –OH, 2.83 (sharp) and 2.91 μ (broad); pmr δ 4.36 (1 H) d of d of d, $J_{2,3\text{-cis}}$ = 9.0 Hz, $J_{3,4}$ = 3.2 Hz, $J_{3,5\text{-exo}}$ = 1.2 Hz; 3.78 (1 H) d of d of d, $J_{2,3\text{-cis}}$ = 9.0 Hz $J_{3,4}$ = 3.2 Hz, $J_{3,5\text{-exo}}$ = 1.2 Hz; 3.78 (1 H) d of d of d, $J_{2,3\text{-cis}}$ = 9.0 Hz, $J_{1,2}$ = 3.3 Hz, $J_{2,6\text{-exo}}$ = 1.0 Hz.

endo-3-Bromobicyclo[2.2.1]heptan-2-*exo*-ol (18).—*exo*-3-Mercurichloridebicyclo[2.2.1]heptan-2-*exo*-ol (19)[22] (86 g, 0.25 mol) was dissolved in carbon tetrachloride (2 l.) and, with stirring, bromine (40 g, 0.5 mol) in CCl_4 (500 ml) was added through a pressure-equilibrated dropping funnel. The reaction was permitted to stir overnight at room temperature and the precipitate which formed was removed with suction filtration. The CCl_4 filtrate was washed with water and 10% sodium carbonate, and dried over magnesium sulfate. Removal of the solvent at reduced pressure yielded a dark oil (30.7 g) a portion of which (9.50 g) was chromatographed (3.5 cm i.d., 1000 g), 250-ml fractions being taken. Fractions 12–15 (0.965 g) consisted of nearly pure 14 (pmr). Fractions 17–21 (1.524 g) consisted of 16 while fractions 24–35 (1.625 g) were a new compound which crystallized on standing and was identified as 18, mp 80–81°, by (a) elemental analysis (*Anal.* Calcd for $C_7H_{11}OBr$: C, 43.98; H, 5.75; Br, 41.88. Found: C, 43.88; H, 5.76; Br, 41.26); (b) spectra [ir –OH 2.78 (sharp) and 2.90 μ (broad); pmr δ 3.91 (1 H) complex multiplet ($W_{1/2}$ = 9.0 Hz), 3.76 (1 H), t, $J_{2,3,trans} = J_{2,7\text{-}anti} = 2.1$ Hz].

Attempted Isomerization of Products in DMSO in the Presence of NBS.—The product (1.5 g) was dissolved in DMSO (25 ml). Water (0.5 ml) was added and this was followed by NBS (2.0 g). The mixture was heated to 60° and allowed to cool and stir for 0.5 hr. The work-up then paralleled that of the original reaction mixture. The resulting product (1.35–1.45 g) was examined by pmr and tlc. No evidence for rearrangement, within the limits of detectability (*ca.* 2–3%), by comparison to known mixtures, was found.

Registry No.—**1**, 498-66-8; **3**, 32819-60-6; **4**, 695-02-3; **5**, 32784-96-6; **5** *p*-nitrobenzoate, 32819-61-7; **6**, 32819-62-8; **7**, 7176-91-2; **8**, 32819-64-0; **9**, 7242-94-6; **10**, 2843-52-9; **11**, 32346-69-3; **12**, 7242-95-7; **14**, 1073-25-2; **14** 2,4-DNP, 32784-98-8; **15**, 1073-24-1; **15** 2,4-DNP, 32819-68-4; **16**, 4321-51-1; **17**, 32819-70-8; **18**, 4321-52-2; dimethyl sulfoxide, 67-68-5; NBS, 128-08-5.

A Novel Anodic Synthesis of Sulfonium Salt from Diphenyl Sulfide[1]

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Diphenyl sulfide (1), dissolved in acetonitrile containing $LiClO_4$, was electrolyzed at 30° to give diphenyl *p*-(phenylthio)phenyl sulfonium perchlorate (**3**), diphenyl sulfoxide (**4**), and 1,4-bisphenylthiobenzene (**5**). Sulfonium salt **3** predominated in the absence of water, while **4** increased as the concentration of water was raised.

The anodic oxidation of organic sulfides examined by Fichter, *et al.*,[2] gave corresponding sulfoxides, sulfones, and sulfonic acids in the mixed media of water and protic solvents such as methanol and acetic acid, but the reaction in aprotic media has received little attention except for some polarographic studies.[3,4] In the previous paper,[1] we reported an anodic oxidation of some phenyl sulfides in acetonitrile in which substrates competitively undergo either sulfoxidation or S–R bond cleavage to thiyl radical PhS· and cation R^+ through electron deficient divalent sulfide of the type $PhS\overset{+}{\underset{\cdot}{}}R$ and that the reaction pathways are controlled by the stability of the cation R^+. As an extention of the work, this paper describes a novel anodic synthesis of a sulfonium salt from diphenyl sulfide **1**.

Diphenyl sulfide **1** (465 mg, 2.5×10^{-3} mol) dissolved in 10 ml of acetonitrile containing 500 mg of $LiClO_4$ was electrolyzed at 30° using 3 cm^2 platinum foils as electrodes without separation of the anodic compartment from the cathodic. One equivalent of constant current (200 mA) was applied while terminal voltage range was 6–10 V.

Products were diphenyl *p*-(phenylthio)phenyl sulfonium perchlorate (**3**), diphenyl sulfoxide (**4**), and 1,4-bisphenylthiobenzene (**5**). No diphenyl disulfide was detected by vpc. Sulfonium salt **3** predominated in the absence of water, while sulfoxide **4** increased as the concentration of water was raised (Table I).

TABLE I

PRODUCTS OF ANODIC OXIDATION OF 1 IN ACETONITRILE

$[H_2O]^a$	1[b]	3[c]	4[c]	5[c]
0	19	71	1	4
0.1	25	63	4	3
1.0	27	46	25	2

[a] Milliliters of water in 10 ml of acetonitrile solution. [b] Recovered phenyl sulfide **1**. [c] Per cent on the basis of starting material **1**.

Sulfonium salt **3**, a slightly brown colored amorphous solid, showed a positive Beilstein test and was soluble in chloroform and acetone and insoluble in ether, benzene, and *n*-hexane. Its ir spectrum showed a strong band at 1090 cm^{-1} corresponding to sulfonium perchlorate and the nmr revealed a singlet (10 H) at τ 2.30 in $CDCl_3$ which is consistent with that of triphenyl sulfonium perchlorate.[5]

Oxidation of **3** with hydrogen peroxide in acetic acid afforded sulfone **6** (Scheme I). The sulfone **6** was subjected to nucleophilic substitution with sodium ethoxide in ethanol–tetrahydrofuran at room temperature to afford **1** (50%), *p*-ethoxyphenyl phenyl sulfone (**7**, 62%), and phenyl *p*-(phenylsulfonyl)phenyl sulfide (**8**, 2%) and phenetole **9** (2%). Treatment of **6** with benzenethiol in pyridine provided **1** (62%) and **8** (68%). Thus, sodium ethoxide and benzenethiol preferentially attack the *p*-phenylsulfonylphenyl ring to split out **1**.[6] The structures of **4**, **5**, **7**, and **8** were assigned by comparing their spectrum data with those of authentic samples prepared by the routes as described in the Experimental Section.

It was previously proposed that anodic oxidation of

(1) Electrochemistry of Organic Sulfur Compounds. III. (a) K. Uneyama and S. Torii, *Tetrahedron Lett.*, 329 (1971). (b) K. Uneyama, S. Torii, and S. Oae, *Bull. Chem. Soc. Jap.*, **44**, 815 (1971).

(2) F. Fichter, P. Sjöstedt, W. Wenk, and F. Braun, *Chem. Ber.*, **43**, 3422 (1910); **45**, 1373 (1912); **47**, 1526 (1914).

(3) M. M. Nicholson, *J. Amer. Chem. Soc.*, **76**, 2539 (1954). A. Zweig, G. Metzler, A. H. Maurer, and B. G. Roberts, *ibid.*, **89**, 4091 (1967). D. L. Coffen, J. Q. Chambers, D. R. Williams, P. E. Garrett, and N. D. Canfield, *ibid.*, **93**, 2258 (1971).

(4) P. T. Cottrell and C. K. Mann, *J. Electrochem. Soc.*, **116**, 1499 (1969).

(5) S. Oae and Y. H. Khim, *Bull. Chem. Soc., Jap.*, **42**, 1622 (1969).

(6) C. G. Swain and E. R. Thornton, *J. Org. Chem.*, **26**, 4803 (1961); H. M. R. Hoffmann, *J. Chem. Soc.*, 823 (1965); S. Oae and Y. H. Khim, *Bull Chem. Soc., Jap.*, **42**, 3528 (1969).

some phenyl sulfides affords electron-deficient intermediates of the type $PhSR^{+\cdot}$ which undergo either sulfoxidation or S–R bond cleavage depending on the stability of cation R^+. Thus, phenyl triphenylmethyl sulfide afforded diphenyl disulfide and triphenylcarbinol while phenyl methyl sulfide gave the corresponding sulfoxide as a main product. Since phenyl cation is too unstable to leave from 2, intermediate 2 would undergo electrophilic attack instead of S–Ph bond cleavage. Therefore, 2 would suffer either hydrolysis to sulfoxide 4 after disproportionation to dication and 1, or nucleophilic attack by water at the same time as further one-electron oxidation, while in the absence of water 2 or its dication would attack preferentially the para position of the phenyl ring of 1 to afford sulfonium salt 3.

Vpc analysis of the electrolysis products revealed absence of 4-(phenylthio)phenol (10) and 4-(phenylthio)acetanilide (11). This fact suggests that the cation center of 2 predominantly localizes on the sulfur atom. Formation of 5 would result from cathodic reduction of 3 as similarly as proposed in the reduction of phosphonium[7] and sulfonium salts[8] since 5 was not actually produced in the electrolysis in which the anodic compartment was separated from the cathodic with a glass filter.

The good current yield of 3 has prompted us to use the anodic reaction for a synthesis of other sulfonium salts.

Experimental Section

Materials.—Diphenyl sulfide (1)[9], phenyl sulfoxide (4),[10] benzyl phenyl sulfide,[11] 4-(phenylthio)acetanilide (11),[12] 4-(phenylthio)phenol (10),[13] 4-(phenylthio)aniline (12),[13] and 4-chlorophenyl phenyl sulfide (13)[14] were prepared as described in the literature.

1,4-Bisphenylthiobenzene (5).—The diazonium salt obtained from 1 g of 12 in a sulfuric acid solution was decomposed at 50° for 2 hr in aqueous sodium thiophenoxide (4 g of thiophenol). The neutral ether extract was dried (Na_2SO_4) and concentrated. The resulting oil was subjected to an elution column chromatography on silica gel using *n*-hexane to afford a slightly red-brown oil. The oil was fractionated by preparative vpc (SE-30, 70 cm column, 200°) to give 5 as crystals, mp 79–80.5° (lit.[15] mp 81.5°).

4-Ethoxyphenyl Phenyl Sulfone (7).—The phenol 10 (0.15 g) was stirred with 1 g of ethyl bromide in 10 ml of 1 *M* sodium ethoxide–ethanol solution for 15 hr at room temperature. The reaction mixture was poured onto ice and extracted with ether. The extract was treated as an usual manner to provide a yellow oil. Then, without purification, the oil was dissolved in 2 ml of acetic acid and stirred with 0.5 g of 30% aqueous hydrogen peroxide at room temperature for 2 hr and at 60° for 1 hr. The reaction mixture was poured on ice water and extracted with ether. The extract was concentrated to afford an oily product which was kept under suction to solidify. The solid was recrystallized twice from *n*-hexane–benzene to give 0.12 g of colorless crystals: mp 113–114°; ir (Nujol) 1595 (m), 1300–1315 and 1153 (s, $-SO_2-$), 1108 (m), and 809 cm^{-1} (w); nmr ($CDCl_3$) τ 8.63 (t, 3, $-OCH_2CH_3$), 5.96 (q, 2, $-OCH_2CH_3$), 3.10 (d, 2, ortho to ethoxy, J = 9 Hz), 2.17 (d, 2, meta to ethoxy, J = 9 Hz), 2.4–2.7 (m, 3), 2.0–2.3 (m, 2).

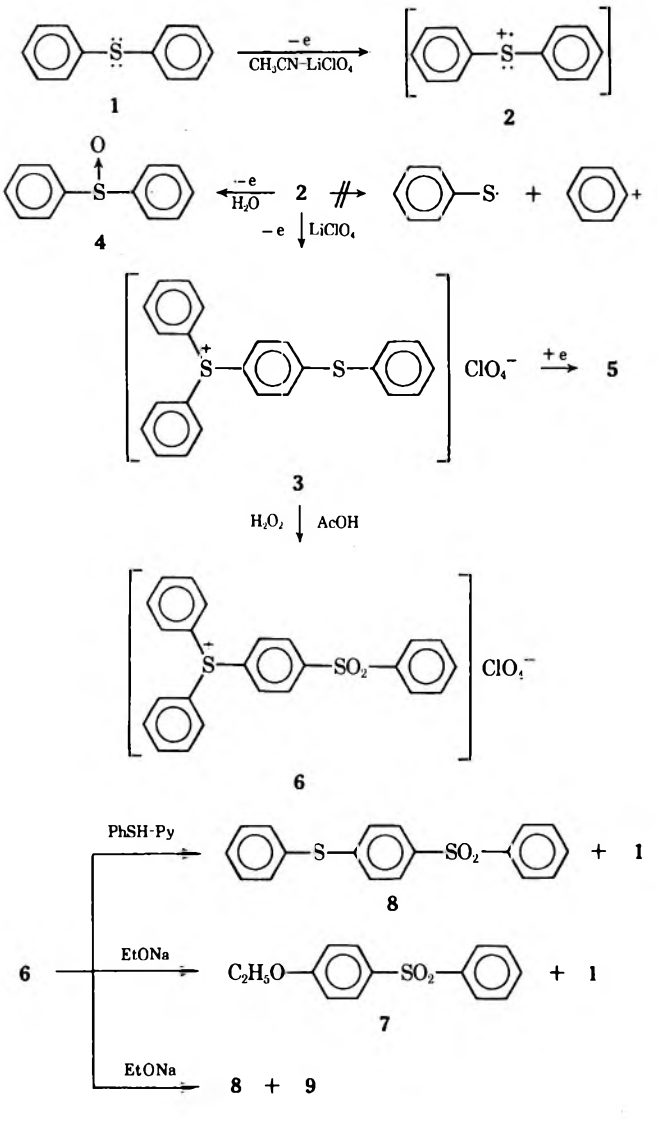
Anal. Calcd for $C_{14}H_{14}O_3S$: C, 64.10; H, 5.38. Found: C, 64.35; H, 5.36.

Phenyl *p*-(phenylsulfonyl)phenyl Sulfide (8).—The sulfide 13 (1.2 g, 5×10^{-3} mol) was stirred with 30% aqueous hydrogen peroxide (0.9 g, 1.5×10^{-2} mol) in 5 ml of acetic acid at 30° for 2 hr and 50° for 30 min. The reaction mixture was evaporated under suction and the residual oil was extracted with chloroform. The extract was washed with water, 10% aqueous sodium hydroxide and finally twice with water, dried (Na_2SO_4), and concentrated to afford crystalline product. The crude crystals, without purification, were dissolved in 10 ml of ethanol–tetrahydrofuran (1:2 mixture) containing 5×10^{-3} mol of sodium thiophenoxide and warmed with stirring at 70° for 10 hr. After evaporating the solvent, the resulting oil was combined with 100 ml of chloroform and 50 ml of water. The extract was washed with 10% aqueous sodium hydroxide and then water twice, dried (Na_2SO_4), and concentrated to give crude crystals, which were recrystallized from *n*-hexane–benzene to afford 8 as colorless crystals: mp 97–98°; ir (Nujol) 1580 (m, SPh), 1320–1310 and 1157 (s, $-SO_2-$), 820 cm^{-1} (w); nmr ($CDCl_3$) τ 2.58 (s, 5, –SPh), 2.84 (d, 2, ortho to SPh, J = 9 Hz), 2.24 (d, 2, meta to SPh, J = 9 Hz), 2.4–2.7 (m, 3), 2.0–2.2 (m, 2).

Anal. Calcd for $C_{18}H_{14}O_2S_2$: C, 66.24; H, 4.32. Found: C, 66.45; H, 4.44.

Electrolysis.—A typical run of the electrolyses was as follows. Diphenyl sulfide (0.465 g, 2.5×10^{-3} mol) was dissolved in 10 ml of acetonitrile containing 0.5 g of lithium perchlorate in a 20-

SCHEME I



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(10) A. Schönberg, *Chem. Ber.*, **56**, 2275 (1923).

(11) R. L. Shriner, H. C. Struck, and W. J. Jorison, *J. Amer. Chem. Soc.*, **52**, 2066 (1930).

(12) F. Kehrmann and R. Bauer, *Ber.*, **29**, 2365 (1896).

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(15) E. Bourgeois and A. Fouassin, *Recl. Trav. Chim. Pays-Bas*, **30**, 426 (1911).

ml tall beaker. The solution was electrolyzed at 30° using 3-cm² platinum foils without separation of an anodic compartment from a cathodic. One equivalent of constant current (200 mA) was applied while the terminal voltage was 6–10 V. An electrolysis in which an anodic compartment was separated from a cathodic was done using a cell described previously[1].

Product Analysis and Assignment.—The reaction mixture was combined with 0.100 g (5×10^{-4} mol) of benzyl phenyl sulfide as an internal standard for vpc and evaporated by suction. The resulting oily materials were extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and concentrated. The residual oil was dissolved in 50 ml of ether and stirred for 30 min. Ether was removed by decantation. The ether-insoluble product was washed twice again with each 50 ml of ether and dried under vacuum, giving 0.41 g of a slightly brown colored amorphous solid. The solid, diphenyl *p*-(phenylthio)phenyl sulfonium perchlorate (**3**), showed a positive Beilstein test: ir (Nujol) 1573 (m, SPh), 1080–1100 (s, broad, sulfonium), 815 (w), 745 (s), 683 cm^{-1} (m); nmr ($CDCl_3$) τ 2.30 (s, 10), 2.53 (s, 5), 2.41 (d, 2, J = 9 Hz), and 2.74 (d, 2, J = 9 Hz).

The ether layer was dried (Na_2SO_4) and concentrated, giving an oily material. The oil was then subjected to vpc analysis (SE-30, 1-m column, 170°) showing the existence of products, **1**, **4**, and **5**. Yields of sulfoxide **4** and sulfides **1** and **5** were obtained by calculating each peak area as compared with that of the internal standard.

To the sulfonium salt **3** (0.30 g) dissolved in 10 ml of acetic acid, 0.2 g of 30% aqueous hydrogen peroxide was added dropwise. The mixture was stirred at room temperature for 1 hr and at 50° for 1 hr and evacuated by suction to remove acetic acid. The resulting oil was dissolved in 50 ml of chloroform. The extract was washed with 5% aqueous sodium hydroxide and twice with water, dried (Na_2SO_4), and concentrated. After the resulting product was washed twice with each 50 ml of ether, the ether-insoluble product was dried and solidified under vacuum, giving diphenyl *p*-(phenylsulfonyl)phenyl sulfonium perchlorate (**6**) as an almost colorless amorphous solid (0.28 g): ir (Nujol) 1590 (w), 1330 and 1160 (s, $-SO_2-$), 1090–1100 (vs, sulfonium), 830 (w), 750 cm^{-1} (vs); nmr ($CDCl_3$) τ 2.28 (s, 10, Ph_2S^+-), 1.75–2.55 (m, 9).

Anal. Calcd for $C_{24}H_{19}O_6S_2Cl$: C, 57.30; H, 3.81. Found: C, 56.94; H, 3.95.

Reaction of 6 with Sodium Ethoxide.—Sulfonium salt **6** (0.3 g, 6×10^{-4} mol) was dissolved in 5 ml of tetrahydrofuran and 2 ml of ethanol containing 50 mg of sodium metal. The reaction mixture was stirred at room temperature for 1 day and at 70° for 20 min and then combined with 50 mg (2.5×10^{-4} mol) of benzyl phenyl sulfide as an internal standard for vpc analysis and suctioned out to remove solvent. The resulting products were washed with water and extracted with chloroform. The extract was concentrated to give oily products, which were analyzed by vpc (SE-30, 80-cm column, at 120–190°, scan rate 4°/min) giving **1** (50%), **7** (62%), **8** (2%), and **9** (2%). The product mixture was kept at room temperature overnight to crystallize in part. The crude crystals were collected and recrystallized from *n*-hexane–benzene to give colorless crystals whose ir spectrum and melting point are consistent with those of the authentic sample **7**.

Reaction of 6 with Thiophenol.—Sulfonium salt **6** (0.32 g) was stirred with 1 g of thiophenol and 1.5 g of pyridine at room temperature for 2 days. Products were analyzed by vpc as similarly as described above giving **1** (62%) and **8** (68%). Crystals obtained from the product mixture were recrystallized from *n*-hexane–benzene and were identified by comparing with authentic sample **8**.

Registry No. —**1**, 139-66-2; **3**, 32958-90-0; **6**, 32958-91-1; **7**, 14193-13-6; **8**, 32846-68-7.

The Alkaline Decomposition of Organic Disulfides. VI. Further Examples of Elimination Reactions (1,2-Dithiolanecarboxylic Acids) and of Nucleophilic Substitution

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In aqueous, alkaline solution 1,2-dithiolane-4-carboxylic acid (**1**) appears to undergo a β elimination, the primary product of which decomposes to yield α-(mercaptomethyl)acrylic acid, which has been isolated as its *S*-ethyl derivative, and hydrogen sulfide. The corresponding polymeric disulfide, $(-SCH_2CH(COOH)CH_2S-)_n$, depolymerizes to **1** instantly in alkaline solution and at measurable rates at pH values as low as 4.2. The profile of pH *vs.* rate suggests that the carboxylate ion participates in this depolymerization, a conclusion which is confirmed by the stability of the methyl ester of the polymer. In aqueous, alkaline solution both *rac*- and *meso*-1,2-dithiolane-3,5-dicarboxylic acids decompose at the same rate to yield 2-mercapto-2-pentenedioic acid by a process which is probably an α elimination initially. Dithiobis(methylcyclopropane-1-carboxylic acid) decomposes very slowly by direct nucleophilic attack of hydroxide ion on disulfide sulfur.

It has been amply demonstrated experimentally that the alkaline decomposition of organic disulfides takes place by one of three alternative pathways, as determined by secondary features of their molecular structures:[2] α elimination,[3,4] β elimination,[5] or direct nucleophilic displacement of sulfur from sulfur by hydroxide ion.[5-7] Several more disulfides have now been found to decompose *via* the pathways predictable from their structures. However, those of this group which undergo an initial elimination gave unstable intermediates which decompose further to unsaturated compounds which were not anticipated.

Jansen[8] isolated from asparagus a crude disulfide which he could not crystallize but which he successfully reduced to 2-mercaptomethyl-3-mercaptopropionic acid. Schotte and Ström[9] found that the 1,2-dithiolane-4-carboxylic acid (**1**) which they obtained by the aerial oxidation of the dithiol was appreciably contaminated by the isomeric polymeric disulfide **2**. Pure **1** was obtained by recrystallization from benzene, in which **2** is insoluble. Schotte and Ström conjectured that **1** exists in the asparagus plant and that some of it had undergone polymerization during Jansen's recovery procedure. Analogously, we recently suggested that "...

(1) Postdoctoral Research Associate, 1969–1971.
(2) J. P. Danehy, *Int. J. Sulfur Chem. B*, **6**, 103 (1971).
(3) J. P. Danehy and J. A. Kreuz, *J. Amer. Chem. Soc.*, **83**, 1109 (1961).
(4) J. P. Danehy and V. J. Elia, *J. Org. Chem.*, **36**, 1394 (1971).
(5) J. P. Danehy and W. E. Hunter, *ibid.*, **32**, 2047 (1967).
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(7) J. P. Danehy, C. J. Lavelle, and V. J. Elia, *ibid.*, **36**, 1005 (1971).
(8) E. F. Jansen, *J. Biol. Chem.*, **176**, 657 (1948).
(9) L. Schotte and H. Ström, *Acta Chem. Scand.*, **10**, 687 (1956).

all of the dihtiol passes through the dithiolane form upon oxidation by iodine."[10] As will be shown a little later, a quite different view of the relation between **1** and **2** has emerged from the present study.

The quantitative data obtained for the decomposition of **1** in aqueous, alkaline solutions are presented in Table I. Several generalizations can be drawn from them. The initial rates of decomposition are, approximately, directly proportional to the concentration of sodium hydroxide. As with so many other disulfides, there appear to be asymptotically approached levels of decomposition corresponding to each concentration of base: ~15, 37, and 45% at 0.2, 0.5, and 1.0 *N* NaOH, respectively. The ratio of H_2S to RSH increases both with increasing percentage decomposition and with increasing time to an observed high value of ~0.5. When the initial concentration of disulfide is increased ~10-fold, the ratio of H_2S to RSH does not increase further; if anything, it is somewhat lower than might have been expected. The percentage of sulfur accounted for as RSH and H_2S formed, and RSSR remaining, slowly and steadily decreases with time.

TABLE I

DECOMPOSITION OF 1,2-DITHIOLANE-4-CARBOXYLIC ACID (1) IN AQUEOUS ALKALINE SOLUTIONS AT 35.2° [a]

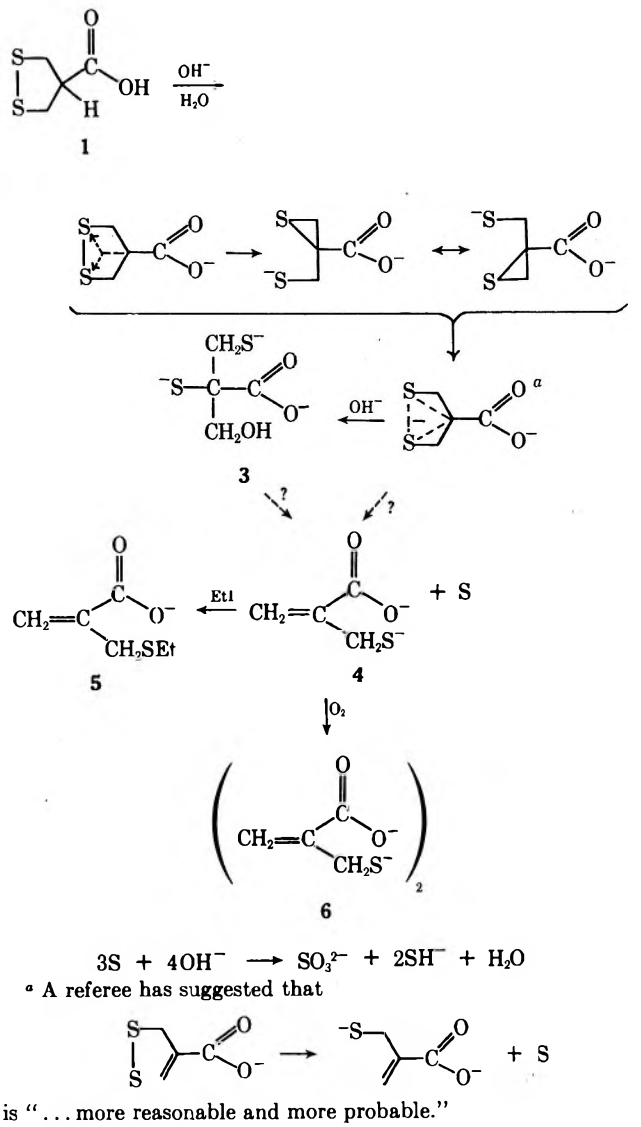
Time, hr	RSSR	RSH	H_2S	% dec	% S accounted for
0	9.36[b]				
0.33	9.14	0.44[b]	0.00[b]	2.4	100.0
0.67	9.01	0.77	0.00	3.7	100.2
1.0	8.56	0.98	0.00	8.5	96.8
2.0	8.42	1.15	0.00	10.1	96.3
7.0	8.24	1.26	0.14	12.1	95.5
23.0	8.03	1.45	0.14	14.2	94.4
0	9.49[c]				
0.33	8.99	0.99[c]	0.00[c]	5.3	100.0
0.67	8.78	1.41	0.00	7.4	100.0
1.0	8.54	1.79	0.31	9.0	100.9
2.0	8.36	2.03	0.36	11.8	100.6
23.0	7.59	2.56	0.52	20.0	96.3
168.0	5.97	3.36	1.82	37.0	90.4
0	10.50[d]				
0.33	9.09	2.82[d]	0.00[d]	13.5	100.0
0.67	8.52	3.97	0.00	18.8	100.0
1.0	8.38	4.25	0.32	20.3	101.3
2.0	7.59	4.85	0.69	27.8	98.7
6.0	7.36	4.53	0.70	29.8	95.0
8.5	6.55	4.65	0.72	37.6	88.0
24.0	6.03	5.45	1.63	42.6	91.2
52.0	5.90	5.72	2.32	43.8	89.8
0	97.5[e]				
0.33	78.2	26.2[e]	0.00[e]	19.8	93.7
0.67	69.1	39.3	3.70	29.2	93.5
1.0	68.7	40.1	4.5	29.6	93.4
2.0	64.3	46.5	7.2	34.0	93.6
5.0	60.8	37.7	12.0	37.7	88.0
10.0	59.6	40.1	14.8	38.9	89.3

[a] The methods by which the data have been obtained were fully described.[3] [b] $M \times 10^4$ in 0.2018 *N* NaOH. [c] $M \times 10^4$ in 0.508 *N* NaOH. [d] $M \times 10^4$ in 1.010 *N* NaOH. [e] $M \times 10^4$ in 1.102 *N* NaOH.

(10) J. P. Danehy, C. P. Egan, and J. Switalski, *J. Org. Chem.*, **36**, 2530 (1971).

Preparative experiments, designed to isolate the thiol formed as its *S*-ethyl derivative, yielded substantial amounts of a product, mp 49–51°, whose elemental analysis and nmr spectrum are in agreement with the structure of 2-(ethylthiomethyl)acrylic acid (**5**). Somewhat smaller amounts were obtained of a product, mp 167–173°, whose nmr spectrum and the fact that it gives a positive test with Folin's reagent[3] after reduction with zinc amalgam in aqueous hydrochloric acid are consistent with the structure for the disulfide **6** corrresponding to 2-(mercaptomethyl)acrylic acid (**4**). The mechanism presented in Scheme I accounts for, or is at least consistent with, all of these facts. The delayed appearance of the hydrogen sulfide, particularly at higher concentrations of alkali at which the initial reaction is more rapid, suggests that hydrogen sulfide arises from a secondary decomposition. The gradually decreasing sulfur balance corresponds to the stoichiometric requirement that one-third of the inorganic sulfur formed should be sulfite, which we have not determined.

SCHEME I



[a] A referee has suggested that

is "... more reasonable and more probable."

What we have suggested in Scheme I is a β elimination, formally similar to that invoked in the case of the decomposition of 3,3′-dithiodipropionic acid[5] but with several specific differences. First, the "episulfide" here

is actually a resonance-stabilized anion and can have only a partial episulfide character. Second, the hydrogen sulfide does not arise as the indirect result of a thiol–disulfide exchange reaction, as it appears to have done in the earlier case, for the relative amount of the hydrogen sulfide does not increase upon increasing the initial concentration of disulfide. Third, the eliminated moiety here remains part of the same molecule, as it did in the case of the dithiane derivatives recently reported.[4] Finally, the most striking difference is that here the first product of elimination, either the resonance-stabilized anion or **3**, undergoes a second elimination to form **4** and inorganic sulfur.

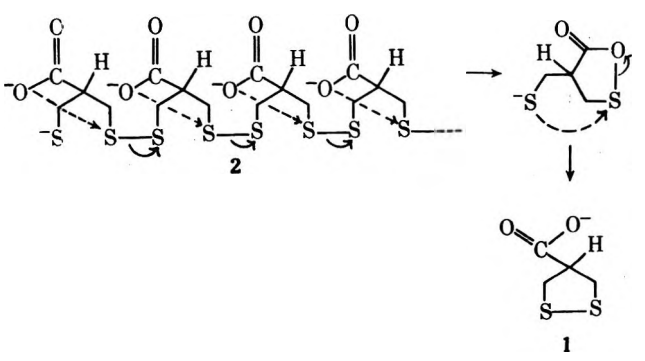
The polymeric disulfide **2** was readily prepared by heating the fused monomer **1** (mp 77°) at 130–140° for a few minutes. Traces of monomer were removed by extraction with benzene.

The results of several quantitative experiments on the alkaline decomposition of **2** matched the corresponding results for the alkaline decomposition of **1** within the range of experimental variance. This apparent identity was completely elucidated on the basis of uv absorption measurements.

Schotte[11] reported the uv absorption spectra of **1** and of its sodium salt in water, both of which have a λ_{max} at 330 nm and a λ_{min} at 280 nm. We have now found that **2** begins to absorb weakly at ~425 nm, has less than half the absorbance of **1** at the latter's maximum, but absorbs very strongly below 300 nm. Therefore, the maximum at 330 nm is a sensitive quantitative measure of the formation of **1** at the expense of **2**.

When **2** was dissolved at room temperature in 0.20 *N* NaOH, and in aqueous buffer solutions at pH 12.0, 10.7, 9.2, and 7.3, the results were the same in each case: immediate and quantitative transformation of **2** into **1**. At pH 6.40 and 5.75 the depolymerization was ~80% completed in 2 and 15 min, respectively. In 1:1 ethanol–water (v/v), self pH of 4.22, **2** was ~25, 50, and 80% depolymerized in 2, 7, and 14 days, respectively. The range of the strong dependence of the rate of decomposition on pH suggests neighboring group participation by the carboxylate anion.[12] Reference to molecular models shows that the mechanism of Scheme II is sterically very favored. The plausi-

SCHEME II



bility of this view is increased by the fact that the methyl ester of **2** in aqueous *p*-dioxane buffer at pH 9.20 shows no sign of depolymerization, even after 24 hr.

These phenomena are not without precedent. Thomas and Reed[15] have studied the linear polymeric disulfide that is related to α-lipoic acid (1,2-dithiolane-3-valeric acid) in the same way that **2** is related to **1**. They have observed both thermal polymerization of the monomer and depolymerization of the polymer in aqueous solution, but the latter ". . . did not proceed to a measurable extent in the absence of alkali . . ." so that the much more remote carboxylate anion is not likely to be involved.

Although it is of lesser interest, it may be noted that alkaline solutions of **1** undergo changes in their uv spectra at rates which depend on the concentration of base. The absorption at 280 nm increases until it no longer represents a minimum and the original λ_{max} at 330 nm is completely engulfed in the intense continuous absorption below 350 nm. These changes, of course, reflect the reactions reported quantitatively in Table I.

Racemic 1,2-dithiolane-3,5-dicarboxylic acid (**7**) was synthesized by Schotte,[16] who subsequently determined its uv and ir spectra[17,18] and resolved its enantiomorphs.[18] The crystalline structure of **7** was determined by Foss and Reistad.[19]

A priori one might expect **7** to undergo an α elimination in alkaline solution, initiated by the abstraction of a proton from one of the two equivalent carbons bonded to both sulfur and carboxylate anion. The subsequent course might correspond to that undergone by the acyclic analog, 2,2′-dithiodipropionic acid,[3] or it might resemble that of the 1,2-dithiane-3,6-dicarboxylic acids.[4] *I.e.*, the initially formed carbanion might isomerize to the thioketone **8**, which would hydrolyze to a ketone and hydrosulfide, or the hemidithioketal **9** could stabilize the molecule against loss of inorganic sulfur (Scheme III).

The quantitative data obtained for the decomposition of **7** in aqueous alkaline solutions are presented in Table II. The eventual attainment of a ~1:1 value for the ratio of hydrogen sulfide to thiol and the high values for accounting of sulfur support the α elimination of Scheme III. They also indicate that **9**, if formed at all, has only a transitory existence, as might have been predicted from its highly strained four-membered ring. The possibility of calculating reasonably satisfactory pseudo-first-order rate constants for these solutions in which alkali is in large excess suggests that proton abstraction is the rate-controlling factor and that collapse of the carbanion to form thiol (either **8** or **9** or both) is relatively rapid. The sensitivity of **7** to alkali more nearly approximates that of the *rac*-1,2-dithiane-3,6-dicarboxylic acid[4] than it does that of the much more sensitive acyclic analog.[3] One might have expected the highly strained ring (27° dihedral angle for the sulfur–sulfur bond in **7**[19] *vs.* ~90° in acyclic disulfides) to potentiate alkaline cleavage, but this is not true.

Yet **12** is not the only final product if, indeed, it is one at all. A preparative experiment, including alkyla-

(11) L. Schotte, *Ark. Kemi*, **9**, 441 (1956).
(12) An exactly analogous five-membered cyclic intermediate, a sulfenic carboxylic anhydride, has recently been invoked twice.[13,14]
(13) J. P. Danehy and M. Y. Oester, *J. Org. Chem.*, **32**, 1491 (1967).
(14) L. Field, P. M. Giles, and D. L. Tuleen, *ibid.*, **36**, 623 (1971).
(15) R. C. Thomas and L. J. Reed, *J. Amer. Chem. Soc.*, **78**, 6148 (1956).
(16) L. Schotte, *Acta Chem. Scand.*, **8**, 130 (1954).
(17) L. Schotte, *Ark. Kemi*, **8**, 579 (1956).
(18) L. Schotte, *ibid.*, **9**, 429 (1956).
(19) O. Foss and T. Reistad, *Acta Chem. Scand.*, **11**, 1427 (1957).

SCHEME III

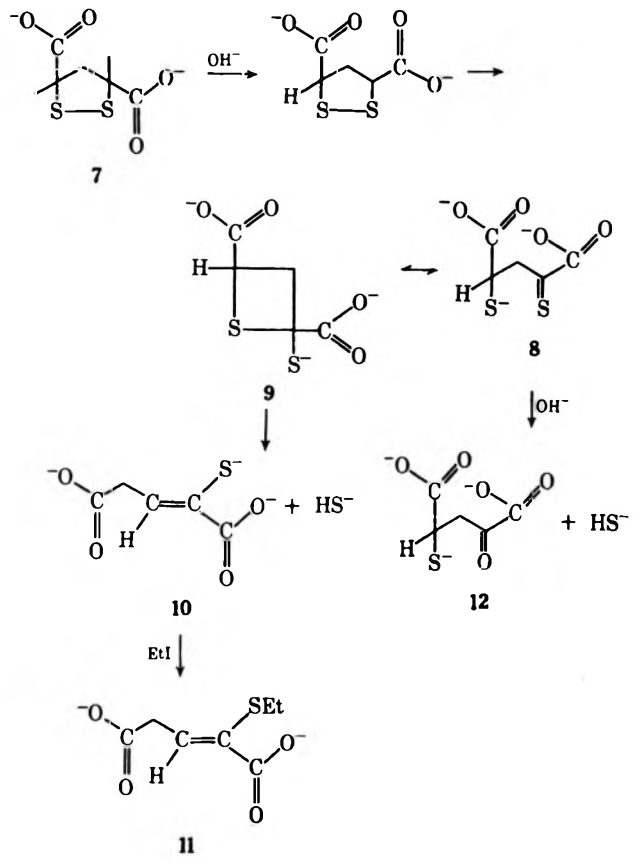


TABLE II

DECOMPOSITION OF *rac*-1,2-DITHIOLANE-3,5-DICARBOXYLIC ACID (7) IN AQUEOUS ALKALINE SOLUTIONS AT 35.2° [a]

Time, hr	RSSR	RSH	H_2S	% dec	% S accounted for	$k \times 10^4$, sec^{-1}
0	8.51[b]					
3.0	8.02	0.64[b]	0.32[b]	5.7	99.9	5.48
6.0	7.30	1.02	0.72	14.2	96.3	7.09
10.0	6.62	1.32	1.24	22.2	93.0	6.97
24.0	5.24	2.70	3.09	38.3	95.8	5.62
0	7.66[b]					
3	7.16	0.53[b]	0.25[b]	6.6	98.5	6.25
6	6.54	0.94	0.52	14.7	95.1	7.32
10.0	5.85	1.22	1.10	23.6	91.4	7.48
24.0	4.90	2.38	2.93	36.2	98.7	5.17
0	8.29[b]					
3.0	7.84	0.80[b]	0.24[b]	5.4	100.8	5.19
6.0	7.25	1.00	0.50	12.5	96.7	6.23
24.0	5.08	2.76	2.87	38.6	95.4	5.68
0	10.32[c]					
1.0	9.78	0.80[c]	0.16[c]	5.3	99.5	14.9
5.0	7.22	2.47	1.44	30.2	88.9	19.9
7.0	6.34	2.94	2.45	38.6	87.7	19.4
10.0	5.12	3.29	3.07	50.5	80.5	19.5
24.0	2.89	5.92	4.89	72.0	80.5	14.8

[a] See footnote *a* of Table I. [b] $M \times 10^4$ in 0.5190 *N* NaOH; average $k = 6.2 \times 10^{-6}$ sec^{-1}. [c] $M \times 10^4$ in 0.7785 *N* NaOH; average $k = 18. \times 10^{-6}$ sec^{-1}.

tion with ethyl iodide, gave a 30% yield of **11**, the structure for which is in agreement with elemental analysis, mass spectrum, nmr, and the fact that it slowly reacts with Folin's reagent,[3] characteristic of vinyl alkyl sulfides.

The quantitative data obtained for the decomposition of *meso*-1,2-dithiolane-3,5-dicarboxylic acid (**13**)[20] in aqueous alkaline solutions are presented in Table III.

TABLE III

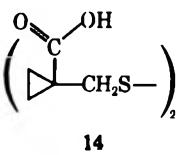
DECOMPOSITION OF *meso*-1,2-DITHIOLANE-3,5-DICARBOXYLIC ACID (13) IN AQUEOUS ALKALINE SOLUTIONS AT 35.2° [a]

Time, hr	RSSR	RSH	H_2S	% dec	% S accounted for	$k \times 10^5$ sec^{-1}
0	7.97[b]					
1.5	7.73	0.16[b]	0.04[b]	3.2	98.3	5.68
3.0	7.42	0.27	0.10	6.8	95.4	6.62
6.0	7.13	0.68	0.42	10.5	96.4	5.13
10.0	6.14	1.08	1.08	23.0	90.7	6.58
24.0	5.10	2.20	3.07	36.2	97.2	5.18
0	8.62[c]					
2.0	7.79	1.08[c]	0.26[c]	9.6	98.3	14.08
3.0	7.05	1.73	0.66	18.2	95.7	18.60
5.0	5.85	2.42	1.73	32.1	92.0	21.48
7.0	5.45	2.74	2.30	36.8	92.7	18.20
10.0	4.83	3.18	2.95	43.9	91.8	16.08
24.0	2.46	5.09	5.25	71.5	88.5	14.50

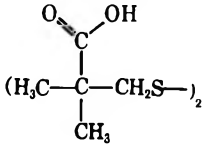
[a] See footnote *a* in Table I. [b] $M \times 10^4$ in 0.5200 *N* NaOH; average $k = 5.8 \times 10^{-6}$ sec^{-1}. [c] $M \times 10^4$ in 0.7785 *N* NaOH; average $k = 17. \times 10^{-6}$ sec^{-1}.

Comparison of the data in Tables II and III shows that the stereomers are equally sensitive to alkaline cleavage. This conclusion is in striking contrast to that drawn from the study of the corresponding dithianedicarboxylic acids[4] in which it was found that the racemic compound decomposed about 100 times more rapidly than the meso one. In that case the result was rationalized by considering that equatorial hydrogens should be more easily abstracted from a dithiane ring than the axial ones, but examination of models shows no reason why, in the rather flat dithiolane cycles, axial ones should be more difficult to abstract.

The quantitative data obtained for the decomposition of dithiobis(methylcyclopropane-1-carboxylic acid) (**14**)[21] in aqueous alkaline solutions are presented in Table IV. This compound, with protons on the carbon



14



15

α to the sulfur, but without protons on the carbon β to the sulfur, is structurally quite analogous to dithiodipivalic acid[5] (**15**), which was found to decompose, but very slowly, probably by direct nucleophilic attack of hydroxide ion on disulfide sulfur. The data in Table IV confirm the prediction: **14** is quite resistant to aqueous alkali, no hydrogen sulfide is formed at all, and at 26% decomposition the percentage of sulfur accounted for (89.8%) corresponds fairly well to the calculated value (93.5%) based on the assumption of the Schiller–Otto stoichiometry[5,6] that 75% of the sulfur from decomposed

(20) A sample of this compound (as well as a sample of **7**) was generously supplied to us by Professor Arne Fredga of the University of Uppsala. **13** had been prepared by Dr. Mats-Olov Hedblom [*Tetrahedron Lett.*, 5159 (1970)] by the oxidation of *meso*-2,4-dimercaptoglutaric acid with aqueous potassium triiodide.

(21) Again we are indebted to Professor Arne Fredga for a sample of **14** which has not yet been described in the literature.

TABLE IV

DECOMPOSITION[a] OF DITHIOBIS(METHYLCYCLOPROPANE-1-CARBOXYLIC ACID) (14) IN AQUEOUS ALKALINE SOLUTIONS AT 35.2° [b]

Time	RSSR	RSH	% dec	% S accounted for
0 day	10.22[c]			
1 day	9.9	0.62[c]	3.1	100.0
2 days	9.86	0.73	3.6	100.0
5 days	9.73	0.87	4.8	99.4
10 days	9.73	0.87	4.8	99.4
0 hr	10.47[d]			
6.0 hr	9.86	0.87[d]	5.5	98.3
11.5 hr	9.44	1.54	10.0	97.5
23.0 hr	8.89	2.55	15.2	97.0
48.0 hr	8.45	2.93	19.3	94.7
96.0 hr	7.75	3.29	26.0	89.8

[a] No H_2S detected at any time. [b] See footnote *a* in Table I. [c] $M \times 10^4$ in 1.002 *N* NaOH. [d] $M \times 10^4$ in 2.50 *N* NaOH.

disulfide shows up as thiol and that 25% of it shows up as sulfinic acid, which we do not measure. In both compounds β elimination is precluded by the absence of appropriately located protons, the carboxylate anion is too remote to labilize protons for an α elimination, and the thiolate anion displaced by nucleophilic attack is a poor leaving group (pK_a of the conjugate thiol > 10.3 in each case).

Experimental Section

Materials.—2-Mercaptomethyl-3-mercaptopropionic acid[22] was a gift from Dr. Daniel L. Klayman of the Walter Reed Army Medical Center, Washington, D. C. 1,2-Dithiolane-4-carboxylic acid (1) (mp 76–78°) was prepared in ~90% yield by the aerial oxidation of the dithiol according to Schotte and Ström[9] with the slight modification that the pH value of the solution was kept between 8 and 9 with sodium bicarbonate so that any polymeric disulfide 2 which might be formed would immediately be isomerized to monomer 1. The methyl ester of 1 was prepared by adding 1.20 g of 1 in 25 ml of ethyl ether to a freshly prepared solution of diazomethane in ethyl ether, allowing the solution to stand overnight, and evaporating the ethereal solution. The neutral yellow oil has a uv spectrum qualitatively identical with that of 1: λ_{max} at 330 nm and λ_{min} at 280 nm; nmr (benzene) δ 2.66–3.58 (J = 160–215 Hz, multiplet, 5 H), 3.30 (J = 198 Hz, s, 3 H, ester methyl). From a solution of the methyl ester of 1 in ethanol the methyl ester of 2 slowly separates as a white, amorphous solid. The uv spectrum of the latter in aqueous *p*-dioxane is qualitatively identical with that of 2. The statement, already made, that the methyl ester of 2 does not undergo depolymerization in aqueous *p*-dioxane, is to be read in the light of the fact that 2 itself does undergo depolymerization as readily in aqueous *p*-dioxane as it does in aqueous solutions at the same pH values. Polymeric disulfide 2 was prepared by heating fused 1 in the absence of air at 130–140° for several minutes until it set to a rubbery solid. The crude product was triturated with benzene to remove residual 1 and dried *in vacuo*. Both racemic 1,2-dithiolane-3,5-dicarboxylic acid (7), meso compound 13, and dithiobis(methylcyclopropane-1-carboxylic acid) (14) were gifts from Professor Fredga.

(22) Prepared by the method of J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **32**, 1261 (1967).

Transformation of 1,2-Dithiolane-4-carboxylic Acid (1) into 2-(Mercaptomethyl)acrylic Acid (4) and of the Latter into 2-(Ethylthiomethyl)acrylic Acid (5).—1 (1.015 g) was dissolved in 200 ml of aqueous sodium hydroxide (40 g of NaOH) under nitrogen at 35.2°. After 2 hr the solution was cooled in an ice bath and neutralized to pH 10 with hydrochloric acid. Ethyl iodide (3.0 g) in 150 ml of ethanol was added and the solution held for several hours until a negative test with Folin's reagent demonstrated the absence of thiol. The solution was evaporated to less than half its original volume on a rotary evaporator, the residue was acidified to pH 1 with hydrochloric acid and extracted four times with 200-ml portions of ethyl ether, and the combined ethereal extracts were dried and evaporated to dryness to leave 0.90 g of yellow oil. The portion of the oil which was soluble in chloroform was placed on a silica gel column from which was eluted, by Skellysolve B with increasing increments of ethyl ether, 0.110 g of white, crystalline material melting at 49–51°: nmr ($CDCl_3$) δ 1.23 (J = 74 Hz, t, 3 H, methyl), 2.50 (J = 150 Hz, q, 2 H, methylene), 3.40 (J = 204 Hz, s, 2 H, methylene), 5.77 (346 Hz, d, 1 H, J = 1.5 Hz, vinyl), 6.37 (J = 381 Hz, d, 1 H, J = 1.5 Hz, vinyl), 11.4 (J = 683 Hz, s, 1 H, carboxyl).

Anal. Calcd for $C_6H_{10}O_2S$ (5): C, 49.29; H, 6.91; S, 21.96. Found: C, 49.64; H, 7.17; S, 21.18.

The residue of the oil after extraction with chloroform was a white solid, melting at 167–173°. After passing through zinc amalgam with dilute hydrochloric acid it gave a strong positive test with Folin's reagent: nmr δ 3.69 (J = 221 Hz, s, methylene), 5.84 (J = 350 Hz, d, vinyl), 6.47 (J = 388 Hz, d, vinyl), in agreement with 6.

Transformation of *rac*-1,2-Dithiolane-3,5-dicarboxylic Acid (7) into 2-Mercapto-2-pentenedioic Acid (10) and of the Latter into 2-Ethylthio-2-pentenedioic Acid (11).—7 (0.535 g) was dissolved in 200 ml of 0.950 *N* NaOH under nitrogen at 35.2°. Analysis[8] showed that decomposition was ~90% complete in 15 hr. The solution was cooled, acidified to pH 1–2 with concentrated hydrochloric acid, and aspirated with nitrogen to remove hydrogen sulfide. The solution was readjusted with aqueous sodium hydroxide to pH 10–11, 1.5 g of ethyl iodide in 150 ml of ethanol was added, and the solution was allowed to stand at room temperature under nitrogen until thiol had disappeared (Folin's reagent). After concentration to half volume on a rotary evaporator the solution was reacidified to pH 1–2 with hydrochloric acid and extracted four times with 200-ml portions of ethyl ether, and the combined ethereal extracts were dried and evaporated to give an oil which, upon elution from a silica gel column with Skellysolve B–ethyl ether, yielded a white product which, after recrystallization from chloroform–Skellysolve B, amounted to 0.150 g, mp 134–136°. With Folin's reagent faint color appears after 15–30 min and rises to a maximal value in ~24 hr. The mass spectrum gave m/e 190 along with informative fragmentation; ir (KBr) 5.9 μ (=C=O), 6.2 (C=C); nmr (DMSO-d_6) δ 1.08 (J = 65 Hz, t, 3 H, methyl), 2.70 (J = 162 Hz, q, 2 H, methylene), 3.40 (J = 204 Hz, d, methylene), 7.15 (J = 429 Hz, t, 1 H, vinyl). This pattern agrees unequivocally with 11 rather than the isomeric possibility, $HO_2CCH{=}CHCH(SEt)CO_2H$.

Anal. Calcd for $C_7H_{10}O_4S$: C, 44.19; H, 5.25; S, 16.86. Found: C, 43.91; H, 5.31; S, 16.97.

Registry No.—**1**, 2224-02-4; **5**, 32687-42-6; **7**, 19307-93-8; **11**, 32687-44-8; **13**, 31413-40-8; **14**, 32687-46-0.

Acknowledgments.—We are grateful to the National Institutes of Health for the support afforded by Grant AM-13109. We are deeply indebted to Professor Arne Fredga and to Dr. Daniel L. Klayman for the gift of compounds without which this investigation could not have been made.

Solvolysis of *cis*-Bicyclo[5.1.0]oct-4-en-3-yl Tosylate

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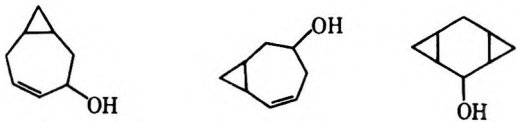
Received May 4, 1971

Bicyclo[5.1.0]oct-4-en-3-ol (1) has been prepared in ten steps from cycloocta-1,5-diene. Acetolysis of its tosylate gives *cis*- and *trans*-bicyclo[5.1.0]oct-2-en-4-yl acetate. As forbidden by orbital symmetry, the cyclopropane ring does not participate in the solvolysis. The cations produced from 1-OTs are not in equilibrium with those produced from the isomeric bicyclo[5.1.0]oct-5-en-3-yl (2) or tricyclo[5.1.0.0^{3,5}]oct-2-yl (3) esters.

The solvolyses of the esters from bicyclo[5.1.0]oct-4-en-3-ol (1), bicyclo[5.1.0]oct-5-en-3-ol (2), and tricyclo[5.1.0.0^{3,5}]octan-2-ol (3) produce ions that are formally valence tautomeric. Each ion represents a



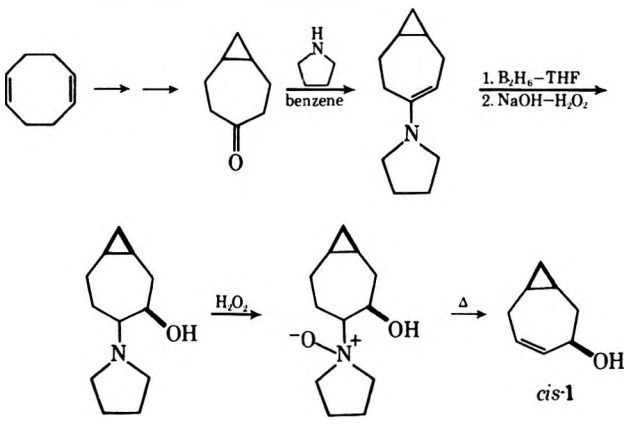
1 2 3

different mode of delocalization of charge over an eight-membered ring with unsaturation at positions 1, 2, 3, 5, and 7 relative to one another. In recent studies[2,3] we have been investigating the energy surface described by these $C_8H_{11}^+$ species. The major thrust of this study has been a description of the reactivity of 2-OTs as a function of conformation.[2] For such a study, however, it is necessary to locate the ions derived from 1 and 3 on the energy surface and to learn whether there exist allowed pathways for mutual interconversions of these ions. We have already described the solvolytic properties of 3 in relation to 2.[3] In the present paper we report the preparation of 1 and the investigations of the solvolytic properties of its tosylate. We find that the ions derived from 1-OTs are wholly insulated from the ionic manifolds generated by 2 and 3.

Results

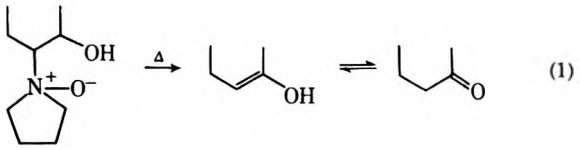
Synthesis.—The desired isomer of 1 has the hydroxyl and cyclopropyl groups cis to each other. A stereoselective synthesis is therefore required. The absence of symmetry in the molecule gives rise to synthetic difficulties, since use of the double bond to introduce the hydroxyl group, or vice versa, can produce undesired isomers. Several approaches of this type invariably gave the wrong isomer. The method depicted in Scheme I was finally developed to produce the desired alcohol *cis*-1. Bicyclo[5.1.0]octan-4-one may be obtained in five steps from cyclooctadiene by the method of Cope, *et al.*[4] The carbonyl group of this ketone lies on a molecular plane of symmetry. The method of Gore, Drouet, and Barieux[5] for conversion of a ketone to an allylic alcohol can therefore proceed in only one

SCHEME I



fashion. By this method the ketone is converted to its pyrrolidino derivative, and the enamine is converted to the saturated alcohol by the hydroboration procedure. Oxidation of the amino alcohol and pyrolysis of the amine oxide produce the desired alcohol.

This sequence was first tested on cycloheptanone and found to be satisfactory. Formation of the enamine in Scheme I was carried out under neutral conditions (refluxing benzene for 14 days), since the usual acid catalysis led to a considerable reduction in yield. A possible explanation of this observation may be drawn from the work of Stephen and Marcus.[6] The direction of the Cope elimination is of interest since an alternative mode of elimination would produce a ketone (eq 1). The end result of such a sequence



(1)

would have been simply the movement of the ketone function α to the original position. The lack of ketone formation has been attributed either to unfavorable eclipsing interactions in the transition state leading to the enol[7] or to unfavorable dipole–dipole interactions.[5] In all cases studied to date, formation of ketone is not an important side reaction.[5]

Structure Proof.—To locate the hydroxyl group both in the material prepared by the method of Scheme I and in the alcohol product of the solvolysis described in the next section, the three ketones 4–6 were prepared. It is to be noted that both 1 and 2 are related to 4. The ketones were prepared by the methods outlined in Scheme II. The structure of alcohol *cis*-2 has been

(1) (a) This work was supported by the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-AC4,5), and by the National Science Foundation (Grants GP-9257 and GP-22942). (b) National Institutes of Health Predoctoral Fellow, 1968–1970. (c) NDEA Fellow, 1967–1969.

(2) J. B. Lambert, J. W. Hamersma, A. P. Jovanovich, F. R. Koeng, S. A. Sweet, and P. J. Kucinski, *J. Amer. Chem. Soc.*, **92**, 6372 (1970).

(3) J. B. Lambert, F. R. Koeng, and J. W. Hamersma, *J. Org. Chem.*, **36**, 2941 (1971).

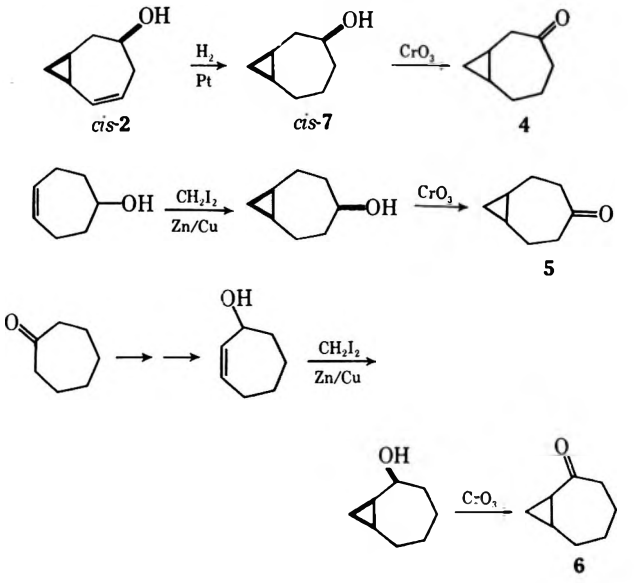
(4) A. C. Cope, S. Moon, and C. H. Park, *J. Amer. Chem. Soc.*, **84**, 4843 (1962).

(5) J. Gore, J. P. Drouet, and J. J. Barieux, *Tetrahedron Lett.*, 9 (1969).

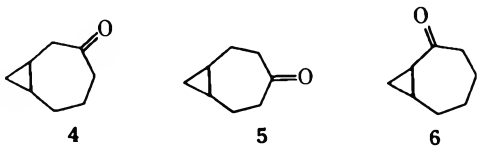
(6) J. F. Stephen and E. Marcus, *J. Org. Chem.*, **34**, 2535 (1969).

(7) A. C. Cope, E. Ciganek, and J. Lazar, *J. Amer. Chem. Soc.*, **84**, 2591 (1962).

Scheme II

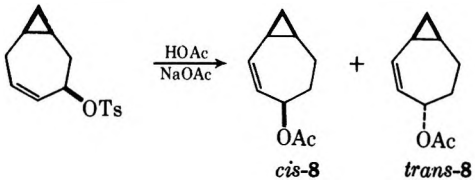


rigorously proved in a previous study.[2] Hydrogenation and Jones oxidation[8] therefore give the 3-ketone (**4**). The 4-ketone (**5**) was available from the synthesis of **1** (Scheme I). An alternative synthesis is given in Scheme II. Cyclohept-4-enol is available by a six-step synthesis due to Stork and Cope.[9] The Simmons–Smith reaction[10] on this alcohol, followed by Jones oxidation,[8] gives **5**. Cycloheptanone may be converted by the Gore procedure[5] to cyclohept-2-enol, which gives the 2-ketone (**6**) by the Simmons–Smith reaction[10] and the Jones oxidation.[8] All three ketones were easily differentiable by analytical vapor phase chromatography.



The alcohol produced by the procedure of Scheme I possessed the expected nmr and ir spectra. Hydrogenation with the Adams catalyst (PtO_2) and Jones oxidation[8] gave a ketone that proved to be **4**. The intermediate saturated alcohol was found to be identical with *cis*-**7** (Scheme II), for which an authentic sample of proved structure was available for comparison.[2] The alcohol *trans*-**1** has been produced by another procedure[11] and found to give the known[2] *trans*-**7** on hydrogenation and the same ketone **4** on subsequent oxidation. The hydroxyl group of the synthesized alcohol is therefore in the 3 position and the stereochemistry is unequivocally cis. Finally, manganese dioxide oxidation, a reaction specific for allylic alcohols,[12] gave an α,β-unsaturated (ν_{CO} = 1660 cm^{-1}) ketone. The double bond must therefore be in the assigned position. The nonallylic isomer *cis*-**2** was inert to treatment with manganese dioxide.

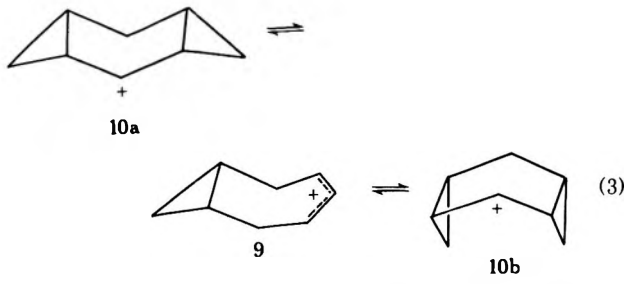
Solvolysis.—*cis*-Bicyclo[5.1.0]oct-4-en-3-ol was converted to the tosylate by Tipson's method.[13] The tosylate was solvolyzed in acetic acid buffered with sodium acetate for 14 hr at 45°. The products were isolated and reduced with lithium aluminum hydride to give two alcohols in about a 60:40 ratio. The mixture was hydrogenated and then oxidized with Jones reagent. Two different saturated alcohols in the same ratio remained after hydrogenation, but only one ketone was produced after subsequent oxidation. This material was identical with the authentic sample (Scheme II) of bicyclo[5.1.0]octan-4-one (**5**). The double bond may be introduced into the 4-alcohol in only one fashion; so the two products must be the *cis*- and *trans*-bicyclo[5.1.0]oct-2-en-4-yl acetates (**8**) (eq 2). The stereochemistry of the individual isomers in the 60:40 mixture could not be determined.



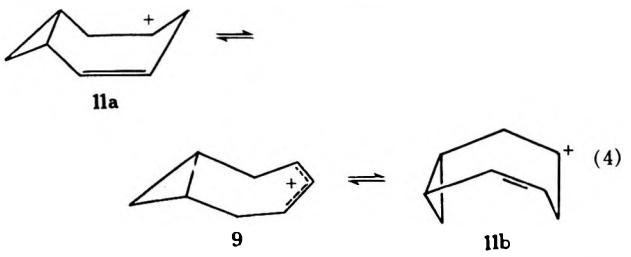
(2)

Discussion

The primary question we desired to answer was whether the allylic ion formed from *cis*-**1**-OTs is in equilibrium with the ions formed from *cis*-**2**-OTs and *cis,cis*-**3**-OPNB.[14] The allylic ion **9** may be obtained from the tricyclic ions **10** by the process depicted in eq 3[15] (note that **9** is rotated by 90° with respect to **10a** and **10b**). The ion(s) from 2-OTs (**11**, drawn without the delocalization of charge demonstrated elsewhere[2]) can give **9** by the process in eq 4 (again note the 90° rotation). Both processes have the appearance of simple valence tautomerizations to form the presumably more stable planar allylic ion, although there are also small attendant conformational



(3)



(4)

(8) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1968, p 142.

(9) G. Stork and H. Landesman, *J. Amer. Chem. Soc.*, **78**, 5129 (1956); A. C. Cope and G. L. Woo, *ibid.*, **85**, 3601 (1963); A. C. Cope C. H. Park, and P. Scheiner, *ibid.*, **84**, 4862 (1962).

(10) H. E. Simmons and R. D. Smith, *ibid.*, **84**, 4843 (1962).

(11) A. P. Jovanovich, Ph.D. Dissertation, Northwestern University, 1969.

(12) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 86 ff.

(13) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

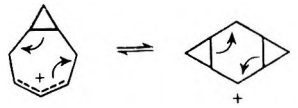
(14) The tosylate of **3** was not prepared.[2]

(15) Although there are two conformational forms of **10** and **11** (and even of **9**, not shown), the arguments presented herein are applicable to either.

changes. It has previously been demonstrated that the ions from 2-OTs and 3-OPNB are in equilibrium.[2,3]

We look to the solvolysis products to give information concerning possible ion equilibration. Under appropriate conditions,[2,3] both ions **10** and **11** give a product mixture containing *cis*-**2**, *trans*-**1**, cycloocta-3,5-dienol, and *trans*-2-vinylcyclohex-4-enol in similar proportions. Under no conditions does either 2-OTs or 3-OPNB produce the materials **8** obtained from the acetolysis of 1-OTs. Conversely, it is seen that 1-OTs produces none of the solvolytic products of **2** or **3**. Thus, although the ions **10** and **11** are in equilibrium, the allylic ion **9** appears to reside in an isolated region of the energy surface without communication with the other ions under consideration.

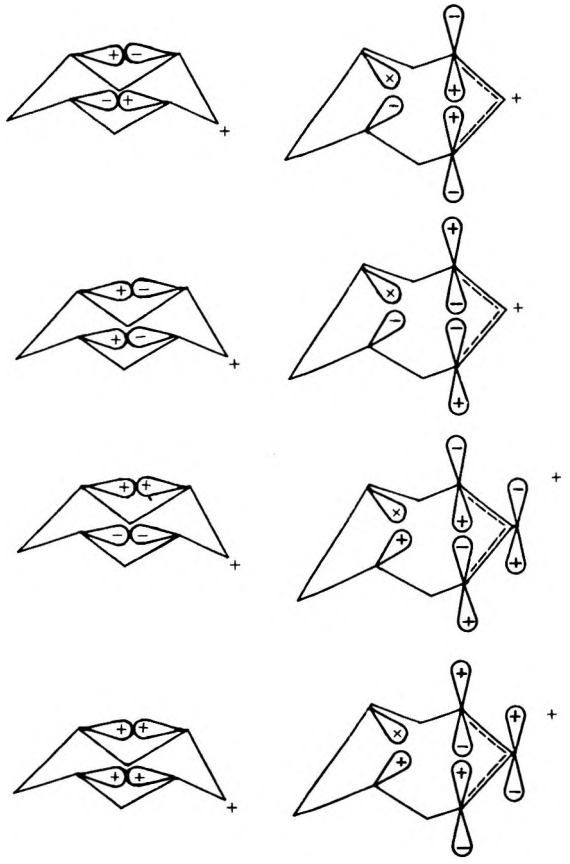
The absence of cyclopropyl participation (**9** $\rightleftharpoons$ **10**) can be understood if the process is considered to be a 2 + 2 cycloaddition of one cyclopropane bond to the allylic cation (eq 5). A concerted addition of the 2_s



(5)

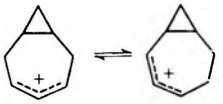
+ 2_s type is thermally forbidden by orbital symmetry. The orbitals of interest are given in Chart I for one of

CHART I



the conformations.[15] Although the lower energy bonding orbitals correlate with each other and the higher energy antibonding orbitals correlate, the reaction is forbidden because the higher bonding orbitals correlate with the lower antibonding orbitals. Other modes of cycloaddition are forbidden because they would give rise to trans-fused cyclopropane rings.[16]

Without the option of simple cyclopropane participation, the modes of reactivity available to the allylic ion are severely limited. Stepwise isomerization of **9** to the more stable allylic ion **12** (eq 6) occurs under the reaction conditions, and the products are derived from this cation.



cis- and *trans*-**8** (6)

9 **12**

Experimental Section

Infrared spectra were measured on Beckman IR-5 and IR-10 infrared spectrometers. Nmr spectra were taken on Varian Associates A-60 and T-60 nuclear magnetic resonance spectrometers. A Consolidated Electrodynamics Corp. 21-104 mass spectrometer was used for the mass spectral work. Analytical vapor phase chromatography was carried out on either a Hewlett-Packard Model 700 laboratory chromatograph or a Varian Associates Aerograph Series 1520B. Preparative vpc work was performed on the Hewlett-Packard chromatograph. Elemental analyses were performed by Miss H. Beck, Analytical Services Laboratory, Northwestern University.

Bicyclo[5.1.0]octan-4-one (**5**) was made by the method of Cope, *et al.*[4] According to this procedure, cycloocta-1,5-diene is converted to bicyclo[6.1.0]non-4-ene by the Simmons–Smith reaction,[10] and this material is oxidized to *cis*-1,2-cyclopropanedipropionic acid by $KMnO_4$. The diacid is converted to the methyl diester with diazomethane, and the diester is cyclized (NaH) to 3-carbomethoxybicyclo[5.1.0]octan-4-one, which is hydrolyzed and decarboxylated (NaOH, HCl, 100°) to the desired product. The alternative procedure[9] (Scheme II) is more laborious and lower in yield.

4-Pyrrolidinobicyclo[5.1.0]oct-4-ene.[5]—A mixture of 7.6 g (0.061 mol) of bicyclo[5.1.0]octan-4-one (**5**), 13 g (0.18 mol) of pyrrolidine, and 60 ml of benzene was refluxed for 6 days in a flask equipped with a Dean-Stark trap and a magnetic stirrer. The calculated amount of water was removed from the trap (1.1 ml). The mixture was distilled under vacuum to give 10.3 g of crude product (95%).

4-Pyrrolidinobicyclo[5.1.0]octan-3-ol.[5]—Boron trifluoride etherate (20 g, 0.14 mol) was added dropwise to a solution of lithium aluminum hydride (3.2 g, 0.084 mol) in 200 ml of ether contained in a three-necked flask equipped with a stirrer and a nitrogen-inlet tube. The solution was stirred and cooled in an ice bath, as a slow stream of dry nitrogen swept the diborane through a sintered-glass stick into a second flask containing 10.3 g (0.058 mol) of 4-pyrrolidinobicyclo[5.1.0]oct-4-ene in 70 ml of dry tetrahydrofuran. The addition of boron trifluoride took 60 min, and the nitrogen sweep was continued for another 2 hr. The tetrahydrofuran solution of the organoboron compound was kept at room temperature for an additional 12 hr. The solution was then evaporated under vacuum to give a solid product.

The solid was dissolved in 150 ml of 95% ethanol. Sodium hydroxide (8 g, 0.2 mol) was added, followed by the dropwise addition of 24 ml of 30% H_2O_2 to give an exothermic reaction. Additional ethanol (30 ml) was added, and the mixture was heated at reflux for 2 hr. It was then continuously extracted with ether for 36 hr. The organic phase was dried over $MgSO_4$ and after distillation gave 9 g (80%) of crude product, bp 81° (0.2 mm).

***cis*-Bicyclo[5.1.0]oct-4-en-3-ol** (*cis*-**1**).—To a solution of 5 g (26 mmol) of the amino alcohol in 3.5 ml of methanol was added 2.9 g (26 mmol) of 30% H_2O_2. A considerable amount of heat was generated after the peroxide addition. After 2 hr at room temperature, another portion (2.9 g) of H_2O_2 was added. A third portion (2.9 g) of peroxide was added after an additional 4 hr. The reaction mixture was allowed to stand for 45 hr, and

(16) Since the preparation of this manuscript, the failure of a cyclopropane ring to cycloadd to an allylic cation has also been demonstrated in a different system by A. F. Diaz, D. L. Harris, M. Sakai, and S. Winstein, *Tetrahedron Lett.*, 303 (1971).

excess H_2O_2 was destroyed with platinum black. Most of the methanol and water in the reaction mixture was removed on a rotary evaporator. The residue was then dried under vacuum to give a white solid (the amine oxide).

The flask containing the dry white solid was connected to a Dry Ice–acetone trap by means of a stopcock adapter. The system was evacuated to <0.3 mm. The flask containing the solid was then heated slowly to 150° and kept at this temperature until no further material distilled from the flask. The distillate in the trap was transferred to a separatory funnel with 120 ml of ether. The ether solution was extracted three times with 30-ml portions of 1 *N* HCl. The aqueous acid extracts were combined and extracted once with 50 ml of ether. The ether solutions were combined, extracted twice with 20-ml portions of saturated aqueous $NaHCO_3$ solution, and dried over $MgSO_4$. The solution was filtered and stripped of solvent. The reaction mixture was purified by column chromatography with silica gel as the solid phase and 15% ether–85% hexane (by volume) as the eluent. A mass spectrum of the purified product had the correct parent at *m/e* 124. *Anal.* Calcd for $C_8H_{12}O$: C, 77.38; H, 9.74. Found: C, 77.19; H, 9.52.

That the product possessed the correct structure was shown by the following chemical tests. Approximately 75 mg of the product was stirred with 0.5 g of MnO_2 in 5 ml of $CHCl_3$ for 48 hr at room temperature. The mixture was filtered and the solvent removed under aspirator vacuum distillation. The infrared spectrum of this product had a strong absorption at 1660 cm^{-1}, indicating than an α,β-unsaturated ketone was present and consequently that the starting material was an allylic alcohol. The position and stereochemistry of the hydroxyl group was proved by hydrogenation over platinum and subsequent Jones oxidation[8] of the purified pyrolysis product. The hydrogenation product was *cis*-7 and not *trans*-7, as indicated by comparison with an authentic sample (ir spectrum and vpc retention time with 20 ft × 1/8 in. 12% Carbowax on Chromosorb G column). The ketone obtained after Jones oxidation was **4** (verified by vpc retention time and ir analysis). Prominent infrared absorptions (cm^{-1}) of *cis*-**1** are as follows: 3350 (s), 3010 (m), 2870 (m), 2720 (w), 1650 (w), 1465 (m), 1040 (s), and 990 (s). The nmr spectrum ($CDCl_3$) consisted of δ 0.1 (m, 2, cyclopropane ring), 1.5 (m, 6, cyclopropane and cycloheptane ring), 3.2 (s, 1, OH), 4.2 (m, 1, CHO), and 5.7 (m, 2, alkenic protons).

***cis*-Bicyclo[5.1.0]oct-4-en-3-yl tosylate** (*cis*-**1**-OTs) was prepared by Tipson's method.[13] Though not crystalline, the material was pure by nmr spectroscopy. The tosylate was subjected to buffered acetolysis for 14 hr at 45°[3] and analyzed by the procedures previously described (acetates → unsaturated alcohols → saturated alcohols → ketone). The products from this solvolysis were identified as the *cis*- and *trans*-bicyclo[5.1.0]-oct-2-en-4-yl acetates.

Bicyclo[5.1.0]octan-2-one (**6**) was obtained by the method of Scheme II. Since the material is not related to any described in this study, the details have been recorded elsewhere.[11]

***cis*-Bicyclo[5.1.0]octan-3-ol** (*cis*-**7**) was obtained by hydrogenation of *cis*-bicyclo[5.1.0]oct-5-en-3-ol[2] over the Adams catalyst (hydrogenated PtO_2). This catalyst was found not to open the three-membered ring, whereas palladium on charcoal gave considerable ring opening. Cope, *et al.*,[4] prepared the identical material by a different route.

Bicyclo[5.1.0]octan-3-one (**4**) was prepared by the Jones oxidation[8] of *cis*-**7**. This material was identical with that prepared by Cope, *et al.*[4]

Registry No.—*cis*-**1**, 32675-19-7; *cis*-**1** tosylate, 31026-60-5; **4**, 32675-20-0; 4-pyrrolidinobicyclo-[5.1.0]octan-3-ol, 32675-21-1.

The Persistence of the 1-Axial Preference in Thianes

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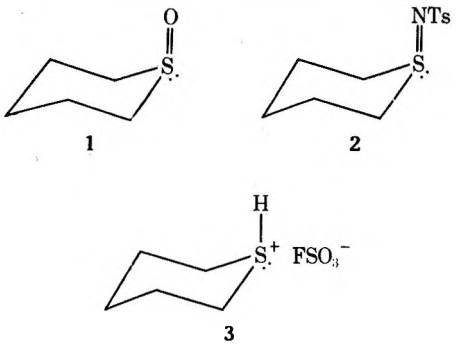
Received May 27, 1971

The axial preference of the oxide in thiane 1-oxide and of the imide in thiane 1-(*N*-tosyl)imide is reversed in the presence of a 3,3-dimethyl group, because of the syn-axial interaction. In protonated 3,3-dimethylthiane, however, the 1 proton persists in the axial position, despite the syn-axial interaction. The 4,4-dimethyl derivatives of the 1-oxide, the 1-(*N*-tosyl)imide, and the protonated form all have the normal 1-axial preference. 4,4-Dimethylthiane 1-oxide 1-imide and its *N*-tosyl derivative have also been examined and found to exist as two conformers.

A curious property of the thiane system is the preference of certain 1 substituents for the axial position. Thus in thiane 1-oxide (**1**),[2] thiane 1-(*N*-tosyl)imide (**2**),[3] and protonated thiane (**3**),[4] the 1-axial conformation is favored, respectively, by 175 cal/mol (−90°), 145 cal/mol (−89°), and >1500 cal/mol (−30°). An attractive interaction between the 1 substituent and the 3,5-axial protons has been invoked to explain this unusual preference for the case of the 1-oxide.[5] The preference must be unrelated to similar observations recently reviewed in terms of the "gauche effect,"[6] of which the anomeric effect is one example, since interactions between two polar bonds are the determining factor in these systems.



1 2 3

If the 1-axial preference is caused by an attractive 1,3 interaction, replacement of a 3-axial proton by a methyl group should make the interaction repulsive (or less attractive) and decrease the proportion of the 1-axial isomer. We have previously used this technique to explore the NH axial preference in piperidine[7] and the methyl–halogen syn-axial interaction in the 1-halo-

(1) (a) This work was supported by the National Science Foundation (Grants GP-9257 and GP-22942) and the Petroleum Research Fund, administered by the American Chemical Society (Grant 2970-AC4,5). (b) National Science Foundation Trainee, 1968–1969.

(2) J. B. Lambert and R. G. Keske, *J. Org. Chem.*, **31**, 3429 (1966).

(3) J. B. Lambert, C. E. Mixan, and D. S. Bailey, *Chem. Commun.*, 316 (1971).

(4) J. B. Lambert, R. G. Keske, and D. K. Weary, *J. Amer. Chem. Soc.*, **89**, 5921 (1967).

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

(6) S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc. B*, 136 (1971).

(7) J. B. Lambert, D. S. Bailey, and B. F. Michel, *Tetrahedron Lett.*, 691 (1970).

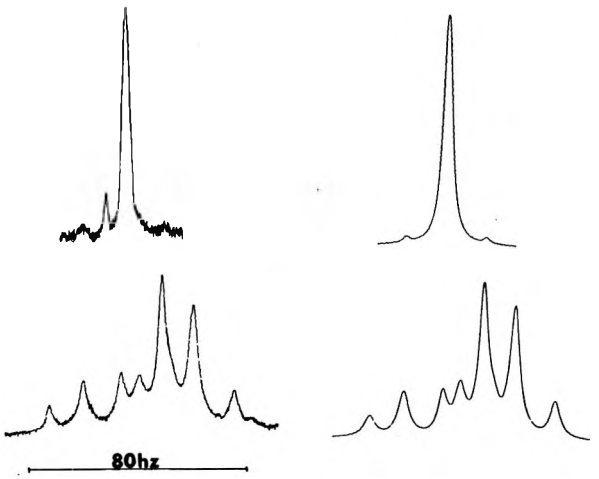
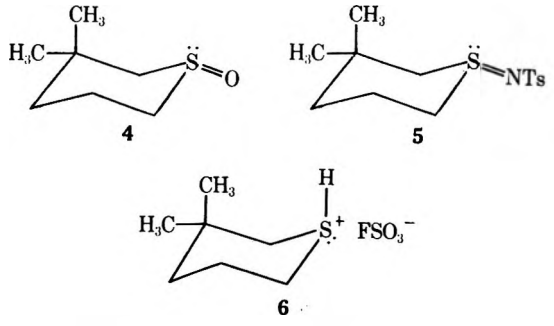


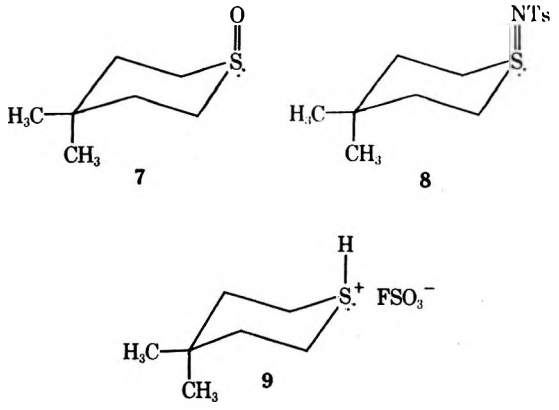
Figure 1.—The observed (left) and calculated 90-MHz spectra of the 6α protons of 4,4-dimethylthiane-2,2,6,6-d_4 1-oxide (7-d_4) in $CHClF_2$ at 30° (upper) and −90°. The small impurity peak visible to the left of the 30° spectrum is due to the sulfone.

3,3-dimethylcyclohexanes.[8] In piperidine, the proportion of the NH-equatorial isomer is increased, and in the halocyclohexanes the proportion of equatorial halogen is raised in an increasing fashion in the order F < Cl < Br < I.

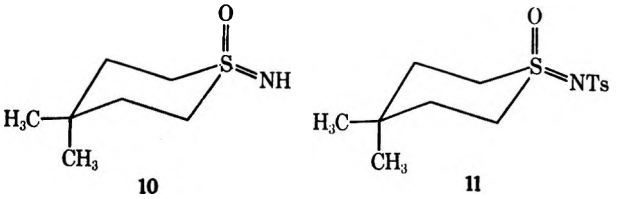
To explore the reasons for the axial preferences in the thiane series, we have prepared the 3,3-dimethyl derivatives of thiane 1-oxide (**4**), thiane 1-(*N*-tosyl)imide (**5**), and protonated thiane (**6**). We find that the oxide



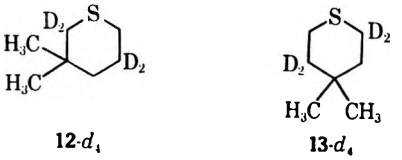
and imide become all (>95%) equatorial, but that the protonated compound remains in the axial conformation. As models for assessing the effect of a geminal dimethyl grouping, the 4,4-dimethyl derivatives **7**–**9** have



also been prepared. These compounds maintain a predominance of the 1-axial isomer. We have also examined the sulfoximides **10** and **11** to determine whether oxide or imide has the greater preference for the axial position.

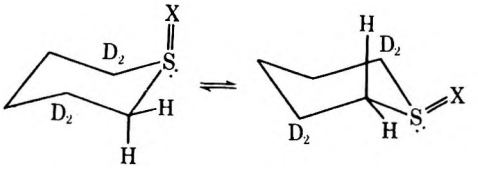


Synthesis.—3,3-Dimethylthiane (**12**) and 4,4-dimethylthiane (**13**) are the sources of all eight compounds under study (**4**–**11**). To assign the configuration of the 1 substituent, chemical-shift and coupling-constant data must be obtained for the α protons[2-4] (*vide infra*). There are two different sets of α protons (2 and 6) in the 3,3-dimethyl case. Only the unperturbed set on the side opposite the methyl groups (the 6 protons) gives unambiguous shielding information. To isolate the α protons from coupling to the β protons and to remove the 2α protons for the 3,3-dimethyl case, the deuterated derivatives **12**-d_4 and **13**-d_4 are required. Both compounds come from the same synthetic route, outlined in Scheme I. The 3,3-dimethyl- and 4,4-dimethylthianes were separated by preparative gas chromatography. The alterations of the functionality at sulfur are illustrated for the 4,4-dimethyl series in Scheme II.



Results and Discussion

The Oxides and the Imides.—The two possible conformers, with methyl substitution omitted, are given by the structures in eq 1. In the 4,4-dimethyl



(1)

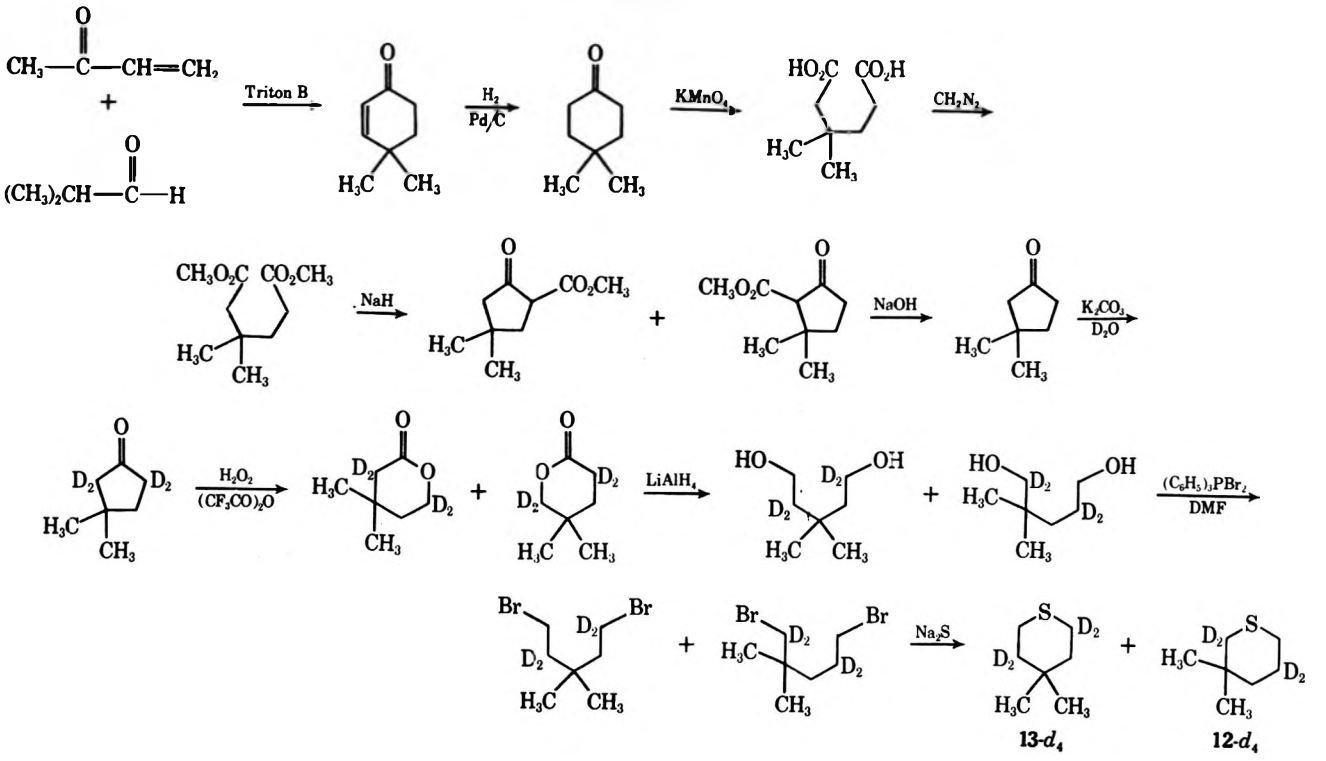
series, both forms are present at equilibrium for both the oxide **7**-d_4 and the imide **8**-d_4, since the α-proton resonance consists of two AB spectra at −90° (Figure 1). The AB quartet from the isomer with the oxide or imide group equatorial (lone pair axial) has been found always to have the larger chemical-shift difference [$\delta_{ae}(\alpha)$], the smaller coupling constant [$J_{ae}(\alpha)$], and the lower field centerpoint.[2,3,9]

In the spectrum (Figure 1) for 4,4-dimethylthiane 1-oxide (**7**) at −90°, peaks 1, 2, 4, and a shoulder on the right side of peak 5 correspond to the equatorial-oxide isomer, whereas peaks 3, 5, 6, and 7 correspond to the axial-oxide isomer. Configuration was assigned by the

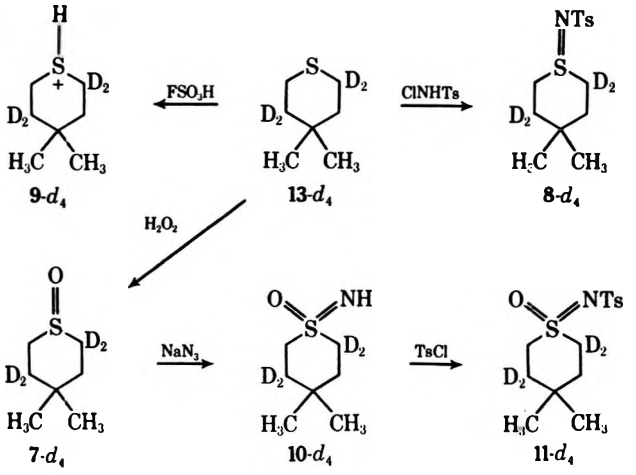
(8) D. S. Bailey, J. A. Walder, and J. B. Lambert, *J. Amer. Chem. Soc.*, **94**, 177 (1972).

(9) (a) J. B. Lambert, C. E. Mixan, and D. S. Bailey, *ibid.*, **94**, 208 (1972); (b) A. B. Foster, T. D. Inch, M. H. Qadir, and J. M. Webber, *Chem. Commun.*, 1086 (1968); (c) R. R. Fraser and F. J. Schuber, *Can. J. Chem.*, **48**, 633 (1970); (d) B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky, *J. Amer. Chem. Soc.*, **91**, 3839 (1969); (e) D. H. R. Barton, F. Comer, and P. G. Sammes, *ibid.*, **91**, 1529 (1969); (f) Y. Allingham, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **24**, 1989 (1968); (g) P. J. Chivers and T. A. Crabb, *ibid.*, **26**, 3389 (1970).

Scheme I



Scheme II



above criteria, and the populations were determined during the process of spectral fitting. The chemical-shift, coupling-constant,and population data are listed in Table I. The axial-oxide isomer predominates by a 70:30 ratio at −90°, compared to 62:38 in the unmethylated compound.[2]

4,4-Dimethylthiane 1-(*N*-tosyl)imide (**8**) gives a very similar spectrum, and the axial-imide isomer was found to predominate by 73:27 ratio (Table I), compared to 60:40 in the unmethylated compound.[3] One anomaly is noted in the spectrum, since $\delta_{ae}(\alpha)$ is smaller for the equatorial than for the axial isomer. The 4-axial methyl group is expected to have this kind of shielding effect on the α protons.[10] Thus, $\delta_{ae}(\alpha)$ is sensitive not only to the configuration at sulfur but also to substitution elsewhere in the molecule. The criterion is quite reliable in molecules unsubstituted except at the 1 position, but introduction of substituents elsewhere can lead to extraneous effects on $\delta_{ae}(\alpha)$. The coupling-constant criterion is not subject to this limitation; so it is reliable for any kind of substitution. Henceforward in this paper we will use the coupling-constant criterion exclusively.

As the temperature is raised, the axial and equatorial forms of **7** and **8** interconvert more rapidly (eq 1), so that the spectrum at room temperature represents an average for the two conformers (Figure 1).

The β-proton resonances of **7** and **8** have also been analyzed (Table II). The only important points to note are that the proportions agree with those from the α resonances (Table I) and that $J_{ae}(\beta)$ is normal (~14 Hz). For the α protons, J_{ae} is normal when the lone pair is equatorial, but small (~12 Hz) when the lone pair is axial (oxide or imide equatorial). The fact that $J_{ae}(\beta)$ for both isomers in eq 1 is the same as $J_{ae}(\alpha)$ for the axial-oxide or -imide isomer demonstrates that a vicinal axial lone pair is required for observation of the "abnormal" 12-Hz coupling.[2,3,9]

In contrast to the 4,4-dimethyl cases, the low-temperature spectra of 3,3-dimethylthiane 1-oxide (**4**) and 3,3-dimethylthiane 1-(*N*-tosyl)imide (**5**) show only a single AB quartet for the α protons, indicative of the presence of only one isomer. A second AB quartet could not be found even at high gain. For the oxide, $J_{ae}(\alpha)$ is 12.0 Hz from room temperature to −110°; for the imide, $J_{ae}(\alpha)$ is 12.4 Hz from room temperature to −80° (Table I). Since these coupling constants are "abnormal," the AB spectrum is attributed to the equatorial isomer (axial lone pair) for both the oxide and the imide. The AB quartet does not collapse to an A_2 spectrum at higher temperatures because only one form is present. The constancy of $J_{ae}(\alpha)$ with temperature is a further indication that the equatorial isomer is present exclusively (>95%). The spectra of the γ protons have also been analyzed for both compounds (Table II).

(10) H. Booth, *Tetrahedron*, **22**, 615 (1966).

TABLE I

SPECTRAL PARAMETERS FOR THE α PROTONS OF THE *gem*-DIMETHYL DERIVATIVES OF THIANE 1-OXIDE AND THIANE 1-(*N*-TOSYL)IMIDE[a]

	7	8	4	5	1[b]	2[b]
$\delta_{ae}(\alpha)$	30.8	6.0	94.0[c]	46.0	78.3[d]	33.2
$\lvert J_{ae}(\alpha)\rvert$	12.4	12.5	12.0	12.4	11.7	12.0
Pop.	0.30	0.27	>0.95	>0.95	0.38	0.40
$\delta_{ae}'(\alpha)$	21.0	15.4	*e*	*e*	43.2[d]	2.0
$\lvert J_{ae}'(\alpha)\rvert$	14.9	14.8			13.7	14.4
Pop.′	0.70	0.73			0.62	0.60
Solvent	$CHClF_2$	CH_2Cl_2–$CHClF_2$	$CHClF_2$	CH_2Cl_2–$CHClF_2$	CH_2Cl_2	$CHClF_2$
Temp, °C	−90	−90	−90	−80	−90	−89
$\Delta G°$, kcal/mol[f]	−305	−360	>+1300	>+1300	−175	−145

[a] All chemical-shift differences are in hertz at 90 MHz, and coupling constants are in hertz; δ, *J*, and Pop. (population) refer to the lower field (equatorial) isomer; δ′, *J*′, and Pop.′ refer to the higher field (axial) isomer. [b] Data from ref 2 and 3. [c] The magnitude of $\delta_{ae}(\alpha)$ for **4** is temperature dependent (73.5 Hz at 35°), but $J_{ae}(\alpha)$ is constant. [d] Data from 60 MHz converted to 90 MHz. [e] The axial isomer was not observed. [f] A positive sign for $\Delta G°$ denotes an excess of equatorial oxide or imide.

TABLE II

SPECTRAL PARAMETERS FOR THE β AND γ PROTONS OF THIANE 1-OXIDE, THIANE 1-(*N*-TOSYL)IMIDE, AND THEIR *gem*-DIMETHYL DERIVATIVE[a]

	7	8	4	5	1[b]	2[b]
$\delta_{ae}(\beta)$	62.0	73.0	*c*	*c*	*c*	*c*
$\lvert J_{ae}(\beta)\rvert$	14.3	14.4				
Pop.	0.70	0.73				
$\delta_{ae}'(\beta)$	3.6	7.0				
$\lvert J_{ae}'(\beta)\rvert$	14.0	14.4				
Pop.′	0.30	0.27				
$\delta_{ae}(\gamma)$	*d*	*d*	8.35	11.0	30.6[e]	40.0
$\lvert J_{ae}(\gamma)\rvert$			14.8	13.6	14.0	14.4
Pop.			>0.97	>0.97	0.62	0.60
$\delta_{ae}'(\gamma)$			*f*	*f*	36.2[e]	41.6
$\lvert J_{ae}'(\gamma)\rvert$					14.3	14.2
Pop.′					0.38	0.40

[a] All chemical-shift differences are in hertz at 90 MHz, and coupling constants are in hertz; δ, *J*, and Pop. refer to the lower field isomer; δ′, *J*′, and Pop.′ refer to the higher field isomer; the solvents and temperatures are given in Table I. [b] Data from ref 2 and 3. [c] No data on the β protons are available. [d] No data on the γ protons are available. [e] Data from 60 MHz converted to 90 MHz. [f] Only one isomer is observable.

Again, in both cases only one AB quartet is found over the entire temperature range and $J_{ae}(\gamma)$ is normal.

From the data in Table I, it is seen that the 4,4-dimethyl oxide and imide have an even greater proportion of the axial isomer than do the unmethylated compounds. The quaternary carbon at position 4 is puckered from the normal position because the C(3)–C(4)–C(5) angle is reduced. As a result, the 3- and 5-axial protons are bent away from the 1 position, thereby permitting a larger proportion of axial oxide or imide. This effect has also been observed in the 1-halo-4,4-dimethylcyclohexanes.[8] The increase in the proportion of the 1-axial conformer thus seems to be general for molecules with the 4,4-dimethyl grouping.

Introduction of the *gem*-dimethyl grouping at the 3 position, on the other hand, completely obliterates any axial isomer. The syn-axial interaction between the methyl group and the oxide or imide must be greater than 2 kcal/mol to reverse the preference so drastically.

Protonated Thianes.—Thiane is readily protonated in FSO_3H–SO_2.[4] The solution is indefinitely stable at room temperature, but spectra must be taken below −20° in order to slow down exchange of the proton on sulfur. For the parent, unmethylated compound (β deuterated), the resonance for the S proton is a triplet of triplets, with the 1,2-vicinal couplings analyzed to be $J_{H_{ax}CSH}$ = 14.1 Hz and $J_{H_{eq}CSH}$ = 2.3 Hz. A considerable volume of data is available that attests to the fact that H–X–C–H couplings follow a Karplus-like curve.[11] The 14.1-Hz vicinal coupling therefore requires that the proton on sulfur be axial. No resonances were observed for the equatorial isomer.

4,4-Dimethylthiane-*2,2,5,5*-d_4 was dissolved in FSO_3–H–SO_2 and the proton spectrum of **9**-d_4 was examined at −40° and 90 MHz. The 3β proton was a closely coupled AB quartet, $\delta_{ae}(\beta)$ = 21 Hz, $J_{ae}(\beta)$ = 15.3 Hz. The 6α resonance consisted of an AB quartet distorted to ABX by coupling with the proton on sulfur (Figure 2). Analysis of the three-spin system gave $\delta_{ae}(\alpha)$ = 9 Hz, $J_{ae}(\alpha)$ = 15.0 Hz. The 4-axial methyl group, as noted before, decreases $\delta_{ae}(\alpha)$.[10] The S–H resonance was a second-order quartet (the X part of the ABX spectrum), from which were obtained $J_{H_{ax}CSH}$ = 12.7 Hz and $J_{H_{eq}CSH}$ = 5.2 Hz. The value of 12.7 Hz for the vicinal coupling requires that the proton on sulfur be in the axial position. The normal value of the geminal coupling, $J_{ae}(\alpha)$ = 15.0 Hz, further indicates that the lone pair is equatorial. No resonances were discernible for an equatorial isomer. Since a 4,4-dimethyl grouping is known to enhance the proportion of a 1-axial substituent, this result is fully expected.

The spectrum of 3,3-dimethylthiane-*2,2,5,5*-d_4 in FSO_3H–SO_2 (**6**-d_4) at −40° resembled very closely that of **9**-d_4. The γ resonance was an AB quartet, $\delta_{ae}(\gamma)$ = 9.5 Hz, $J_{ae}(\gamma)$ = 14.8 Hz, and the α resonance (Figure 3) was the AB part of an ABX spectrum, $\delta_{ae}(\alpha)$ = 29 Hz, $J_{ae}(\alpha)$ = 14.5 Hz. The S-proton resonance again was a quartet, from which were obtained $J_{H_{ax}CSH}$ = 13.7 Hz and $J_{H_{eq}CSH}$ = 2.5 Hz. The 13.7-Hz coupling again requires that the proton on sulfur be axial. The normal value of $J_{ae}(\alpha)$, 14.5 Hz, reinforces this assignment. The axial preference (**6**) therefore persists even in the presence of a 3-axial methyl group. The syn-axial CH_3–H interaction must not force the proton into the equatorial position, as occurred for the oxide **4** and the imide **5**. According to the currently accepted interpretation,[4,5] the interaction between the S proton and the 3-axial methyl group must in fact be attractive to maintain the axial preference. The longer

(11) See, *inter alia*, H. Booth and R. U. Lemieux, *Can. J. Chem.*, **49**, 777 (1971); R. R. Fraser, M. Kaufman, P. Morand, and G. Govil, *ibid.*, **47**, 403 (1969); J. B. Lambert, W. L. Oliver, Jr., and G. F. Jackson, III, *Tetrahedron Lett.*, 2027 (1969).

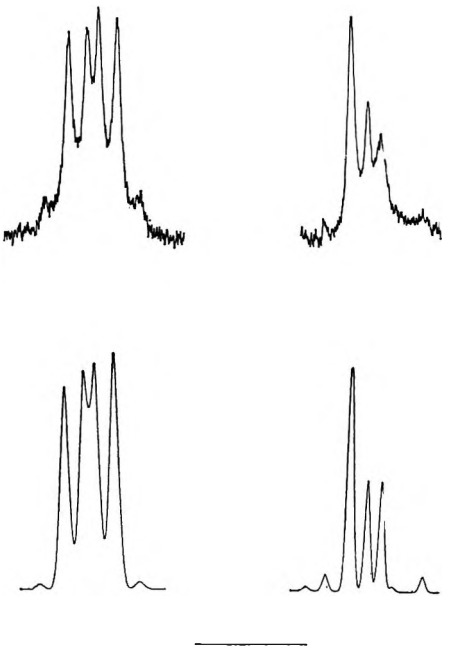


Figure 2.—The observed (upper) and calculated 90-MHz spectra for the 6α protons (right) and the S proton of 4,4-dimethylthiane-*2,2,5,5-d*$_4$ (9-d_4) in FSO_3H–SO_2 at −40°. The gain is different for the two resonances; so the 2:1 ratio is not reproduced. The calibration bar represents 40 Hz.

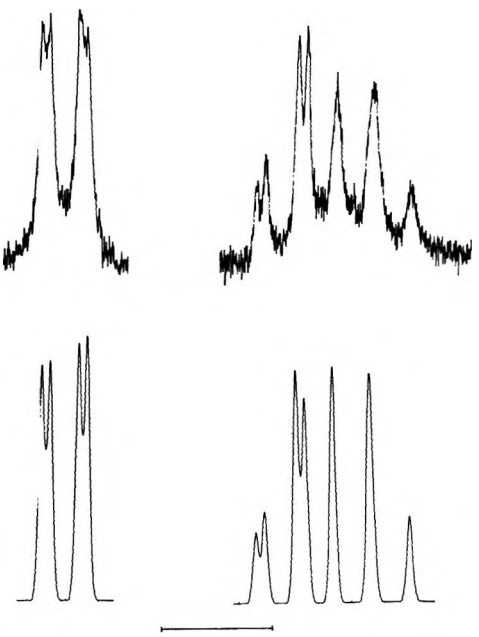


Figure 3.—The observed (upper) and calculated 90-MHz spectra for the 6α protons (right) and the S proton of 3,3-dimethylthiane-*2,2,5,5-d*$_4$ (6-d_4) in FSO_3H–SO_2 at −40°. The calibration bar represents 40 Hz.

C–S bond permits such a diaxial arrangement without the onset of a repulsive interaction. Classical calculations[8] show that the CH_3–H syn-axial interaction is attractive almost to the distances of carbocyclic systems. Replacement of H by a larger and more electronegative atom such as F, O, or N makes the interaction much more repulsive.[8] Thus the CH_3-oxide and CH_3-imide interactions in **4** and **5** must be sufficiently repulsive to give the equatorial preference. These experiments demonstrate the rather impressive preference that the 1 proton has for the axial position.

Sulfoximides.—Because sulfoximides are readily prepared from sulfoxides (Scheme I), we have also examined 4,4-dimethylthiane-*2,2,5,5-d*$_4$ 1-oxide 1-imide (**10**) and its *N*-tosyl derivative (**11**). Insufficient material was available for examination of the 3,3-dimethyl series. The spectrum of the α protons of **10** at −105° consists of two AB spectra (Figure 4). The AB quartets average to a single AB at room temperature by rapid ring reversal. The β protons exhibit only a single AB quartet at −105°, presumably by accidental superposition. The spectral data are collected in Table III. The population ratio is 55:45 at −105°. No comparison can be made with the unmethylated sulfoximide, because the parent compound gave no equilibrium data.[9a] The ratio is therefore the first measured for a simple sulfoximide. We hypothesize that the favored conformation has an axial oxide and an equatorial imide, because thiane 1-oxide is 62% axial oxide and thiane 1-imide is 55% equatorial imide.

4,4-Dimethylthiane-*2,2,5,5-d*$_4$ 1-oxide 1-(*N*-tosyl)-imide (**11**) exhibits a low-temperature α resonance similar to that of **10**. The data for the two AB quartets are given in Table III. It is noted that all the values of $J_{ee}(\alpha)$ for **10** and **11** are normal, *i.e.*, close to 14 Hz. Sulfoximides have no sulfur lone pair, and it is an axial lone pair that is the cause of the abnormally low values observed for sulfoxides and sulfimides.[3,9] For

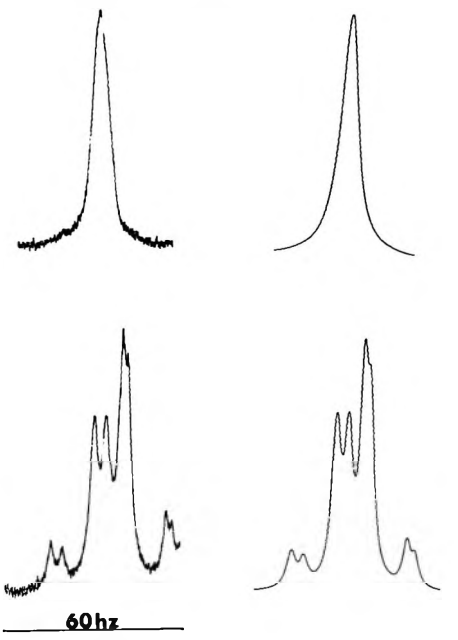


Figure 4.—The observed (left) and calculated 90-MHz spectra of the 6α protons of 4,4-dimethylthiane-*2,2,5,5-d*$_4$ 1-oxide 1-imide (10-d_4) in $CHClF_2$ at 30 (upper) and −90°.

the *N*-tosylimide **11**, the β protons also give two AB quartets at −85°[c] (Table III). The populations corroborate those determined from the α resonances. The isomer ratio of 62:38 compares to 67:33 for the unmethylated case.[9a] We believe that the *N*-tosylimide group in **11** is equatorial and oxide axial, because the imide group generally has a lower axial preference than the oxide. This point is by no means certain.

Conclusions

We have found that a 3,3-dimethyl grouping on thiane 1-oxide and thiane 1-(*N*-tosyl)imide reverses a slight preference of the 1 substituent for the axial position in the unmethylated compounds to a complete

TABLE III

SPECTRAL PARAMETERS FOR THE α, β, AND γ PROTONS IN SULFOXIMIDES[a]

	10	11	14[b]	15[b]
$\delta_{ae}(\alpha)$	18.6	45.4	*c*	74.8
$J_{ae}(\alpha)$	14.6	14.4		13.7
Pop.	0.55	0.62		0.67
$\delta_{ae}'(\alpha)$	16.4	19.8		47.6
$J_{ae}'(\alpha)$	14.8	13.5 ± 1[d]		14.8
Pop.′	0.45	0.38		0.33
$\delta_{ae}(\beta,\gamma)$	27.0[e,f]	26.4[f]	40.5[e,g]	40.2[g]
$J_{ae}(\beta,\gamma)$	14.6	14.4	14.1	14.8
Pop.		0.62		0.33
$\delta_{ae}'(\beta,\gamma)$	27.0[e]	15.4	40.5[e]	45.2
$J_{ae}'(\beta,\gamma)$	14.6	14.0	14.1	14.4
Pop.′		0.38		0.67
Solvent	$CHClF_2$	CH_2Cl_2–$CHClF_2$	CH_2Cl_2	$CHClF_2$
Temp, °C	−85	−85	−85	−89
$\Delta G°$, kcal/mol	±75	±180	*h*	±250

[a] See footnote *a*, Table II. [b] Data from ref 9a. [c] The α resonance of **14** remains a broad singlet down to −89°.[9a] [d] Due to peak overlap, this quantity could not be measured accurately. [e] Only one AB quartet is observed, so both isomers must have the same parameters. [f] Parameters for β protons. [g] Parameters for γ protons. [h] An equilibrium constant is not measurable.[9a]

preference for the equatorial position. In protonated thiane, however, the 3,3-dimethyl grouping has no effect on the strong preference of the proton on sulfur for the axial position. The original 1-axial preferences of the proton, the oxide, and the imide in the parent systems are due to attractive interactions with the 3,5-axial protons. Replacement of one of these protons with a methyl group gives rise to a sufficiently repulsive interaction with the 1-axial substituent to make the oxide and the imide prefer the equatorial position. For the protonated case, the syn–axial interaction between the methyl group and the S proton must still be attractive since the 1-axial preference persists. The long C–S bonds and the small size of the 1 proton makes this example unique in our studies of 3,3-dimethyl ring systems.

Experimental Section

Infrared spectra were measured on a Beckman IR-5. Routine nmr spectra were recorded on Varian T-60 and A-60 spectrometers. Low-temperature experiments were carried out on the Bruker HFX-10 at 90 MHz.[12] Computer analyses were performed on a CDC-6400 with Calcomp plotting accessories. Elemental analyses were executed by Miss H. Beck, Analytical Services Laboratory, Department of Chemistry, Northwestern University.

1,5-Dibromo-2,2-dimethylpentane-*1,1,4,4-d*$_4$ and 1,5-Dibromo-3,3-dimethylpentane-*1,1,4,4-d*$_4$.—The preparation of these compounds as a mixture has been described in a previous paper in this series.[13]

3,3-Dimethylthiane-*2,2,5,5-d*$_4$ (12) and 4,4-Dimethylthiane-*2,2,5,5-d*$_4$ (13).[2]—To a 100-ml, round-bottomed flask equipped with a heating mantle, a magnetic stirrer, and a reflux condenser and containing 3.0 g of sodium sulfide nonahydrate in 30 ml of refluxing 50% aqueous ethanol, was added (separately) 3.5 g of the dibromodimethylpentane mixture and 3.0 g of sodium sulfide nonahydrate in 30 ml of 50% ethanol. The mixture was refluxed for 3.5 hr. The thianes were distilled along with the ethanol from the reaction mixture, extracted into CH_2Cl_2, washed twice with H_2O, and dried ($MgSO_4$). The CH_2Cl_2 was removed by distillation, leaving the thianes as a residue. The isomeric thianes (in a 70:30 ratio favoring the 4,4 isomer) were preparatively separated on a 7 ft × 0.25 in. 12% Carbowax 20M on Chromasorb G-DMCS-AW 60/80 at 130° and 70 ml/min. The products were identical with known materials.[14]

Protonated Dimethylthianes (6, 9).[4]—About 100 mg of the deuterated thiane was placed in the bottom of an nmr tube. Three times this volume of freshly distilled FSO_3H and of SO_2 were placed in the tube, which was then sealed. The nmr spectra were recorded at −40°.

The oxides (4, 7), the imides (5, 8), and the sulfoximides (10, 11) were prepared as outlined in Scheme II by methods reported in detail for the unsubstituted series.[9a] The oxides (**4**, **7**) and the sulfoximide **10** were extremely hygroscopic, so good elemental analyses and melting points were not obtained. The structures are not in doubt because of their nmr spectra and because the derivative *N*-tosylsulfoximide (**11**) gave good analytical results.

3,3-Dimethylthiane 1-(*N*-tosyl)imide (5) had mp 172–173°. *Anal.* Calcd for $C_{14}H_{21}NO_2S_2$: C, 56.18; H, 7.02; N, 4.68. Found: C, 55.72; H, 7.20; N, 4.55.

4,4-Dimethylthiane 1-(*N*-tosyl)imide (8) had mp 185–186°. *Anal.* Calcd for $C_{14}H_{21}NO_2S_2$: C, 56.18; H, 7.02; N, 4.68. Found: C, 55.81; H, 7.20; N, 4.70.

4,4-Dimethylthiane 1-oxide 1-(*N*-tosyl)imide (11) had mp 183–184°. *Anal.* Calcd for $C_{14}H_{21}NO_3S$: C, 53.33; H, 6.67; N, 4.44. Found: C, 53.26; H, 6.77; N, 4.36.

Registry No.—**4**, 31815-13-1; **5**, 31815-14-2; **7**, 31815-15-3; **8**, 31815-16-4; **10**, 31815-17-5; **11**, 31815-18-6.

(12) We thank the National Science Foundation for an equipment grant to purchase signal-averaging accessories for the HFX-10.

(13) J. B. Lambert, D. S. Bailey, and B. F. Michel, submitted.

(14) L. Schmerling and J. P. West, *J. Amer. Chem. Soc.*, **74**, 2885 (1952).

The Chlorination of Aldehyde and Ketone Phenylhydrazones

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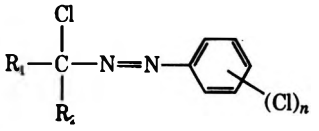
Received July 29, 1971

Azo compounds have been prepared by reaction of aldehyde and ketone phenylhydrazones with chlorine. Chlorination of propionaldehyde (2,4,6-trichlorophenyl)hydrazone or propionaldehyde phenylhydrazone gave 1′,1′,2,4,6-pentachlorobenzeneazopropane (**3**). The product, an orange liquid, was thermally stable up to 250° and was stable in acidic or basic media at room temperature. Chlorination of acetone (2,4,6-trichlorophenyl)-hydrazone gave 1′,2,4,6-tetrachloro-1′-methylbenzeneazoethane (**9**). Nucleophilic displacement of the 1′-chlorine substituent in **9** by cyanide and acetate gave the corresponding azo cyanide (**10**) and azo acetate (**11**). The azo products obtained by chlorination of other ketone phenylhydrazones are described.

We have recently found that chlorination of aldehyde and ketone phenylhydrazones affords a convenient synthesis for the 1′-chlorobenzeneazoalkanes of structure **1**. The azo compounds formed from aldehyde phenyl-

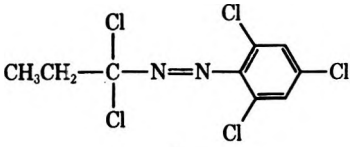


1

R_1 = alkyl or phenyl
R_2 = alkyl, phenyl, or chlorine
For nature of n, see text.

hydrazones are stable compounds, whereas those formed from ketone phenylhydrazones are somewhat unstable, reactive chemicals. The chlorination of benzaldehyde phenylhydrazones to benzoyl chloride phenylhydrazones and ketone phenylhydrazones to the corresponding ring chlorinated ketone phenylhydrazones has been reported,[1,2] but little was reported concerning the formation of azo compounds in these reactions.[3]

Treatment of a solution of propionaldehyde (2,4,6-trichlorophenyl)hydrazone in benzene with chlorine followed by distillation of the reaction product afforded 1′,1′,2,4,6-pentachlorobenzeneazopropane (**3**) in high yield (76%). The same orange-colored liquid was obtained by chlorination of propionaldehyde phenylhydrazone in chloroform. That the product was the azo compound **3** and not the isomeric *N*-chloro compound **4** was indicated by spectral comparisons with



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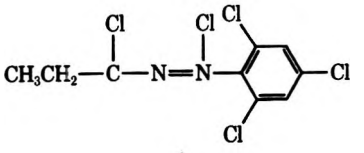

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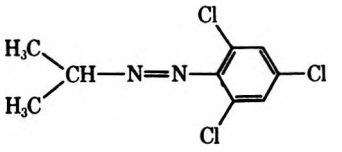
2,4,6-trichloro-1′-methylbenzeneazoethane[4] (**5**), prepared from acetone (2,4,6-trichlorophenyl)hydrazone.



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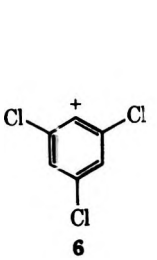
Compounds **3** and **5** showed a weak intensity absorption near 405 mμ (ε 100–400) characteristic of the phenylazo linkage[5] and also showed strong ir bands at 1550 and 1570 cm^{-1} that appear characteristic for the (2,4,6-trichlorophenyl)azo structure.[6] The mass spectra of **3** and **5** show, in addition to the molecular ion, major peaks for ions **6** and **7**. Similar mass spectral fragmentation has been reported for azobenzenes,[7a] while phenylhydrazones show instead **8** as a major ion.[7b]



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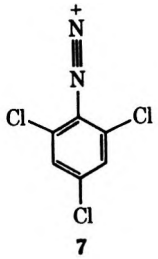

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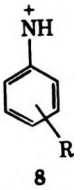
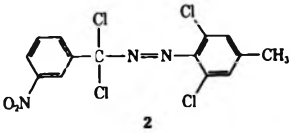


8

(1) J. E. Humphries, H. Humble, and R. Evans, *J. Chem. Soc.*, **127**, 1304 (1925).

(2) (a) F. D. Chattaway and A. B. Adamson, *ibid.*, 843 (1930); (b) J. M. Burgess and M. S. Gibson, *ibid.*, 1500 (1964).

(3) We believe that the initial product obtained on chlorination of *m*-nitrobenzoyl chloride (2,6-dichloro-*p*-tolyl)hydrazone[2a] is 1′,1′,2,6-tetrachloro-4-methyl-1′-(*m*-nitrophenyl)benzeneazomethane (**2**) and not the



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isomeric *N*-chloro compound reported by Chattaway. While we have not repeated this reaction, Mr. V. L. Rizzo of these laboratories has observed that benzoyl chloride (2,4,6-trichlorophenyl)hydrazone reacts slowly (*ca.* 24 hr) with chlorine in carbon tetrachloride with formation of 1′,1′,2,4,6-pentachloro-1′-phenylbenzeneazomethane. The compound was purified by chromatography on silica gel; the nmr, ir, and uv spectral data were consistent with the proposed structure. The structure of a second compound described by Chattaway[2a] was recently revised; see M. S. Gibson, *ibid.*, 2270 (1962). The *N*-chloro compounds reported in ref 2b are also probably azo compounds; all show the low-intensity band near 410 mμ expected for the azo structure.

(4) The details of the synthesis are given in the Experimental Section. 1′-Methylbenzeneazoethane has been prepared by the same method; see R. C. Goodwin and J. R. Bailey, *J. Amer. Chem. Soc.*, **47**, 167 (1925).

(5) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," E. Arnold, London, 1958, p 127; A. Burawoy, *J. Chem. Soc.*, 1177 (1939).

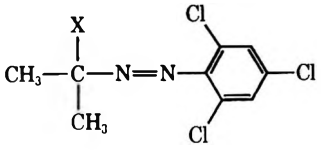
(6) We have prepared a large number of compounds containing the (2,4,6-trichlorophenyl)azo group. Additional examples are given in an accompanying paper. All the compounds prepared show the two characteristic ir bands at about 1550 and 1570 cm^{-1}.

(7) (a) J. H. Bowie, G. E. Lewis, and R. G. Cooks, *J. Chem. Soc. B*, 621 (1967); (b) W. D. Crow, J. L. Occolowitz, and R. K. Solly, *Aust. J. Chem.*, **21**, 761 (1968).

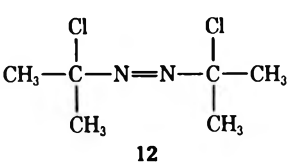
Compound **3** was thermally stable up to 250°. Above this temperature it decomposed with evolution of 1 molar equiv of gas, presumably nitrogen, leaving a viscous residue. The azo compound was stable at room temperature in ethanolic solutions of hydrochloric acid or sodium hydroxide.[8]

Several azo compounds were formed by chlorination of ketone phenylhydrazones. They were all unstable to chromatography on silica gel and some decomposed when stored at room temperature for several months.

A solution of acetone (2,4,6-trichlorophenyl)hydrazone in chloroform reacted with chlorine to give 1′,2,4,-6-tetrachloro-1′-methylbenzeneazoethane (**9**). Com-



9, X = Cl
10, X = CN
11, X = O—C(=O)—CH$_3$



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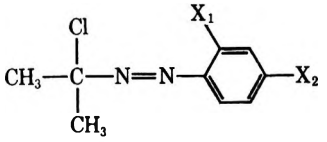
pound **9** showed the uv and ir bands found characteristic for the azo products **3** and **5** and a similar mass spectral fragmentation pattern. Unlike **3**, **9** is a reactive compound, the 1′-chlorine substituent being readily displaced by nucleophiles. Thus, **9** reacted with potassium cyanide to give **10** and with sodium acetate in acetic acid to give **11**.[9] Such reactivity has been observed by Benzing[10] for the related azo product **12** prepared by chlorination of acetone azine.

Acetone (2,4-dichlorophenyl)hydrazone gave a single azo product **13**, when chlorinated, while acetone phenylhydrazone gave a mixture of products, mainly **13**, **14**, and **15**, upon chlorination.[11] This mixture of products



13, $X_1 = X_2 = Cl$
14, $X_1 = H$; $X_2 = Cl$
15, $X_1 = Cl$; $X_2 = H$

could be separated only by vpc, and was characterized by vpc comparison with the azo mixtures obtained by chlorination of the three isomeric acetone monochlorophenylhydrazones. The nmr spectra of all the azo mixtures show a characteristic singlet methyl absorption at about δ 1.90 and the expected aromatic absorption patterns.

Chlorination of the (2,4,6-trichlorophenyl)hydrazones of acetophenone and benzophenone gave the crystalline azo derivatives 1′,2,4,6-tetrachloro-1′-phenylbenzeneazoethane and 1′,2,4,6-tetrachloro-1′,1′-diphenylbenzeneazomethane, respectively. We have extended our studies to include other classes of phenylhydrazones and have found that azo compounds are usually formed during the chlorination reactions. A part of this work is reported in an accompanying paper.[12]

(8) Stability to base would be unexpected if the structure of the chlorination product was the acid chloride phenylhydrazone **4**.

(9) Azo acetates related to **11** have previously been prepared by reaction of acetone phenylhydrazones with lead tetraacetate; see D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, **83**, 749 (1961).

(10) E. Benzing, *Justus Liebigs Ann. Chem.*, **631**, 10 (1960).

(11) A recent publication describes the preparation of the fluoro azo compound 1′-fluoro-1′-methylbenzeneazoethane by action of lead diacetate difluoride on acetone phenylhydrazone; see J. Bornstein and L. Skarlos, *J. Org. Chem.*, **35**, 1230 (1970).

Experimental Section[13]

The apparatus used for the chlorination reactions was routinely fitted with a condenser cooled with a mixture of Dry Ice and acetone to prevent loss of chlorine but allow hydrogen chloride generated in the reaction to escape. Chlorination was effected by condensing a measured volume of liquid chlorine in a separate container and allowing it to pass by evaporation into the reaction vessel.

1′,1′,2,4,6-Pentachlorobenzeneazopropane (3). Method A.—A mixture of (2,4,6-trichlorophenyl)hydrazine (48 g, 0.23 mol) and propionaldehyde (17.5 g, 0.30 mol) in benzene (300 ml) was refluxed for 1 hr, a Dean and Stark apparatus being used to remove the water formed by the reaction. The solution of propionaldehyde (2,4,6-trichlorophenyl)hydrazone thus obtained was cooled to 0° and stirred while chlorine (35 ml liquid, 0.74 mol) was added. After 2 hr the benzene was removed under reduced pressure, Skellysolve B (500 ml) was added to the residual oil, and the solution was filtered to remove a small quantity of insoluble tar. After removal of the Skellysolve B the residue was distilled to give 56 g (76%) of 1′,1′,2,4,6-pentachlorobenzeneazopropane: bp 145° (0.4 mm); ir (film) 1550 (s) and 1570 cm^{-1} (s); nmr ($CDCl_3$) δ 1.25 (t, 3, CH_3), 2.64 (q, 2, CH_2), and 7.30 (s, 2, ArH); λ_{max}^{hexane} 236 mμ (shoulder, ε 7300), 280 (5000), and 408 (317); mass spectrum *m/e* for ^{35}Cl (rel intensity, number of Cl atoms in ion) 318 (2, 5), 283 (8, 4), 207 (100, 3), and 179 (65, 3).

Anal. Calcd for $C_9H_7Cl_5N_2$: C, 33.73; H, 2.20; Cl, 55.32; N, 8.74. Found: C, 33.80; H, 2.18; Cl, 55.60; N, 8.98.

Method B.—A mixture of phenylhydrazine (54 g, 0.5 mol) and propionaldehyde (35 g, 0.6 mol) in benzene (300 ml) was refluxed for 1 hr, a Dean and Stark apparatus being used to remove the water formed by the reaction. Evaporation of the benzene gave a residue of propionaldehyde phenylhydrazone which was dissolved in chloroform (500 ml). Chlorine (190 ml liquid, 4.1 mol) was added to the stirred reaction solution while maintaining the temperature at −40°. The solution was allowed to warm and held at 10° for 3 hr. The solvents were removed under reduced pressure, Skellysolve B (500 ml) was added, and the solution was filtered to remove the insoluble tars. After removal of the Skellysolve B, the residue was distilled to give 109.6 g (68%) of 1′,1′,2,4,6-pentachlorobenzeneazopropane, bp 145–150° (0.4 mm); the product was identical with that obtained by method A by ir, vpc, nmr, and tlc analysis.

Stability of Compound 3.—Two solutions of **3** (1 g) in ethanol (50 ml) were prepared. To one of these was added a solution of sodium hydroxide (1.0 g) in water (5 ml). To the second solution was added concentrated hydrochloric acid (3 ml). After 2 hr at 25° the reaction mixtures were diluted and extracted with chloroform. In each case evaporation of the chloroform gave an oil (85–90% recovery), identified as unchanged **3** by nmr, ir, and tlc analysis.

2,4,6-Trichloro-1′-methylbenzeneazoethane (5).—Platinum oxide (1 g) was added to a solution of acetone (2,4,6-trichlorophenyl)hydrazone (25 g, 0.1 mol) in ethanol (180 ml) containing concentrated hydrochloric acid (10 ml). The solution was hydrogenated for 15 min until 0.12 mol of hydrogen had been absorbed. The solution was filtered, the filtrate was diluted with ice–water, and concentrated hydrochloric acid (10 ml) was added. A solution of sodium nitrite (7.5 g, 0.11 mol) in water was added to the

(12) M. W. Moon, *J. Org. Chem.*, **37**, 386 (1972).

(13) Melting points were taken in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer and the uv spectra on a Cary Model 15 spectrophotometer. The nmr spectra were recorded on a Varian A-60A spectrometer; chemical shifts are reported in δ units using $CDCl_3$ as solvent and tetramethylsilane as the internal standard. (In nmr descriptions s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.) Vpc data were obtained using a Micro Tek gas chromatograph Model 220, a column (45 cm × 3 mm i.d.) of 3% QF-1 on 100–120 mesh Gas-Chrom Q, a helium carrier gas (flow rate 85 ml/min), and a hydrogen flame ionization detector. The mass spectra were recorded at 70 eV on an LKB 9000A gas chromatograph–mass spectrometer using a column of 3% QF-1 (4 ft × 3 mm i.d.) maintained at 95°.

stirred reaction mixture. After 10 min an unstable solid (13.4 g) was filtered off. Nmr analysis indicated that this was the *N*-nitroso derivative of 1-isopropyl 2-(2,4,6-trichlorophenyl)hydrazine: nmr ($CDCl_3$) δ 1.60 [d, 6, $(CH_3)_2$], 4.44 (m, 1, CH), 7.30 (s, 2, ArH), and 7.90 (s, 1, NH).

The above solid was dissolved in Skellysolve B (80 ml) at 25°; it decomposed with evolution of nitrous fumes within 1 hr. The solution was applied to a column (50 × 2 cm diameter) of silica gel which was eluted with benzene. The fractions containing the yellow azo compound were pooled and the solvent was removed at 110° (5 mm) to give 8.4 g of 2,4,6-trichloro-1′-methylbenzeneazoethane: ir (film) 1550 (s), and 1570 cm^{-1} (s); nmr ($CDCl_3$) δ 1.44 [d, 6, $(CH_3)_2$], 4.16 (m, 1, CH), and 7.34 (s, 2, ArH); λ_{max}^{hexane} 247 mμ (ε 7600), 275 (shoulder, 2400), and 403 (169); mass spectrum *m/e* for ^{35}Cl (rel intensity, number of Cl atoms in ion) 250 (5, 3), 207 (79, 3), 179 (54, 3), and 43 (100, 0).

Anal. Calcd for $C_9H_9Cl_3N_2$: C, 42.97; H, 3.60; Cl, 42.29; N, 11.14. Found: C, 43.47; H, 3.65; Cl, 42.62; N, 11.04.

1′,2,4,6-Tetrachloro-1′-methylbenzeneazoethane (9).—Chlorine (10 ml liquid, 0.22 mol) was added to a stirred solution of acetone (2,4,6-trichlorophenyl)hydrazone (37.5 g, 0.1 mol) in chloroform (200 ml) at −40°. The reaction solution was held at 0° for 1 hr and was then evaporated under reduced pressure to 41.0 g of 1′,2,4,6-tetrachloro-1′-methylbenzeneazoethane. A portion (10 g) of the product was distilled to give the analytical sample: bp 120–122° (0.15 mm); ir (film) 1550 (s) and 1570 cm^{-1} (s); nmr ($CDCl_3$) δ 1.98 [s, 6, $(CH_3)_2$] and 7.34 (s, 2, ArH); λ_{max}^{hexane} 242 mμ (ε 7850), 272 (3800), and 403 (232); mass spectrum *m/e* for ^{35}Cl (rel intensity, number of Cl atoms in ion) 207 (75, 3), 194 (37, 3), 179 (45, 3), 74 (100, 0), and 41 (96, 0).

Anal. Calcd for $C_9H_8Cl_4N_2$: C, 37.79; H, 2.82; Cl, 49.59; N, 9.80. Found: C, 37.97; H, 2.90; Cl, 49.05; N, 9.43.

2-Methyl-2-[(2,4,6-trichlorophenyl)azo]propionitrile (10).—Potassium cyanide (10 g, 0.15 mol) in water (50 ml) was added to a stirred solution of 1′,2,4,6-tetrachloro-1′-methylbenzeneazoethane (7.5 g, 0.026 mol) in ethanol (100 ml). After 15 min the precipitate was filtered off, washed well with water, and air dried to give 5.3 g (74%) of 2-methyl-2-[(2,4,6-trichlorophenyl)azo]propionitrile, mp 72–76°. Two recrystallizations from petroleum ether (bp 30–60°) gave the analytical sample: mp 76–78°; ir (Nujol) 1555 (s) and 1575 cm^{-1} (s); nmr ($CDCl_3$) δ 1.81 [s, 6, $(CH_3)_2$] and 7.28 (s, 2, ArH); λ_{max}^{hexane} 288 mμ (ε 5320) and 414 (362).

Anal. Calcd for $C_{10}H_8Cl_3N_3$: C, 43.43; H, 2.91; Cl, 38.35. Found: C, 43.55; H, 3.07; Cl, 38.47.

1′-Acetoxy-2,4,6-trichloro-1′-methylbenzeneazoethane (11).—1′-2,4,6-Tetrachloro-1′-methylbenzeneazoethane (7.5 g, 0.026 mol) was added to a stirred suspension of anhydrous sodium acetate (10 g, 0.12 mol) in acetic acid (40 ml). After 1 hr water was added and the precipitate was filtered off, washed well with water, and air dried to give 7.7 g (96%) of 1′-acetoxy-2,4,6-trichloro-1′-methylbenzeneazoethane, mp 44–48°. Two recrystallizations from petroleum ether gave the analytical sample: mp 48–50°; ir (Nujol) 1750 (vs, C=O), 1545 (s), and 1565 cm^{-1} (s); nmr δ 1.72 [s, 6, $(CH_3)_2$], 2.08 (s, 3, CH_3C=O), and 7.24 (s, 2, ArH).

Anal. Calcd for $C_{11}H_{11}Cl_3N_2O_2$: C, 42.67; H, 3.58; Cl, 34.35; N, 9.05. Found: C, 42.97; H, 3.86; Cl, 34.55; N, 8.74.

1′,2,4-Trichloro-1′-methylbenzeneazoethane (13).—Chlorine (10.5 ml liquid, 0.23 mol) was added to a stirred solution of acetone (2,4-dichlorophenyl)hydrazone (18.8 g, 0.087 mol) in chloroform (200 ml) at −40°. The reaction solution was warmed to 0° for 1 hr and was then concentrated to give 20.8 g of red oil. This was distilled to give 1′,2,4-trichloro-1′-methylbenzeneazoethane in high yield: bp 114–116° (0.30 mm); ir (film) 1575 (s), 1530 (m), and 1510 cm^{-1} (m); nmr δ 1.88 [s, 6, $(CH_3)_2$] with aromatic hydrogens at 7.08 (d of d, J = 2 and 8 Hz), 7.30 (d, 1, J = 8 Hz), and 7.37 (d, 1, J = 2 Hz).

Anal. Calcd for $C_9H_9Cl_3N_2$: C, 42.98; H, 3.61; Cl, 42.29; N, 11.14. Found: C, 42.78; H, 3.59; Cl, 42.52; N, 11.28.

Chlorination of Acetone Phenylhydrazone.—Chlorine (20 ml liquid, 0.43 mol) was added to a stirred solution of acetone phenylhydrazone (14.8 g, 0.1 mol) in chloroform (100 ml) at −40°. The solution was warmed to 10° for 30 min and was then concentrated to a gum. Skellysolve B (200 ml) was added and the solution was filtered to remove insoluble tars. Evaporation of the Skellysolve B gave 13.1 g of dark red oil which was characterized as a mixture of **13**, **14**, and **15** by nmr and vpc methods. The nmr spectrum showed a singlet methyl absorption at δ 1.89 and about four aromatic hydrogens absorbing between δ 7.0 and 7.8. Vpc[11] showed the presence of **14** and **15** (retention times at 75°, 2.2 and 2.6 min, respectively) and **13** (retention time 5.4 min at 75°); the ratio of (**14** and **15**):**13** was 56:44.

Acetone phenylhydrazones were not present in the reaction products. Vpc retention times for the various acetone phenylhydrazones at 75° were as follows: phenylhydrazone, 3.4 min; (*o*-chlorophenyl)hydrazone, 3.4 min; (*m*-chlorophenyl)hydrazone, 13.0 min; (*p*-chlorophenyl)hydrazone, 12.6 min; (2,4-dichlorophenyl)hydrazone, 9.6 min.

Under the conditions used for the chlorination of acetone phenylhydrazone (a) acetone (*p*-chlorophenyl)hydrazone gave a mixture of **13** (25%) and **14** (75%); (b) acetone (*o*-chlorophenyl)-hydrazone gave a mixture of **13** (25%) and **15** (75%); (c) acetone (*m*-chlorophenyl)hydrazone gave a product showing peaks with retention times of 2.4 (50%) and 6.2 min (50%), presumably 1′,3-dichloro-1′-methylbenzeneazoethane and the related trichloroazo compound.

1′,2,4,6-Tetrachloro-1′-phenylbenzeneazoethane.—A stirred mixture of acetophenone (2,4,6-trichlorophenyl)hydrazone (9 g, 0.029 mol) and chlorine (2.5 ml, 0.055 mol) in chloroform (100 ml) was kept at −20° for 1 hr and the solvent was then evaporated under reduced pressure. The residual oil was crystallized from petroleum ether to give 7.7 g of 1′,2,4,6-tetrachloro-1′-phenylbenzeneazoethane, mp 41–44°. Recrystallization from the same solvent gave the analytical sample: mp 40–44°; nmr δ 2.33 (s, 3, CH_3) and 7.28–7.80 (m, 7, ArH).

Anal. Calcd for $C_{14}H_{10}Cl_4N_2$: C, 48.31; H, 2.90; Cl, 40.75; N, 8.05. Found: C, 48.38; H, 3.00; Cl, 41.08; N, 8.02.

1′,2,4,6-Tetrachloro-1′,1′-diphenylbenzeneazomethane.—Chlorine (5 ml liquid, 0.11 mol) was added to a stirred solution of benzophenone (2,4,6-trichlorophenyl)hydrazone (18.75 g, 0.05 mol) in carbon tetrachloride (200 ml) at −10°. After 30 min the solvent was evaporated and the residual oil was crystallized from Skellysolve B to give 18.5 g of 1′,2,4,6-tetrachloro-1′,1′-diphenylbenzeneazomethane, mp 76°. Recrystallization from the same solvent gave the analytical sample, mp 74–76°.

Anal. Calcd for $C_{19}H_{12}Cl_4N_2$: C, 55.64; H, 2.95; Cl, 34.58; N, 6.83. Found: C, 55.62; H, 3.27; Cl, 34.56; N, 6.61.

Registry No.—**3**, 32974-64-4; **5**, 32974-65-5; **9**, 32974-66-6; **10**, 32974-67-7; **11**, 32974-68-8; **13**, 32974-69-9; 1′,2,4,6-tetrachloro-1′-phenylbenzeneazoethane, 32974-70-2; 1′,2,4,6-tetrachloro-1′,1′-diphenylbenzeneazomethane, 32974-71-3.

Acknowledgments.—The author wishes to thank Mr. G. H. Smith for technical assistance and the Physical and Analytical Chemistry Department of The Upjohn Company for analytical and mass spectral data.

The Chlorination of Alkyl Glyoxylate Phenylhydrazones and Triketone Phenylhydrazones

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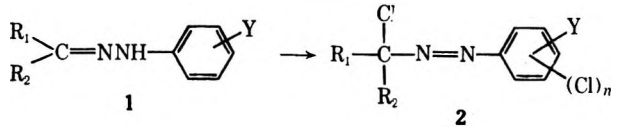
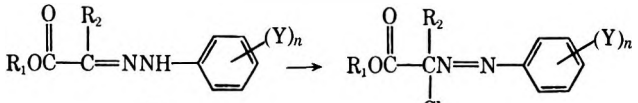
Alkyl glyoxylate phenylhydrazones (**3**, where R_2 = Cl, CH_3, or C_6H_5) reacted with chlorine or *tert*-butyl hypochlorite to give azo esters (**4**). Chlorination proceeds rapidly when the R_2 substituent is methyl or phenyl and relatively slowly when R_2 is chlorine. The azo esters are orange-colored compounds that decompose above 200° with evolution of nitrogen. Ethyl 2-chloro-2-[(*o*-methoxyphenyl)azo]propionate (**14a**) rearranged on heating in acetic acid to ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)hydrazone] (**13**). Methyl dichloro[(2,4,6-trichloro-*m*-tolyl)azo]acetate (**10**) decomposed in refluxing aqueous acetic acid to phosgene (2,4,6-trichloro-*m*-tolyl)-hydrazone (**15**). Reaction of 2,3,4-pentanetrione 3-(phenylhydrazone) with *tert*-butyl hypochlorite followed by methanolysis of the initially formed 3-chloro-3-phenylazo-2,4-pentanedione (**17**) afforded a new synthesis for pyruvoyl chloride 1-(phenylhydrazone).

We have recently prepared a variety of α-chlorophenylazo compounds (**2**) by chlorination of phenylhydrazones (**1**).[1] The preparation has wide utility provided that the substituent groups R_1, R_2, and Y are stable to the reaction conditions. Chlorination of the aromatic ring[2] often occurs before chlorination at the carbon–nitrogen double bond. When these competing chlorination reactions proceed at similar rates, mixtures of azo compounds, differing in the number or position of the ring chlorine atoms, are formed.[1] The reaction solvent and chlorinating agent can also be important in determining the structure of the reaction product.[3]



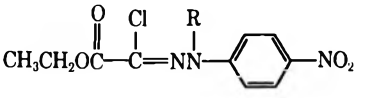
1 **2**

In this paper we describe the azo esters **4** obtained by reaction of alkyl glyoxylate phenylhydrazones (**3**, where R_2 is Cl, CH_3, or C_6H_5) with chlorine or *tert*-butyl hypochlorite. The pronounced effect of the substituent group R_2 on the rate of the chlorination reaction and some properties of the azo esters are also described.

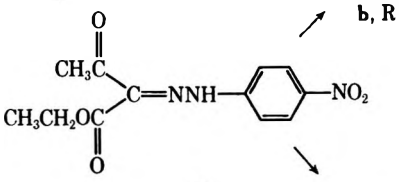


3 **4**

The intermediate alkyl chloroglyoxylate phenylhydrazones (**3**, R_2 = Cl) are conveniently prepared by chlorination of alkyl 2,3-dioxobutyrate 2-(phenylhydrazones).[3,4] For example, Chattaway and Ashworth[3] described the chlorination of ethyl 2,3-dioxobutyrate 2-[(*p*-nitrophenyl)hydrazone] (**5**) to **6a**. In the same study, conversion of **5** to the *N*-chloro compound **6b** was reported. We have resynthesized these compounds and have found from spectral studies that the compound



6a, R = H
b, R = Cl



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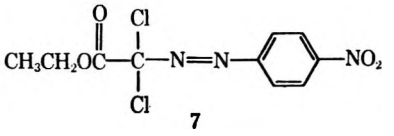


7

reported as **6b** by Chattaway should be re-formulated as the isomeric ethyl dichloro[(*p*-nitrophenyl)azo]acetate (**7**). The product showed a low-intensity absorption at 398 mμ (ε 324) characteristic for the phenylazo structure[5] and a carbonyl absorption at 1755 cm^{-1} as expected for a nonconjugated, α-chlorinated ester.[6] The presence of strong ions corresponding to $O_2NC_6H_4^+$ and $O_2NC_6H_4N_2^+$ in the mass spectral fragmentation pattern of **7** is also consistent with the phenylazo structure.[1,7]

Compound **7** is the only azo ester of structure **4** reported in the literature. We have prepared related products by chlorination of other alkyl 2,3-dioxobutyrate 2-(phenylhydrazones). Unless strong electron-withdrawing substituents are present in the phenylhydrazone ring, the aromatic ring is chlorinated before the carbon–nitrogen double bond. For example, **8** reacted with excess chlorine in chloroform to give **10** in good yield (61%); at short reaction times **9** was the major product.

Treatment of methyl 2,3-dioxobutyrate 2-(*p*-tolylhydrazone) with chlorine gave methyl dichloro[(2,6-dichloro-*p*-tolyl)azo]acetate (*ca.* 25%). A second compound isolated in similar yield from this reaction was shown by mass spectral and elemental analysis to have

(1) Part of this work has been reported; see M. W. Moon, *J. Org. Chem.*, **37**, 383 (1971).

(2) J. E. Humphries, H. Humble, and R. Evans, *J. Chem. Soc.*, **127**, 1304 (1925).

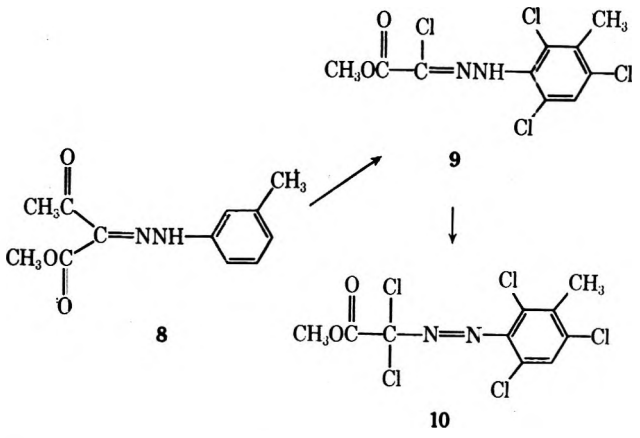
(3) F. D. Chattaway and D. R. Ashworth, *ibid.*, 1143 (1933); solvent effects in the chlorination of phenylhydrazones are described by these workers.

(4) An alternate synthesis for alkyl chloroglyoxylate phenylhydrazones involves reaction of an alkyl 2-chloroacetoacetate with a benzenediazonium chloride; see G. Favrel, *Bull. Soc. Chim. Fr.*, **31**, 150 (1904).

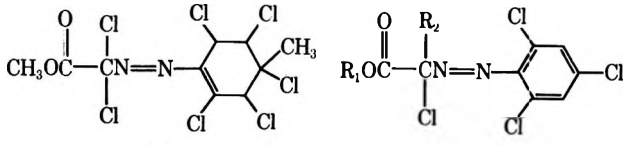
(5) A. E. Gillam and E. S. Stern, "An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry," E. Arnold, London, 1958, p 127; A. Burawoy, *J. Chem. Soc.*, 1177 (1939).

(6) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1959, p 179. Compound **6a** shows a carbonyl band at 1705 cm^{-1}.

(7) J. H. Bowie, G. E. Lewis, and R. G. Cooks, *J. Chem. Soc. B*, 621 (1967).



a molecular formula $C_{10}H_9Cl_7N_2O_2$. Structure **11** is proposed for this compound on the basis of the nmr, uv,



12a, $R_1 = CH_2CH_3$; $R_2 = CH_3$
b, $R_1 = CH_3$; $R_2 = C_6H_5$
c, $R_1 = CH_3$; $R_2 = Cl$
d, $R_1 = CH_2CH_3$; $R_2 = Cl$

and ir spectral data (λ_{max}^{hexane} 232 mμ, C=O absorption at 1750 cm^{-1}). We have found that chlorination of other *o*- and *p*-tolylhydrazones gives similar perchlorinated products[8] whose formation probably involves addition of chlorine at the aromatic ring carbon bearing the methyl substituent[9] followed by further chlorination of the resulting cyclohexadienone azine; chlorination of anilines in an inert solvent results in similar perchlorination of the aromatic ring.[10]

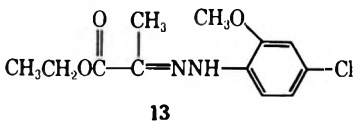
The intermediate hydrazones **3**, where R_2 is methyl or phenyl, were prepared by reaction of substituted phenylhydrazines with esters of pyruvic acid or phenylglyoxylic acid. The alkyl pyruvate phenylhydrazones were obtained as mixtures of the syn and anti isomers about the carbon–nitrogen double bond. While separation of the mixtures before chlorination was unnecessary,[11] the isomers were readily separated by chromatography on silica gel and the structures were assigned by nmr spectroscopy. The NH of the intramolecularly hydrogen bonded syn isomer absorbs near δ 12.0, while that of the anti isomer appears at about δ 8.0.[12a]

Alkyl pyruvate phenylhydrazones react with chlorine rapidly at the carbon–nitrogen double bond; chlorination in the aromatic ring occurs only when it is highly activated. The compounds may also be chlorinated using *tert*-butyl hypochlorite in an inert solvent. This reagent, a less powerful chlorinating agent than chlorine,[13] does not convert the alkyl chloroglyoxylate phenylhydrazones described earlier into azo esters.

Reaction of the (2,4,6-trichlorophenyl)hydrazones of ethyl pyruvate and methyl phenylglyoxylate with chlorine in chloroform gave **12a** and **12b**, respectively. The reactions were complete within 1 hr, whereas chlorination of methyl and ethyl chloroglyoxylate 2-[(2,4,6-trichlorophenyl)hydrazone] to give **12c** and **12d** under similar conditions was incomplete after 24 hr, illustrating the pronounced effect substituent R_2 has on the rate of chlorination of related phenylhydrazones of structure **3**.

Ethyl pyruvate 2-[(2,4,6-trichlorophenyl)hydrazone] reacted with trifluoromethyl hypofluorite to give ethyl 2-fluoro-2-[(2,4,6-trichlorophenyl)azo]propionate. The structure of this fluoroazo compound is supported by the nmr spectrum which shows the methyl group adjacent to the fluorine substituent as a doublet (J = 20 Hz).[12b]

Ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)-hydrazone] (**13**) gave **14a** when treated with *tert*-butyl hypochlorite. Chlorination of ethyl pyruvate 2-[(*o*-



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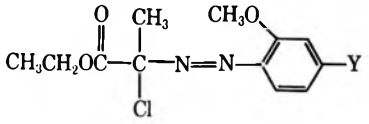
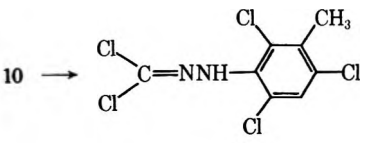


14a, Y = Cl
b, Y = H

methoxyphenyl)hydrazone] with the same reagent gave a mixture of **14a** (30%) and **14b** (70%) that was separated only by vpc. It was further characterized by vpc–mass spectrum and by identification of the hydrazones obtained on catalytic hydrogenation of the mixture.

The azo esters reported herein are orange-colored liquids or low-melting solids. They decompose with evolution of nitrogen when heated at temperatures above 200°. While most of the compounds are readily purified by chromatography on silica gel, **14a** and **14b** decomposed on attempted chromatography. The mixture of **14a** and **14b** rearranged slowly at room temperature, or more rapidly when heated in acetic acid with formation of ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)hydrazone] (**13**). As **13** was not obtained when **14a** was heated in acetic acid, we believe that it was formed by rearrangement of **14b**; related rearrangements of azo compounds have been reported.[14]

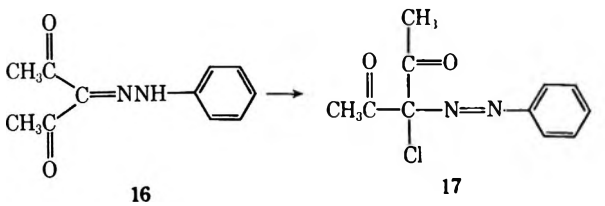
Compound **10** decomposed when heated in aqueous acetic acid to phosgene (2,4,6-trichloro-*m*-tolyl)hydrazone (**15**). This reaction may involve Japp–Klingemann displacement of the carbomethoxy group[15] or stepwise hydrolysis of **10** followed by decarboxylation of the resulting azo acid.



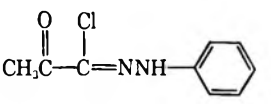
15

(8) M. W. Moon, unpublished results.
(9) M. S. Gibson, *J. Chem. Soc.*, 2270 (1962).
(10) W. J. Hickinbottom in "Chemistry of Carbon Compounds," Vol. IIIA, E. H. Rodd, Ed., Elsevier, Amsterdam, 1954, p 212.
(11) Both isomers of a given phenylhydrazone react with chlorine to give the same azo ester.
(12) (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 1969, pp 103, 216; (b) p 348.
(13) M. Anbar and D. Ginsburg, *Chem. Rev.*, **54**, 925 (1954).
(14) The Chattaway–Adamson rearrangement involves an α-chloro phenylazo compound; see ref 1, footnote 3, and ref 9. Intramolecular rearrangements of α-nitro phenylazo compounds have also been reported: G. Ponzio, *Gazz. Chim. Ital.*, **39**, 535 (1909); **42**, 525 (1912).
(15) R. R. Phillips, *Org. React.*, **10**, 143 (1959).

We have found *tert*-butyl hypochlorite a valuable, mild reagent for the preparation of other α-chlorophenylazo compounds. This reagent reacted with 2,3,4-pentanetrione 3-(phenylhydrazone) (**16**) to give 3-chloro-3-phenylazo-2,4-pentanedione (**17**), identical



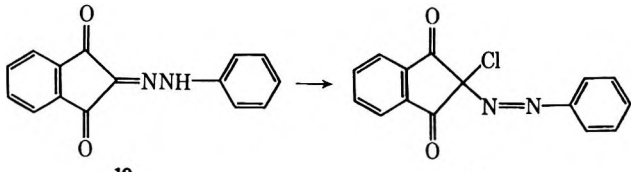
16 **17**



18

with the product obtained by reaction of 3-chloro-2,4-pentanedione with benzenediazonium chloride.[16] Compound **17** was converted in refluxing methanol to pyruvoyl chloride 1-(phenylhydrazone) (**18**).[15,17] This reaction sequence provides a convenient synthesis of **18** from **16**; reaction of **16** with limited amounts of chlorine cannot be controlled to give **18**, but gives instead pyruvoyl chloride 1-(*p*-chlorophenyl)hydrazone.

Reaction of 1,2,3-indantrione 2-(phenylhydrazone) (**19**) with chlorine and *tert*-butyl hypochlorite also gave different products. Chlorine converted **19** to 2,2-di-



19 **20**

chloro-1,3-indandione[18] and benzenediazonium chloride,[19] while *tert*-butyl hypochlorite reacted with **19** to give **20**.

Experimental Section[20]

The phenylhydrazone intermediates used in this study were prepared by standard procedures; spectral data are presented as well as analytical data for new compounds.

Ethyl chloroglyoxylate 2-[(*p*-nitrophenyl)hydrazone] (**6a**) gave the following data: mp 193–195°; ir (Nujol) 1705 cm^{-1} (C=O); nmr [$(CD_3)_2NCDO$] δ 1.34 (s, 3, CH_3), 4.34 (q, 2, CH_2), 7.50 (d, 2, ArH), 8.15 (d, 2, ArH), and 11.14 (s, 1, NH); λ_{max}^{EtOH} 237 mμ (ε 7250), 284 (3750), and 365 (29,950); mass spectrum *m/e* for ^{35}Cl (rel intensity) 271 (100), 137 (15), and 136 (62).

Methyl chloroglyoxylate 2-[(2,4,6-trichlorophenyl)hydrazone] gave the following data: mp 82–84°; ir (Nujol) 1725 (C=O) and 1550 cm^{-1}; λ_{max}^{hexane} 296 mμ (ε 19,400).

Anal. Calcd for $C_9H_6Cl_4N_2O_2$: C, 34.21; H, 1.91; Cl, 44.88; N, 8.87. Found: C, 34.21; H, 2.13; Cl, 44.88; N, 9.00.

Ethyl pyruvate 2-[(2,4,6-trichlorophenyl)hydrazone] was obtained as a liquid isomer mixture and was readily separated by chromatography on silica gel into the syn and anti isomers.

Syn isomer: mp 51–53°; nmr ($CDCl_3$) δ 1.38 (t, 3, CH_3), 2.20 (s, 3, CH_3), 4.40 (q, 2, CH_2), 7.46 (s, 2, ArH), and 12.14 (s, 1, NH).

Anal. Calcd for $C_{11}H_{11}Cl_3N_2O_2$: C, 42.67; H, 3.58; Cl, 34.33; N, 9.05. Found: C, 42.58; H, 3.51; Cl, 34.22; N, 8.83.

Anti isomer: mp 64–68° nmr ($CDCl_3$) δ 1.35 (t, 3, CH_3), 2.20 (s, 3, CH_3), 4.40 (q, 2, CH_2), 7.48 (s, 2, ArH), and 7.75 (s, 1, NH).

Anal. Calcd for $C_{11}H_{11}Cl_3N_2O_2$: C, 42.67; H, 3.58; Cl, 34.33; N, 9.05. Found: C, 42.89; H, 3.71; Cl, 34.52; N, 8.96.

Methyl phenylglyoxylate 2-[(2,4,6-trichlorophenyl)hydrazone] was obtained as an isomer mixture: mp 111–123°; ir (Nujol) 1680 cm^{-1} (C=O); λ_{max}^{hexane} 238 mμ (ε 16,405) and 346 (18,590).

Anal. Calcd for $C_{15}H_{11}Cl_3N_2O_2$: C, 50.37; H, 3.10; Cl, 29.74; N, 7.84. Found: C, 50.36; H, 3.13; Cl, 29.87; N, 7.79.

Ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone], mp 58–83°, was separated into the syn and anti isomers by chromatography on silica gel.

Syn isomer: mp 86–88°; ir (Nujol) 1680 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.30 (t, 3, CH_3), 2.14 (s, 3, CH_3), 3.82 (s, 3, OCH_3), 4.25 (q, 2, CH_2), 6.86 (m, 3, ArH), 7.50 (m, 1, ArH), and 12.0 (s, 1, NH); λ_{max}^{hexane} 239 mμ (ε 10, 500) and 360 (17,800).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.77; H, 6.91; N, 11.65.

Anti isomer: mp 72–74°; ir (Nujol) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.33 (t, 3, CH_3), 2.05 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 4.26 (q, 2, CH_2), 6.86 (m, 3, ArH), 7.55 (m, 1, ArH), and 8.10 (s, 1, NH); λ_{max}^{hexane} 240 mμ (ε 10,200), 276 (7550), 285 (9150), and 322 (21,150).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.11; H, 6.83; N, 11.87.

Ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)hydrazone] (**13**), mixed isomers, was separated by chromatography into its syn and anti isomers.

Syn isomer: mp 109–111°; ir (Nujol) 1680 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.28 (t, 3, CH_3), 2.06 (s, 3, CH_3), 3.76 (s, 3, OCH_3), 4.18 (q, 2, CH_2), 11.90 (s, 1, NH) with aromatic hydrogens at 6.68 (d, 1, J = 2 Hz), 6.76 (d of d, 1, J = 2 and 8 Hz), and 7.30 (d, 1, J = 8 Hz); λ_{max}^{hexane} 243 mμ (ε 10,250) and 362 (20,200).

Anal. Calcd for $C_{12}H_{15}ClN_2O_3$: C, 53.24; H, 5.59; Cl, 13.10; N, 10.35. Found: C, 53.39; H, 5.86; Cl, 13.23; N, 10.75.

Anti isomer: mp 92–94°; ir (Nujol) 1680 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.34 (t, 3, CH_3), 2.04 (s, 3, CH_3), 3.78 (s, 3, OCH_3), 4.24 (q, 2, CH_2), 7.88 (s, 1, NH), with aromatic hydrogens at 6.72 (d, 1, J = 2 Hz), 6.81 (d of d, 1, J = 2 and 8 Hz), and 7.38 (d, 1, J = 8 Hz); λ_{max}^{hexane} 290 mμ (ε 12,600) and 327 (22,750).

Anal. Calcd for $C_{12}H_{15}ClN_2O_3$: C, 53.24; H, 5.59; Cl, 13.10; N, 10.35. Found: C, 53.47; H, 5.52; Cl, 13.08; N, 10.29.

Ethyl dichloro[(*p*-nitrophenyl)azo]acetate (**7**) was prepared as described by Chattaway[3] and purified before recrystallization by chromatography on silica gel using benzene as eluent: mp 64–66°; ir (Nujol) 1755 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.35 (t, 3, CH_3), 4.40 (q, 2, CH_2), 8.00 (d, 2, ArH), and 8.40 (d, 2, ArH); λ_{max}^{hexane} 278 mμ (ε 19,350) and 394 (324); mass spectrum *m/e* (rel intensity) 150 (59), 136 (5), and 122 (100).

Anal. Calcd for $C_{10}H_9Cl_2N_3O_4$: C, 39.23; H, 2.96; Cl, 23.17; N, 13.72. Found: C, 38.81; H, 2.88; Cl, 23.25; N, 13.78.

Methyl Chloroglyoxylate 2-[(2,4,6-trichloro-*m*-tolyl)hydrazone] (**9**).—Chlorine (10 ml, 0.22 mol) was added to a stirred solution of methyl 2,3-dioxobutyrate 2-(*m*-tolylhydrazone)[21] (5 g, 0.021 mol) in chloroform (50 ml) at −50°. The solution was allowed to warm to 0° and then immediately evaporated under reduced pressure. The solid obtained was recrystallized from Skellysolve B to give 3.0 g of **9**, mp 95–98°. Two recrystallizations from methanol gave the analytical sample: mp 96–98°; ir 1720

(16) W. Dieckmann and L. Platz, *Chem. Ber.*, **38**, 2986 (1905); the reaction product was extracted into Skellysolve B after 5 min to prevent hydrolysis to **18**.

(17) Alternate syntheses of pyruvoyl chloride phenylhydrazones have been described by (a) C. Bülow and P. Neber, *ibid.*, **46**, 2370 (1913); (b) G. Favrel, *Bull. Soc., Chim. Fr.*, **41**, 1494 (1927); (c) R. Huisgen and H. J. Koch, *Justus Liebigs Ann. Chem.*, **591**, 200 (1955).

(18) Identical with a sample prepared by the method of S. Ruhemann, *J. Chem. Soc.*, **97**, 2025 (1910).

(19) The formation of diazonium salts when phenylhydrazones are chlorinated in ethanol has been reported: C. Bülow, *Chem. Ber.*, **51**, 399 (1918).

(20) The mass spectra of solid products were recorded at 70 eV on an Atlas CH4 spectrometer; mass spectra of liquid products were recorded at 70 eV on an LKB 9000A gas chromatograph–mass spectrometer using a column of 1% QF-1 (2 ft × 3 mm i.d.) on 100–120 mesh Gas-Chrom Q maintained at 125°. Other analytical and chlorination procedures are described in ref 1.

(21) H. G. Garg and S. S. Joshi, *J. Indian Chem. Soc.*, **37**, 626 (1960).

cm^{-1} (C=O); nmr δ 2.46 (s, 3, CH_3), 3.91 (s, 3, CH_3O), 7.42 (s, 1, ArH), and 8.27 (s, 1, NH); λ_{max}^{hexane} 295 mμ (ϵ 20,090).

Anal. Calcd for $C_{10}H_8Cl_4N_2O_2$: C, 36.39; H, 2.44; Cl, 42.98; N, 8.49. Found: C, 36.47; H, 2.56; Cl, 43.14; N, 8.32.

Methyl Dichloro[(2,4,6-trichloro-*m*-tolyl)azo]acetate (10).—A stirred solution of methyl 2,3-dioxobutyrate 2-(*m*-tolylhydrazone)[21] (100 g, 0.43 mol) in chloroform (400 ml) at −40° was treated with chlorine (200 ml, 4.3 mol). The solution was stirred at 10° for 18 hr and was then evaporated to give 157 g of oil; tlc analysis indicated that the reaction was complete after *ca.* 2 hr. A portion (100 g) of the product was crystallized from methanol and gave 57 g of **10**, mp 42–45°. The analytical sample was recrystallized from petroleum ether (bp 30–60°): mp 44–46°; ir 1765 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.47 (s, 3, CH_3), 3.96 (s, 3, OCH_3), and 7.42 (s, 1, ArH); λ_{max}^{hexane} 256 mμ (ϵ 5360), 291 (5360), and 408 (429).

Anal. Calcd for $C_{10}H_7Cl_5N_2O_2$: C, 32.95; H, 1.94; Cl, 48.64; N, 7.69. Found: C, 33.21; H, 2.00; Cl, 48.09; N, 7.77.

Chlorination of Methyl 2,3-Dioxobutyrate 2-(*p*-Tolylhydrazone).—Chlorine (100 ml, 2.15 mol) was added at −40° to a stirred solution of methyl 2,3-dioxobutyrate 2-(*p*-tolylhydrazone)[21] (60 g, 0.255 mol) in chloroform (500 ml). The solution was stirred at room temperature for 18 hr and was then evaporated. The residual oil was dissolved in benzene–Skellysolve B (1:1) and chromatographed on silica gel. Methyl dichloro[(2,6-dichloro-*p*-tolyl)azo]acetate (10.2 g) was the first (yellow) band eluted from the column. This was crystallized from methanol and recrystallized from petroleum ether to give the analytical sample: mp 48–51°; ir (Nujol) 1770 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.36 (s, 3, CH_3), 3.95 (s, 3, OCH_3), and 7.25 (s, 2, ArH).

Anal. Calcd for $C_{10}H_8Cl_4N_2O_2$: C, 36.39; H, 2.44; Cl, 42.98; N, 8.48. Found: C, 36.39; H, 2.68; Cl, 42.69; N, 8.48.

Continued elution of the column gave 6.4 g of material that was discarded, followed by 17.5 g of material that was dissolved in hot methanol. On cooling 10.2 g of **11**, mp 114–117°, was obtained. Recrystallization from Skellysolve B gave the analytical sample: mp 116–118°; ir (Nujol) 1750 cm^{-1} (C=O); λ_{max}^{hexane} 232 mμ (ϵ 18,300) and 260 (shoulder, 2900); nmr ($CDCl_3$) δ 2.07 (s, 3, CH_3), 4.00 (s, 3, OCH_3), with cyclohexane ring protons at 4.70 (d, 1, J = 8 Hz), 4.98 (d, 1, J = 8 Hz), and 5.27 (s, 1); mass spectrum m/e for ^{35}Cl (rel intensity, number of chlorines in ion) 434 (10, 7), 399 (100, 6), and 363 (60, 5).

Anal. Calcd for $C_{10}H_9Cl_7N_2O_2$: C, 27.46; H, 2.07; Cl, 56.74; N, 6.40. Found: C, 27.37; H, 1.97; Cl, 56.17; N, 6.36.

Methyl Dichloro[(2,4,6-trichlorophenyl)azo]acetate (12c).—Chlorine (7 ml, 0.15 mol) was added to a stirred solution of methyl chloroglyoxylate 2-[(2,4,6-trichlorophenyl)hydrazone] (4.4 g, 0.014 mol) in chloroform (50 ml). After 18 hr the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using a mixture of benzene and Skellysolve B as solvent to give 2.9 g of the yellow azo product as a liquid: ir (film) 1770 (C=O), 1550 and 1570 cm^{-1}; nmr ($CDCl_3$) δ 3.90 (s, 3, CH_3O) and 7.38 (s, 2, ArH); λ_{max}^{hexane} 255 mμ (shoulder, ϵ 6050), 282 (6300), and 410 (361); the major ions in the mass spectrum (^{35}Cl) were at m/e 207 and 179 (three chlorine pattern).

Anal. Calcd for $C_9H_5Cl_5N_2O_2$: C, 30.85; H, 1.44; Cl, 50.59; N, 7.99. Found: C, 30.79; H, 1.38; Cl, 50.89; N, 7.90.

Ethyl dichloro[(2,4,6-trichlorophenyl)azo]acetate (12d), prepared by the above method from ethyl chloroglyoxylate 2-[(2,4,6-trichlorophenyl)hydrazone],[22] was obtained as an orange oil: ir (film) 1760 (C=O), 1545 and 1570 cm^{-1}; nmr δ 1.37 (t, 3, CH_3), 4.43 (q, 2, CH_2), and 7.46 (s, 2, ArH).

Anal. Calcd for $C_{10}H_7Cl_5N_2O_2$: C, 32.95; H, 1.94; Cl, 48.64; N, 7.69. Found: C, 33.42; H, 1.87; Cl, 48.06; N, 7.99.

Ethyl 2-Chloro-2-[(2,4,6-trichlorophenyl)azo]propionate (12a).—Chlorine (5 ml, 0.11 mol) was added at −10° to a stirred solution of ethyl pyruvate 2-[(2,4,6-trichlorophenyl)hydrazone] (9.0 g mixed isomers, 0.029 mol) in carbon tetrachloride (100 ml). After addition of the chlorine was complete the mixture was evaporated under reduced pressure. The product was chromatographed on silica gel using benzene–Skellysolve B (1:4) as solvent to give 6.9 g of **12a** as a yellow oil. The analytical sample was further purified by distillation under reduced pressure: bp 155° (0.05 mm); ir 1750 (C=O), 1550, and 1570 cm^{-1}; nmr ($CDCl_3$) δ 1.34 (t, 3, CH_3), 2.21 (s, 3, CH_3), 4.40 (q, 2, CH_2), and 7.57 (s, 2, ArH); λ_{max}^{hexane} 240 mμ (ϵ 8710), 274 (4525), and 405 (290).

Anal. Calcd for $C_{11}H_{10}Cl_4N_2O_2$: C, 38.40; H, 2.93; Cl, 41.22; N, 8.14. Found: C, 38.34; H, 3.01; Cl, 41.33; N, 8.31.

Methyl Chlorophenyl[(2,4,6-trichlorophenyl)azo]acetate (12b).—Chlorine (5 ml, 0.11 mol) was added to a stirred solution of methyl phenylglyoxylate 2-[2,4,6-trichlorophenyl)hydrazone] (14 g, 0.04 mol) in chloroform (200 ml) at −30°. After 30 min the chloroform was removed and the residual oil was crystallized from Skellysolve B to give 12.45 g (81%) of **12b**, mp 56–58°. The analytical sample was recrystallized from Skellysolve B: mp 56–58°; ir ($CHCl_3$) 1750 (C=O), 1545, and 1565 cm^{-1}; nmr ($CDCl_3$) δ 3.80 (s, 3, OCH_3), 7.35 (m, 5, ArH), and 7.70 (m, 2, ArH); λ_{max}^{hexane} 240 mμ (shoulder, ϵ 10,130), 278 (6180), and 408 (355).

Anal. Calcd for $C_{15}H_{10}Cl_4N_2O_2$: C, 45.95; H, 2.57; Cl, 36.17; N, 7.15. Found: C, 45.83; H, 2.48; Cl, 36.33; N, 7.33.

Ethyl 2-Fluoro-2-[(2,4,6-trichlorophenyl)azo]propionate.—Excess gaseous trifluoromethyl hypofluorite was passed into a stirred solution of ethyl pyruvate 2-[(2,4,6-trichlorophenyl)-hydrazone] (6.0 g, 0.02 mol) in trichlorofluoromethane (100 ml) at −50°. After 30 min the solution was warmed to room temperature and evaporated. The residual oil was chromatographed on silica gel using benzene–Skellysolve B (1:3) as solvent. The fractions containing the orange azo compound were evaporated at 100° (10 mm) to give 2.1 g of ethyl 2-fluoro-2-[(2,4,6-trichlorophenyl)azo]propionate: ir (film) 1755 (C=O), 1545, and 1570 cm^{-1}; λ_{max}^{hexane} 242 mμ (ϵ 8100), 278 (4375), and 413 (285); nmr ($CDCl_3$) δ 1.28 (t, 3, CH_3), 1.90 (d, 3, J = 20 Hz, CH_3CF), 4.27 (q, 2, CH_2), and 7.35 (s, 2, ArH).

Anal. Calcd for $C_{11}H_{10}Cl_4FN_2O_2$: C, 40.33; H, 3.08; Cl, 32.47; F, 5.08; N, 8.55. Found: C, 40.49; H, 2.97; Cl, 32.70; F, 4.90; N, 8.73.

Ethyl 2-Chloro-2-[(4-chloro-*o*-methoxyphenyl)azo]propionate (14a).—To a solution of *syn*-ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)hydrazone] (3 g, 0.011 mol) in chloroform (25 ml was added 3 ml (0.025 mol) of *tert*-butyl hypochlorite. After 30 min the solution was evaporated at 60° (0.2 mm) to give 3.3 g of **14a** as a yellow oil: ir 1750 cm^{-1} (C=O); λ_{max}^{hexane} 232 mμ (ϵ 8850), 281 (9750), 328 (6700), and 400 (508); nmr ($CDCl_3$) δ 1.26 (t, 3, CH_3), 2.06 (s, 3, CH_3), 3.93 (s, 3, OCH_3), 4.23 (q, 2, CH_2) with aromatic protons at 6.86 (d of d, 1, J = 8 and 2 Hz), 7.00 (d, 1, J = 2 Hz), and 7.34 (d, 1, J = 8 Hz); vpc–mass spectrum, one peak at 125° (retention time 6.2 min); the mass spectrum was complex, but showed a strong ion at m/e 169 for the diazonium ion $C_7H_6ClN_2O^+$.

Anal. Calcd for $C_{12}H_{14}Cl_2N_2O_3$: C, 47.22; H, 4.62; Cl, 23.24; N, 9.18. Found: C, 47.24; H, 4.66; Cl, 23.54; N, 9.65.

Compound **14a** was also obtained when *anti*-ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)hydrazone] (1.0 g) was treated with *tert*-butyl hypochlorite (1.0 ml) in chloroform (10 ml). Evaporation of the chloroform gave an oil identical with **14a** by ir and nmr analysis.

Chlorination of Ethyl Pyruvate 2-[(*o*-Methoxyphenyl)hydrazone].—To a solution of ethyl pyruvate 2-[(*o*-methoxyphenyl)-hydrazone] (25 g of isomer mixture, 0.106 mol) in chloroform (250 ml) at 0° was added 25 ml (0.22 mol) of *tert*-butyl hypochlorite. After 30 min the solution was evaporated at 50° (0.2 mm) to give an orange oil: ir 1750 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.26 (t, 3, CH_3), 2.06 (s, 3, CH_3), 3.93 (s, 3, OCH_3), 4.23 (q, 2, CH_2), 6.98–7.00 (m, 2, ArH), and 7.15–7.45 (m, 1.7, ArH); vpc–mass spectrum, two peaks at 125° (retention times 3.2 and 6.2 min); the mass spectrum for the first peak showed a strong ion at m/e 135 for the diazonium ion $C_7H_7N_2O^+$; the mass spectrum for the second peak was identical with that obtained for **14a** above.

The above experiment was repeated on one-fifth the scale. The azo ester mixture obtained (5.3 g) was immediately dissolved in ethyl acetate (200 ml) and hydrogenated for 1 hr using 10% palladium on charcoal (250 mg) as catalyst. Tlc (250-μ silica gel GF plate) in benzene indicated the presence of four products with R_f values of 0.60, 0.50, 0.23, and 0.13. The bulk of the product was chromatographed on silica gel using benzene

(22) F. D. Chattaway and F. G. Daldy, *J. Chem. Soc.*, 2756 (1928).

as eluent. The first product (0.82 g) eluted from the column was the syn isomer of **13**. Continued elution gave 0.43 g of mixed isomers, followed by 1.35 g of *syn*-ethyl pyruvate 2-[(*o*-methoxyphenyl)hydrazone]. Elution of the column with ethyl acetate gave 1.80 g of a mixture of the anti isomers of **13** and ethyl pyruvate 2-[(*o*-methoxyphenylhydrazone]; the compounds were characterized by tlc, ir, and nmr.[22]

Formation of 13 from the Mixture of 14a and 14b.—The mixture of azo esters prepared above (30.9 g) was heated in acetic acid (150 ml) at 100° for 30 min. The acetic acid was removed under reduced pressure and the residual brown oil was chromatographed on silica gel using benzene as the eluent. The first product eluted from the column was *syn*-ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)hydrazone] (10.2 g); recrystallization from methanol gave 7.8 g, mp 108–112°.

Further elution of the column gave an additional 14 g of dark oil. Crystallization from ethyl acetate–Skellysolve B gave 3.4 g of *anti*-ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)hydrazone], mp 68–96°; recrystallization of the sample raised the melting point to 91–94°.

The syn and anti isomers of ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)hydrazone obtained in this reaction were identical with the samples previously prepared by tlc, nmr, melting point, and mixture melting point.

Action of Acetic Acid on 14a.—Compound **14a** (2 g) was heated at 100° for 2 hr in acetic acid. The acetic acid was removed by evaporation under reduced pressure; tlc and nmr analysis showed that the syn and anti isomers of ethyl pyruvate 2-[(4-chloro-*o*-methoxyphenyl)hydrazone] were not present in the reaction product.

Phosgene (2,4,6-Trichloro-*m*-tolyl)hydrazone (15).—Methyl dichloro[(2,4,6-trichloro-*m*-tolyl)azo]acetate (12 g, 0.03 mol) was heated under reflux in a mixture of acetic acid (125 ml) and water (25 ml) for 4 hr. The solution was cooled, diluted with water, and extracted with Skellysolve B (300 ml). The Skellysolve B was washed with water, dried, and evaporated to give an oil (5.5 g). This was dissolved in benzene–Skellysolve B (1:1) and was chromatographed on silica gel to give 4.4 g of phosgene (2,4,6-trichloro-*m*-tolyl)hydrazone. Recrystallization from petroleum ether gave the analytical sample: mp 39–41°; nmr ($CDCl_3$) δ 2.33 (s, 3, CH_3), 7.20 (s, 1, ArH), and 7.42 (s, 1, NH).

Anal. Calcd for $C_8H_5Cl_5N_2$: C, 31.36; H, 1.64; Cl, 57.86; N, 9.14. Found: C, 31.08; H, 1.61; Cl, 58.12; N, 8.96.

Pyruvoyl Chloride 1-(Phenylhydrazone).—A solution of 2,3,4-pentanetrione 3-(phenylhydrazone)[24] (102.4 g, 0.50 mol) was dissolved in chloroform (250 ml), cooled to 15°, and stirred. The temperature of the solution was maintained between 15 and 25° during the addition of *tert*-butyl hypochlorite (60 ml, 0.5 mol). After 30 min the solvent was evaporated to give **17** as an orange oil: ir 1730 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.34 (s, 6, CH_3), 7.30–7.60 (m, 3, ArH), and 7.70–7.95 (m, 2, ArH).

The product was dissolved in methanol (250 ml) and was heated to 60° for 15 min. On cooling to 0°, 71.3 g (73%) of pyruvoyl chloride 1-(phenylhydrazone) was obtained; mp 134–136°; ir 1665 cm^{-1} (C=O); nmr [$(CD_3)_2SO$] δ 2.48 (s, 3, CH_3), 6.90–7.60 (m, 5, ArH), and 8.50 (s, 1, NH).

Anal. Calcd for $C_9H_9ClN_2O$: C, 54.97; H, 4.61; Cl, 18.03; N, 14.25. Found: C, 54.96; H, 4.65; Cl, 17.90; N, 14.30.

Pyruvoyl Chloride 1-[(*p*-Chlorophenyl)hydrazone].—Chlorine (9.2 ml, 0.2 mol) was added to a stirred solution of 2,3,4-pentanetrione 3-(phenylhydrazone) (20.4 g, 0.1 mol) in chloroform (300 ml) at −50°. The solution was allowed to warm to room temperature and was evaporated after 30 min. The residual solid was recrystallized twice from ethyl acetate to give 6.1 g of pyruvoyl chloride 1-[(*p*-chlorophenyl)hydrazone], mp 169–172°. Recrystallization from ethyl acetate gave the analytical sample, mp 172–174°.

Anal. Calcd for $C_9H_8Cl_2N_2O$: C, 46.77; H, 3.49; Cl, 30.69; N, 12.13. Found: C, 47.07; H, 3.24; Cl, 31.05; N, 12.22.

Preparation of 17 from 3-Chloro-2,4-pentanedione.—Sodium nitrite (6.9 g, 0.1 mol) in water (30 ml) was added at 0° to a stirred mixture of aniline (9.3 g, 0.1 mol), concentrated hydrochloric acid (22 ml), and water (300 ml). Sodium acetate (13.6 g, 0.1 mol) was then added followed by 3-chloro-2,4-pentanedione (6.7 g, 0.05 mol). The resulting inhomogeneous solution was shaken vigorously for 6 min and was then extracted with Skellysolve B (500 ml). The Skellysolve B was washed with water (three 200-ml portions), dried over anhydrous sodium sulfate, and evaporated at 100° (10 mm). The brown oil thus obtained was identical by nmr and ir analysis with **17** prepared from 2,3,4-pentanetrione 3-(phenylhydrazone) and *tert*-butyl hypochlorite.

2-Chloro-2-phenylazo-1,3-indandione (20).—To a cooled (10°) solution of 1,2,3-indantrione 2-(phenylhydrazone)[25] (5 g, 0.02 mol) in chloroform (50 ml) was added 3.4 ml (0.028 mol) of *tert*-butyl hypochlorite. After 1 hr the solvent was removed at reduced pressure and methanol was added. The solid that precipitated was filtered off and recrystallized from ethyl acetate to give 2.5 g of **20**, mp 138–140°.

Anal. Calcd for $C_{15}H_9ClN_2O_2$: C, 63.28; H, 3.19; Cl, 12.46; N, 9.84. Found: C, 62.98; H, 3.16; Cl, 12.47; N, 9.60.

Chlorination of 1,2,3-Indantrione 2-(Phenylhydrazone) (20).—Chlorine (5 ml, 0.11 mol) was added to a stirred solution of **20** (12.5 g, 0.05 mol) in chloroform (200 ml) at −30°. The solution was allowed to warm to room temperature over 30 min and was then concentrated slightly to remove hydrogen chloride and chlorine by evaporation at reduced pressure (50 mm); a crystalline, water-soluble solid (benzenediazonium chloride) separated during the evaporation. The reaction solution was extracted with water (150 ml).

The aqueous solution was added to a stirred solution of 2,4-pentanedione (10 g), sodium hydroxide (4 g), and sodium acetate (26 g of trihydrate) in water (100 ml). A precipitate of 5.4 g of 2,3,4-pentanetrione 3-(phenylhydrazone), mp 82–85°, was obtained: nmr ($CDCl_3$) δ 2.40 (s, 3, CH_3), 2.52 (s, 3, CH_3), 7.0–7.4 (m, 5, ArH), and 14.65 (s, 1, NH). The product was identical with an authentic sample of **16**.

Evaporation of the chloroform gave 11.9 g of material. This was refluxed for 30 min in methanol[26] and cooled to give 5.6 g of 2,2-dichloro-1,3-indandione, mp 121–124°. Recrystallization from methanol gave the analytical sample, mp 124–126°.

Anal. Calcd for $C_9H_4Cl_2O_2$: C, 50.27; H, 1.87; Cl, 32.98. Found: C, 50.32; H, 2.08; Cl, 32.65.

Registry No.—**6a**, 27143-13-1; **7**, 32979-34-3; **9**, 32979-35-4; **10**, 32979-36-5; **11**, 32979-37-6; **12a**, 33020-72-3; **12b**, 32979-38-7; **12c**, 32979-39-8; **12d**, 32979-40-1; **13** isomer a, 32979-65-0; **13** isomer b, 32979-66-1; **14a**, 32974-72-4; **15**, 32974-73-5; **16**, 6134-57-2; **20**, 33020-73-4; methyl chloroglyoxylate 2-[(2,4,6-trichlorophenyl)hydrazone], 32974-75-7; ethyl pyruvate 2-[(2,4,6-trichlorophenyl)hydrazone] isomer a, 32979-67-2; ethyl pyruvate 2-[(2,4,6-trichlorophenyl)hydrazone] isomer b, 32979-68-3; methyl phenylglyoxylate 2-[(2,4,6-trichlorophenyl)hydrazone], 32974-76-8; ethyl pyruvate 2-[(*o*-methoxyphenyl)-hydrazone], 33020-74-5, 32979-69-4 (isomer a), 20538-15-2 (isomer b); methyl dichloro[(2,6-dichloro-*p*-tolyl)azo]acetate, 32974-77-9; ethyl 2-fluoro-2-[(2,4,6-trichlorophenyl)azo]propionate, 32974-78-0; pyruvoyl chloride 1-(phenylhydrazone), 18440-58-9; pyruvoyl chloride 1-[(*p*-chlorophenyl)hydrazone], 18247-78-4; 2,2-dichloro-1,3-indandione, 32974-80-4.

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(23) The syn and anti isomers of ethyl pyruvate 2-(5-chloro-*o*-methoxyphenyl)hydrazone, mp 105–107 and 119–121° respectively, were also synthesized; these compounds, which show an absorption at δ 7.45 (d, 1, J = 2 Hz, ArH) in the nmr ($CDCl_3$), were not present in the reduction mixture.

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(26) Recrystallization of the product from ethyl acetate–Skellysolve B or methanol gave a product with a wide melting range. The methanol reflux was necessary to remove contaminants from the 2,2-dichloro-1,3-indandione.

Limitations for the Addition of Amides to Formaldehyde and Glyoxal[1]

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Factors which limit the addition of amides to formaldehyde and glyoxal, particularly in base-catalyzed reactions, are considered for several types of amides, *e.g.*, imides, carboxylic acid amides, carbamates, and ureas. Complete substitution of all amido hydrogens available is generally limited by steric effects or by low amide acidity in some cases. The additions of imides to formaldehyde or glyoxal in alkaline media are often thwarted in practice because of hydrolysis of the imide. The addition products, if formed, are also susceptible to hydrolysis. However, some imide–aldehyde addition products may be isolated from mild acidic or base-catalyzed reactions. Complete substitution of all amido hydrogens available becomes more general if cyclization occurs during addition to the aldehyde or if a cyclic amide with nitrogen in the ring, rather than an *N*-alkyl amide, acts as nucleophile.

The reversible addition of amides to aldehydes, especially formaldehyde, to produce *N*-hydroxymethylamides (or *N*-methylolamides) has received much attention as noted in recent reviews.[3,4] Aqueous, basic conditions are usually favored for these additions because acidic catalysis is ineffective or causes the formation of other products in subsequent, rapid reactions.

Addition of unsubstituted amides (eq 1, R = H) to glyoxal to form *N*,*N*′-dihydroxyethylenebisamides

$$2\text{-NHR} + (\text{CHO})_2 \rightleftharpoons \text{-NRCHOHCHOHNR-} \quad (1)$$

is also fairly general;[5] however, the addition of N-substituted amides (eq 1, R ≠ H) is limited.[5,6]

Limiting factors for base-catalyzed addition are considered to be steric effects and low amide acidity.[7] These factors can either prevent additions or result in a slow reaction, thereby allowing the competing Cannizzaro reaction to consume base and reduce the pH of the solution. In this work a number of "substituted" amides will be studied in additions to glyoxal or formaldehyde. Imides are of particular interest because, in general, they possess highly acidic protons compared to other amides.

The addition of imides to formaldehyde has received some attention in the past, whereas addition to glyoxal has not. *N*-Methylol derivatives have been prepared in high yields from formalin and phthalimide (pH 3–4) at the boil,[4] and from maleimide[3] or succinimide[9] and aqueous formaldehyde with a small amount of base present. Further, it was suggested that the imide ring in maleimide was sensitive toward strong bases.

In general, attempts were made to study the additions of phthalimide, maleimide, succinimide, or diacetamide to formaldehyde (formalin) (a) with no base added (pH 3.1–4.0), (b) under mild basic catalysis, *i.e.*, sodium hydroxide added until the pH was about 5, and (c) under basic conditions where sodium hydroxide was added until the pH was between 8 and 10. Reactions were generally performed at room temperature, except with phthalimide, where heat was required to dissolve the materials. Additions under similar conditions were attempted with the imides and glyoxal. In case a only *N*-methylolphthalimide and *N*-methylolsuccinimide were formed. In case b high yields of *N*-methylol derivatives were obtained from solutions containing formaldehyde and phthalimide, maleimide, or succinimide. Hydrolysis of the imide or the *N*-methylolimide appeared to be negligible at pH 5. Formation of *N*-methyloldiacetamide did not occur at pH 3–4 or with base added (pH 5).

In case c hydrolysis of the imide was a problem when attempts were made to maintain the reaction mixture of imides and formaldehyde at a pH of 8 to 10 and only *N*-methylolsuccinimide was isolated.

When aqueous solutions of *N*-methylol derivatives of phthalimide, maleimide, or succinimide were adjusted to a pH of 8–10 with sodium hydroxide, the *N*-methylolimides appeared to hydrolyze in the same manner as the unsubstituted imides. The pH for solutions of *N*-methylolmaleimide or *N*-methylolphthalimide (heated) fell rapidly whereas a pH in the range of 8–10 was easily maintained by a solution of *N*-methylolsuccinimide.

Therefore, cyclic imides, in general, act as good nucleophiles in their addition to formaldehyde. However, in systems about pH 7 or higher, hydrolysis of the imide or *N*-methylolimide was often rapid and these conditions for synthesis and isolation of a pure product were generally impractical. The failure of diacetamide to add to formaldehyde is puzzling. Apparently, this linear imide and formaldehyde develop an unfavorable steric interaction, which is not present in additions with cyclic imides, and the addition is prevented.

The addition of imides to glyoxal was limited to base-catalyzed additions of maleimide and succinimide. No additions were successful without base present. The imide–glyoxal addition products which formed from maleimide and succinimide were highly insoluble. Evidently these materials formed and precipitated before much hydrolysis occurred. Yields were low, pH control was difficult, and no specific procedure is expected to yield reproducible results for addition of imides to glyoxal solutions. No addition products from phthalimide or diacetamide and glyoxal under acidic or basic conditions were encountered. These results are in agreement with the prior general success of additions of N-substituted amides to formaldehyde[7]

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(2) One of the laboratories of the Southern Marketing and Nutrition Research Division, ARS, U. S. Department of Agriculture.

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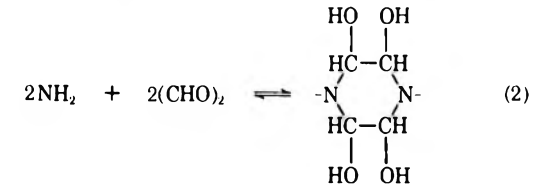
TABLE I

Compd	Mp, °C[a]	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
N,N'-Dihydroxyethylenedisuccinimide	184.5–186	46.88	4.72	10.93	46.99	4.78	11.05
N,N'-Diacetoxyethylenedisuccinimide	~250	49.41	4.74	8.23	49.10	4.56	8.52
N,N'-Dihydroxyethylenedimaleimide	172–173.5	47.63	3.20	11.11	47.58	3.23	11.08
N,N'-Dihydroxyethylenebis(ε-caprolactam)	144–145	59.13	8.51	9.85	58.94	8.65	9.83
N,N'-Dihydroxyethylenebis(methoxyacetamide)	151–153	40.63	6.82	11.85	40.21	7.08	11.88

[a] All compounds displayed signs of decomposition on melting.

compared to the limited successful additions of N-substituted amides to glyoxal.

Similar problems exist which limit additions of amides (other than imides) to glyoxal. For example, cyclizations of *N,N'*-alkylenebisamides with glyoxal to form dihydroxyimidazolidines or dihydroxypiperazines are limited to selected bisamides.[5] Further, the



(2)

cyclization of primary amides with glyoxal to form tetrahydroxypiperazines is limited to formamide and sulfonamides.[5,6,10] The inability of other strongly acidic primary amides and glyoxal to cyclize, as shown in eq 2, has been noted in this and prior[6,10] work. Methoxyacetamide and glyoxal produced only the linear adduct and is another example of an acetamide, substituted with an electron-withdrawing group, which failed to cyclize with glyoxal. It is noted that the linear adduct is not generally isolated in high yield in those reactions which allow formation of the cyclic product.

Limitations for the addition of ureas to formaldehyde and glyoxal follow an interesting pattern. Under the reaction conditions used in this study, urea adds to an excess of formaldehyde to form only the trimethylol derivative. However, if cyclization is allowed to occur and a uron[11] is formed, then urea effectively adds with ease to 4 mol of formaldehyde. Similarly, urea adds to four aldehyde moieties in the formation of the commercially important 1,3-bis(hydroxymethyl)-4,5-dihydroxy-2-imidazolidinone as, again, cyclization occurs (with glyoxal) and urea substitutes at all four positions.

This pattern continues with *N,N'*-dimethylurea and its cyclic (alkylated) counterpart, 2-imidazolidinone, in that 1 mol of 2-imidazolidinone adds readily to 2 mol of formaldehyde, whereas the alkylated, linear urea adds to only 1 mol of formaldehyde. Similarly, *N,N'*-dimethylurea adds readily to two aldehyde moieties when it cyclizes with glyoxal to form the substituted 2-imidazolidinone.[12]

In the addition of N-substituted monoamides to glyoxal (eq 1, R ≠ H) to form linear *N,N'*-dihydroxyethylenebisamides, only the lactam, 2-pyrrolidone, reacted readily with glyoxal. ε-Caprolactam has been found to be less reactive to formaldehyde than 2-pyrrolidone,[13] and some difficulty was encountered in this present work in obtaining addition of ε-caprolactam to glyoxal. Nevertheless, as noted in this paper and references herein, the ability of cyclic amides (ureas, 2-oxazolidone,[14] lactams, and imides) to undergo a high degree of addition to formaldehyde or glyoxal is significant. By comparison the inability of many similar linear N-alkyl substituted amides (ureas, carbamates, and carboxylic acid amides) and linear imides to undergo a high degree of addition (no addition in some cases), certainly indicates a great dependence upon steric effects in these additions.

Experimental Section[15]

A general procedure for attempted imide–aldehyde additions was to mix the reactants at room temperature in stock, aqueous solutions of about 40% formaldehyde or glyoxal. Molar ratios were 1:1 for imide–formaldehyde additions and 2:1 for imide–glyoxal additions. Distilled water was added to the mixture on occasions where it was needed to dissolve the imide or to provide a fluid mixture. The reactants were either left at the pH of the mixture (about 3.1–4), adjusted to a pH of 5.0–5.2 with 20% sodium hydroxide, or adjusted to a pH of about 9 with more sodium hydroxide. The procedures varied widely at this point depending upon conditions and are best discussed under a particular reaction. However, before providing these details, a comparison should be made of the drop in pH above 7 due to imide hydrolysis and the Cannizzaro reaction. Essentially no drop in pH was noted in a 30-min period for formalin or 40% glyoxal adjusted to pH 8–9 at room temperature. At room temperature, aqueous solutions of maleimide and diacetamide adjusted to pH 9–10 decresed rapidly in pH to about 7 or less in 30 min. A heated solution of phthalimide decreased in pH at an even faster rate. On the other hand, the pH of aqueous succinimide in the 8–9 range was constant for 30 min at room temperature. This rapid hydrolysis of the imides, except succinimide, limited potentially successful additions at pH 8–10 to very fast additions at room temperatures. Otherwise, hydrolysis products would be formed which would compete for the aldehyde.

Phthalimide–Formaldehyde.—*N*-Methylolphthalimide is prepared in high yield by heating the reactants (no adjustment in pH) for several minutes on a steam bath. This is the usual procedure for the synthesis of this material.[3,4]

A similar addition at pH 5 (with added water) produced a solution with some solids on heating to 75°. Upon filtration and cooling, *N*-methylolphthalimide was obtained. The melting point of crude product was 143°. The pH of the filtrate was unchanged.

Similar additions at pH 8–10 were attempted with no *N*-methylolphthalimide obtained. Addition of base to the heated solution was followed by a decrease in pH and unreacted phthalimide was recovered. If the pH was allowed to fall after the original adjustment at room temperature to pH 8–10, *N*-methylolphthalimide (mp 145–146°) was obtained in high yield after the mixture had stood at room temperature for several

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(15) All the melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus. Room temperature was 24–25°. Nmr spectra were obtained with a JEOLCO MH-60-II spectrometer. Chemical shifts are reported in hertz downfield from TMS as internal standard. Elemental analyses on new compounds are reported in Table I. DMSO stands for dimethyl sulfoxide.

months (the pH had decreased to 4.4 during this period): nmr (DMSO-d_6) 4 H singlet 471.5 Hz, 1 H triplet 384 Hz (J = 6 Hz), 2 H doublet 298 Hz (J = 6 Hz).

Succinimide–Formaldehyde.—*N*-Methylolsuccinimide was obtained from solutions at pH 3.6, 5.1, and 8–10. For example, the imide and formalin were mixed and the pH was adjusted to 5.0. The mixture was stirred for 30 min, at which time there was complete solution. After 24 hr the pH was 4.8. Water was removed under vacuum on a rotary evaporator at 40° to produce an almost quantitative yield of crude product which crystallized slowly: mp 53–61° [one recrystallization from ethyl acetate raised the melting point to 62–64.5° (lit.[9] mp 66°)]; nmr (DMSO-d_6) 1 H triplet 371 Hz (J = 7.1 Hz), 2 H doublet 282.5 Hz (J = 7.1 Hz), 4 H singlet 157 Hz.

The addition of succinimide to formaldehyde at pH 8–10 was followed closely using nmr and observing changes in pH. Formalin was adjusted to pH 9.5 with dilute NaOD and left overnight. The pH fell to 9.0. Succinimide was partially dissolved in a minimum of D_2O with a slight amount of heat and 1 molar equiv of formaldehyde (pH 9.0) was added. The pH immediately fell to about 7. NaOD was added to increase the pH to 8.7 and the undissolved imide went into solution almost immediately. A spectrum was obtained rapidly. There was no evidence of free formaldehyde in the solution and the pH had increased from 8.7 to 9.3. The spectrum was identical with that of *N*-methylolsuccinimide prepared as directed above at pH 5. The sample of *N*-methylolsuccinimide at pH 9.3 was heated in the nmr spectrometer to 62°. No change was observed except for movement of the HOD peak. To this sample at 62° was added 2–3 drops of 40% NaOD. New peaks occurred rapidly and stopped growing as the pH fell below 7 in about 15 min. Only a slight trace of free formaldehyde was noted. The new peaks were believed to have formed from *N*-methylolsuccinamic acid, because the same pattern of peaks was obtained from heating succinamic acid and formaldehyde at pH 9.

Maleimide–Formaldehyde.—*N*-Methylolmaleimide was obtained from solutions at pH 5.1. After stirring for about 5 min there was an exotherm. The solution was stirred for 30 min and cooled to room temperature, and the product was precipitated. After one recrystallization from ethyl acetate, the product melted at 102–103° (lit.[8] mp 104–106°): nmr (DMSO-d_6) 2 H singlet 421 Hz, 1 H triplet 374 Hz (J = 7.1 Hz), 2 H doublet 287.5 Hz (J = 7.1 Hz).

Reaction at pH 3.1 with or without heating appeared to be questionable—no reaction occurred or it was very slow. In reactions at pH 8–10 only the unreacted imide was isolated. The pH fell rapidly and no attempt was made to maintain the pH in this range.

Diacetamide–Formaldehyde.—The desired addition did not appear to occur under the general conditions at pH 4, 5.1, or 8–10. Unreacted diacetamide was the only product recovered. For those mixtures adjusted to pH 8–10, it was noticed that the pH decreased on standing. A second series of experiments was performed at pH 3 (dilute hydrochloric acid added), 4, 8, and 10 and was followed by nmr. No evidence of the formation of *N*-methyloldiacetamide was encountered.

Acetamide–Formaldehyde.—The addition of acetamide to formaldehyde at pH 9 at 30° was followed by nmr, but the chemical shifts of the peaks of the products and reactants were quite close. The addition appeared to be going very slowly compared to imide–formaldehyde additions. This conclusion was confirmed by titration of the solution for free formaldehyde.[7]

Imide–Glyoxal.—Glyoxal solutions often do not provide a reaction system from which reproducible data can be obtained. This appears to be especially true in those cases when a slow addition of an amide is attempted under basic conditions.[6] The general procedures for imide–aldehyde additions were attempted but in no case was an addition product from phthalimide or diacetamide produced. Heating solutions of phthalimide or diacetamide and glyoxal was also ineffective.

Addition of succinimide or maleimide to glyoxal in the presence of base was achieved; however, results were not reproducible for various glyoxal solutions. Procedures for the synthesis of these addition products are given below.

***N,N'*-Dihydroxyethylenedisuccinimide.**—To 10 g of succinimide were added 50 ml of water and 13.6 g of 40% glyoxal. The pH was adjusted to 8–9 with dilute NaOH. Crystallization of the product commenced with 1 hr. After standing for 3 days, the solution was filtered and the solids were collected and washed with water and then with absolute ethanol. The product melted at 182.5–184.5° dec, yield 24%. The crude compound decomposed easily and attempts to recrystallize it from alcohol caused reversal to the starting materials. Recrystallization from dimethyl sulfoxide raised the melting point to 184.5–186°.

***N,N'*-Dihydroxyethylenedimaleimide.**—To 50 ml of water were added 5 g of maleimide and 3.7 g of 40% glyoxal which had previously been made alkaline (pH 8) with sodium bicarbonate. The desired product crystallized soon after mixing, but additional bicarbonate had to be added to maintain a pH of about 8. After 24 hr at room temperature the mixture, at a pH of 6, was filtered. The precipitate was washed with distilled water and dried over a desiccant, mp 172–173.5° dec, yield 26%.

***N,N'*-(1,2-Diacetoxyethylene)disuccinimide.**—To 3 g of *N,N'*-dihydroxyethylenedisuccinimide were added 50 ml of acetic anhydride and one drop of concentrated sulfuric acid. After standing at room temperature for 1 hr with no apparent change, the mixture was heated slowly to 95° at which point the solids dissolved. The solution was allowed to cool and was left at room temperature overnight. Solids were filtered off and dried, mp 250–260° dec.

Effect of Basic Media on *N*-Methylolimides.—Methylolated imides exhibited a tendency to hydrolyze which paralleled the parent imides. *N*-Methylolsuccinimide was stable at pH 7–9 for at least 2 hr, whereas methylolated maleimide and phthalimide (heated to effect solution) hydrolyzed relatively rapidly; *i.e.*, generally the pH decreased from an 8–10 range to below pH 7 in less than the time required to obtain an nmr spectrum (about 5 min).

***N,N'*-Dihydroxyethylenebis(ε-caprolactam).**—To 22.6 g of ε-caprolactam was added 14.5 g of 40% glyoxal. The pH was adjusted to 10 with 20% sodium hydroxide. The solution was left standing for 48 hr, after which time the pH had decreased to 6.7. The initial level of alkalinity was restored and 20 ml of methanol were added. The solution was chilled for a week, and a small batch of crystals, insoluble in DMSO, was obtained, mp 144–145° dec.

***N,N'*-Dihydroxyethylenebis(methoxyacetamide).**—To 17.8 g of methoxyacetamide was added 14.5 g of 40% glyoxal solution. The pH was adjusted to 9 with 10% sodium hydroxide. Product was obtained by filtration after 2 days. Chilling and working up the filtrate resulted in a 50% yield. After recrystallization from ethanol the solids melted at 151–153° with some decomposition. Much of the work reported by Currie, *et al.*,[6] with acidic carboxylic acid amides was performed in this work and the same results were encountered: nmr (DMSO-d_6) 6 H singlet 198 Hz, 4 H singlet 225 Hz, 2 H multiplet 306 Hz, 2 H singlet (broad) 332 Hz, 2 H doublet 446 Hz (J = 8.0 Hz).

Extent of Addition of Ureas to Formaldehyde.—Procedures for titration of free formaldehyde in the presence of the methylolated product in base-catalyzed additions were described previously.[7] A 50% excess over that quantity require for complete methylolation was used. The following values represent formaldehyde reacted for each amido hydrogen theoretically replaceable: urea, 0.74; *N,N'*-dimethylurea, 0.60; 2-imidazolidinone, 1.0; and 4,5-dihydroxy-2-imidazolidinone, 1.0.

Registry No.—*N,N'*-Dihydroxyethylenedisuccinimide, 32854-87-8; *N,N'*-diacetoxyethylenedisuccinimide, 32854-88-9; *N,N'*-dihydroxyethylenedimaleimide, 32969-93-0; *N,N'*-dihydroxyethylenebis(ε-caprolactam), 32969-94-1; *N,N'*-dihydroxyethylenebis(methoxyacetamide), 32969-95-2; phthalimide, 85-41-6; succinimide, 123-56-8; maleimide, 541-59-3; formaldehyde, 50-00-0; glyoxal, 107-22-2.

The Mechanism of the Acid-Catalyzed Double Bond Migration in 3-Cyclohexen-1-one and 3-Methyl-3-cyclohexen-1-one[1]

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The solvent isotope effect (k_{D_2O}/k_{H_2O}) of 1.3 observed in the acid-catalyzed isomerization of 3-methyl-3-cyclohexen-1-one to 3-methyl-2-cyclohexen-1-one in aqueous sulfuric acid demonstrates that this reaction occurs through a rate-determining enolization. However, the isomerization of 3-cyclohexen-1-one to 2-cyclohexen-1-one has a solvent isotope effect of 0.2, and the rate of hydrogen exchange (enolization) at C-2 is much faster than the rate of isomerization. Thus, it is concluded that this latter reaction occurs through a rate-determining protonation of the enol. The nature of the rate-limiting step in acid-catalyzed double bond migrations in unsaturated ketones is determined by the alkyl substitution at the carbon β to the carbonyl.

Recent results have indicated that the acid-catalyzed isomerization of β,γ to α,β unsaturated ketones proceeds *via* a rate-determining formation of the enol. In a study of the conversion of $\Delta^{5(6)}$- to Δ^4-3-keto steroids, Malhotra and Ringold[3] have concluded that a mechanism of protonation at C-6 followed by deprotonation at C-4 is ruled out by the rate reduction caused by deuterium substitution at C-4 (k_H/k_D = 4.1) and the inverse solvent isotope effect (k_{D_2O}/k_{H_2O} = 1.64). Rather, the data were consistent with an equilibrium protonation on oxygen, followed by a rate-determining formation of the enol 3-hydroxy-3,5-diene.

Closely related work by Talalay,[4] Nes,[5] and their coworkers showed that the reaction rate is proportional to the hydronium ion concentration in the pH region and that the $\Delta^{5(6)}$-3-keto steroids isomerize more than ten times faster than the $\Delta^{5(10)}$ isomers. Others have determined an entropy of activation for the isomerization of a $\Delta^{5(6)}$-3-keto steroid of -19.6 cal/deg mol.[6]

In a study initiated before these results were published, we also have examined the mechanism of this reaction in simple systems. Here we report results for the isomerization of 3-cyclohexen-1-one and 3-methyl-3-cyclohexen-1-one. Our results for 4-methyl-4-penten-2-one and 2-cyclohexen-1-yl methyl ketone are reported in the following paper.[7]

Experimental Section

1-Methoxycyclohexa-1,4-diene and 1-methoxy-5-methylcyclohexa-1,4-diene were prepared by the Birch[8] reductions of methoxybenzene and 3-methylmethoxybenzene using redistilled liquid ammonia. Addition of sodium was stopped when the blue color persisted.

3-Cyclohexen-1-one.—Two drops of 70% perchloric acid were added to a mixture of 4 g of 1-methoxycyclohexa-1,4-diene, 10 ml of carbon tetrachloride, and 25 ml of water. The two-phase system was shaken vigorously. The reaction was monitored by the nmr spectrum of aliquots from the carbon tetrachloride layer (the disappearance of the ether methyl absorbance was particularly apparent). When the reaction was nearly complete, the carbon tetrachloride layer was separated, dried with anhydrous magnesium sulfate, and filtered. After partial removal of the solvent on a rotary evaporator, the product was purified by gas chromatography (Carbowax 20M on Chromosorb W): ir (CCl_4) 1725 cm^{-1} (C=O); nmr (CCl_4) δ 2.4 (m, 4), 2.75 (m, 2), and 5.8 ppm (m, 2).

3-Methyl-3-cyclohexen-1-one.—1-Methoxy-5-methylcyclohexa-1,4-diene was hydrolyzed with a saturated solution of sodium bisulfite in water,[8] and the resulting bisulfite addition compound was converted to the desired ketone with aqueous potassium carbonate. Hydrolysis proceeded quite slowly. Purification was by preparative gas chromatography (Carbowax 20M on Chromosorb W): ir (CCl_4) 1720 cm^{-1} (C=O); nmr (CCl_4) δ 1.7 (m, 3), 2.3 (m, 4), 2.7 (m, 2) and 5.5 ppm (m, 1).

Kinetic Procedures.—Stock solutions of about 10^{-3} mol/l. were prepared by dilution with water of a weighed sample (0.01–0.1 g) of substrate in a volumetric flask (10–100 ml). Aqueous sulfuric acid (3.0 ml) was pipetted into a 1-cm quartz spectrophotometric cell, which was then placed in the water-jacketed cell compartment of a Gilford 2000 spectrophotometer; the circulating water was supplied from a bath thermostated at 25.00 ± 0.02°. Some of the stock solution (0.05–0.1 ml) was added to the cell with a Hamilton syringe. After the solution was stirred with a glass rod, the cell was stoppered and measurements were commenced. The formation of the conjugated isomer was monitored by its absorbance at 235–237 nm.

For the experiments in heavy water solutions, 99.8% deuterium oxide was used for the stock solutions and for dilution of concentrated deuteriosulfuric acid.[9]

After completion of a kinetic run, the acidity of the solution was determined as weight per cent sulfuric acid by titration with standardized sodium hydroxide solutions of weighed aliquots of the kinetic solution to a potentiometric end point with a Metrohm Herisau 336 A potentiograph.

The Hammett acidities, H_0, were determined from the data of Bascombe and Bell[10] and of Jorgenson and Hartter.[11] The corresponding data for the deuterated media, D_0, were from Sierra, Ojeda, and Wyatt.[12]

The reactions showed pseudo-first-order behavior through at least three half-lives. Least-squares rate constants were determined by the use of the computer program LSKIN1.[13] The error limits (standard deviation) were about ±1% of the observed rate constants.

In the exchange experiment for 3-cyclohexen-1-one a mixture of 5 ml of 31.25% D_2SO_4 in D_2O and 1 ml of dioxane was diluted to 10 ml with D_2O. To 1 ml of this solution in an nmr tube was added 40 μl of 3-cyclohexen-1-one. A series of spectra was then taken (Varian A-60).

(1) Supported in part by grants from the National Science Foundation, GP-1572 and GP-6133X.

(2) National Institutes of Health Predoctoral Fellow, 1966–1968 (GM-30, 162).

(3) S. K. Malhotra and H. J. Ringold., *J. Amer. Chem. Soc.*, **87**, 3228 (1965).

(4) F. S. Kawakara, S. F. Wang, and P. Talalay, *J. Biol. Chem.*, **237**, 1500 (1962).

(5) W. R. Nes, E. Loeser, R. Kirdani, and J. Marsh, *Tetrahedron*, **19**, 299 (1963).

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(7) D. S. Noyce and M. Evett, *J. Org. Chem.*, **37**, 397 (1972).

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(10) K. N. Bascombe and R. P. Bell, *J. Chem. Soc.*, 1096 (1959).

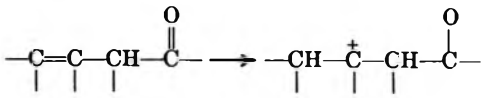
(11) M. J. Jorgenson and D. R. Hartter, *J. Amer. Chem. Soc.*, **85**, 878 (1963).

(12) J. Sierra, M. Ojeda, and P. A. H. Wyatt, *J. Chem. Soc. B*, 1570 (1970).

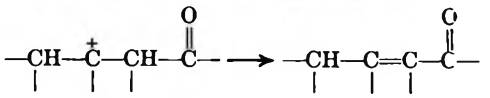
(13) D. F. DeTar and C. E. DeTar in D. F. DeTar, Ed., "Computer Programs for Chemistry," W. A. Benjamin, New York, N. Y., 1968, Chapter 6.

Results and Discussion

There are two plausible mechanisms for the acid-catalyzed isomerization of β,γ to α,β unsaturated ketones. One consists of protonation on the γ carbon, followed by deprotonation from the α carbon (eq 1 and 2). The other involves a dienol intermediate

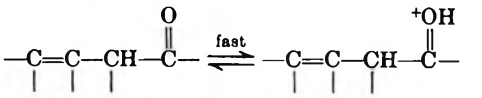


(1)

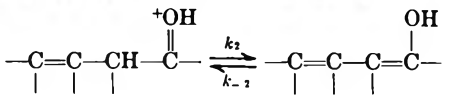


(2)

(eq 3–6). Equations 3 and 6, involving proton transfers to and from oxygen, are expected to be fast with respect to the other processes.[14]



(3)



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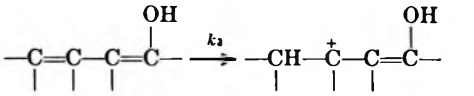

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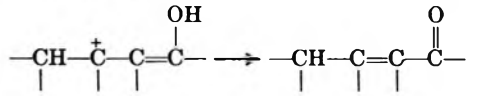


(6)

Of the various ways of distinguishing between these mechanisms, the solvent isotope effect appears to be the most direct and conclusive.[15] Because the enolization mechanism (eq 3–6) involves a prior equilibrium protonation,[14] the solvent isotope effect (k_{D_2O}/k_{H_2O}) is expected to be greater than one. Table I summarizes the solvent isotope effects which

Table I

Solvent Isotope Effect for Rate-Determining Enolizations (Halogenations)

Compd	k_{D_2O}/k_{H_2O}	Ref
Acetaldehyde	1.67	*a*
Acetone	1.67	*a*
Acetone	2.1	*b*
Ethyl methyl ketone	1.67	*c*
Acetophenone	2.5	*c*

[a] P. T. McTigue and J. M. Sime, *Aust. J. Chem.*, 20, 905 (1967). [b] O. Reitz, *Z. Phys. Chem. Abt. A*, 179, 119 (1937). [c] B. T. Baliga and E. Whalley, *Can. J. Chem.*, 42, 1835 (1964).

have been observed for rate-determining acid-catalyzed enolizations.

The expected solvent isotope effect for the direct protonation route (eq 1 and 2) depends upon the fact that the protonation step is rate determining, as established in an important series of experiments with steroids.[16] Thus, in the acid-catalyzed isomerization of 3-methylenecholestane to 3-methylcholest-2-ene, it was observed that the parent compound and its 2α-

(14) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, 3, 1 (1964).
(15) C. A. Bunton and V. J. Shiner, Jr., *J. Amer. Chem. Soc.*, 83, 42, 3207, 3214 (1961).
(16) R. C. Cookson, D. P. G. Hamon, and R. E. Parker, *J. Chem. Soc.*, 5014 (1962).

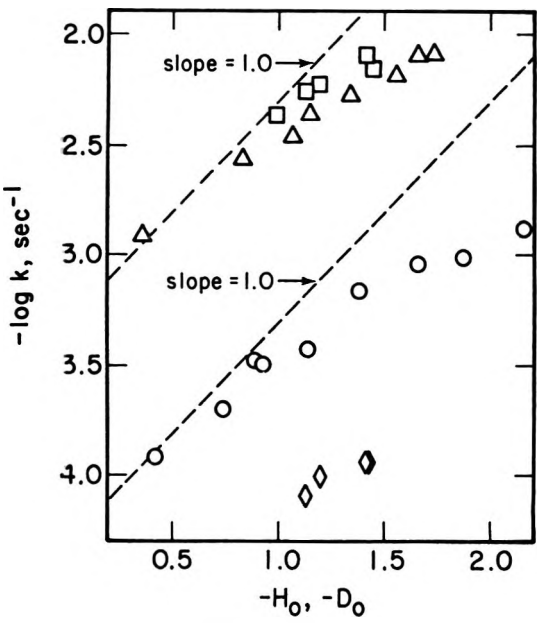


Figure 1.—Rate constants for the isomerization of 3-cyclohex-1-one and 3-methyl-3-cyclohexen-1-one in H_2SO_4 and D_2SO_4: ○, 3-cyclohexen-1-one in H_2O–H_2SO_4; ◇, 3-cyclohexen-1-one in D_2O–D_2SO_4; △, 3-methyl-3-cyclohexen-1-one in H_2O–H_2SO_4; □, 3-methyl-3-cyclohexen-1-one in D_2O–D_2SO_4.

and 2β-deuterio and 2,2,4,4-tetradeuterio derivatives all isomerized at rates which were the same within experimental error. Proton transfers such as the second step of this route should exhibit a primary isotope effect. Since no effect is observed, it must be concluded that the second step occurs *after* the rate-determining step; *i.e.*, the reaction is a rate-determining protonation.

Unfortunately, the solvent isotope effect has not been measured for olefin bond migrations occurring *via* direct protonation. However, the effects are available for other rate-determining olefin protonations. As can be seen from Table II, rate-determining protonations show solvent isotope effects significantly less than one.

Table II

Solvent Isotope Effects for Rate-Determining Olefin Protonations

Substrate	Reaction	k_{D_2O}/k_{H_2O}
Isobutylene	Hydration	0.69[a]
Styrenes	Hydration	0.25–0.53[b]
cis-Stilbenes	Cis-trans isomerization	0.17–0.42[c]
cis-Cinnamic acids	Cis-trans isomerization	0.19–0.27[d]

[a] V. Gold and M. A. Kessick, *Pure Appl. Chem.*, 8, 421 (1964). [b] W. M. Schubert, B. Lamm, and J. R. Keeffe, *J. Amer. Chem. Soc.*, 86, 4727 (1964). [c] D. S. Noyce, D. R. Hartter, and F. B. Miles, *J. Org. Chem.*, 33, 4260 (1968). [d] D. S. Noyce, H. S. Avarbock, and W. L. Reed, *J. Amer. Chem. Soc.*, 84, 1647 (1962).

With these criteria in mind, we have measured the kinetics of the formation of 2-cyclohexen-1-one from 3-cyclohexen-1-one and of 3-methyl-2-cyclohexen-1-one from 3-methyl-3-cyclohexen-1-one in aqueous sulfuric acid and deuteriosulfuric acid at 25°. The results of the pseudo-first-order rate measurements are listed in Tables III–VI and are displayed in Figure 1. The range of acidities covered in H_2SO_4–H_2O is wide enough to show that the logarithm of the rate constant increases less rapidly than the Hammett acidity function,

TABLE III

ISOMERIZATION OF 3-CYCLOHEXEN-1-ONE TO 2-CYCLOHEXEN-1-ONE IN AQUEOUS SULFURIC ACID[a]

% H_2SO_4	$-H_0$	10^4k, sec^{-1}
10.6	0.41	1.18
14.9	0.72	1.97
17.4[b]	0.89	3.23
18.0[b]	0.93	3.15
20.9	1.14	3.73
24.4	1.38	5.38
28.3	1.66	9.05
31.2	1.87	9.79
35.0	2.17	13.3

[a] Temperature = 25.00°. [b] Stock solutions of 3-cyclohexen-1-one in water deteriorate (turn yellow) with time. These runs were done some time after the others.

TABLE IV

ISOMERIZATION OF 3-METHYL-3-CYCLOHEXEN-1-ONE TO 3-METHYL-2-CYCLOHEXEN-1-ONE IN AQUEOUS SULFURIC ACID[a]

% H_2SO_4	$-H_0$	10^4k, sec^{-1}
9.81	0.35	1.20
14.15	0.67	2.24
16.4	0.82	2.71
19.8	1.06	3.46
21.1	1.14	4.23
23.7	1.33	5.26
26.7	1.54	6.46
28.2	1.65	7.88
29.2	1.72	8.06

[a] Temperature = 25.00°.

TABLE V

SOLVENT ISOTOPE EFFECT FOR 3-CYCLOHEXEN-1-ONE

% D_2SO_4	$-D_0$	10^4k, sec^{-1}	k_{D_2O}/k_{H_2O}[a]
19.4	1.12	0.803	0.22
20.4	1.19	0.949	0.24
23.3	1.39	1.13	0.20
23.6	1.41	1.15	0.18
			Av 0.22 ± 0.03

[a] Rates in H_2O–H_2SO_4 interpolated from the data of Table III.

TABLE VI

SOLVENT ISOTOPE EFFECT FOR 3-METHYL-3-CYCLOHEXEN-1-ONE

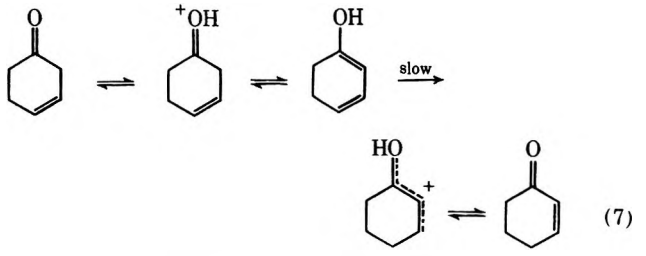
% D_2SO_4	$-D_0$	10^3k, sec^{-1}	k_{D_2O}/k_{H_2O}[a]
17.3	0.96	4.20	1.26
19.3	1.11	5.45	1.35
20.1	1.17	5.93	1.35
23.2	1.38	7.99	1.38
23.5	1.40	7.10	1.18
			Av 1.30 ± 0.08

[a] Rates in H_2O–H_2SO_4 interpolated from the data of Table IV.

as has been observed for rate-determining enolizations.[17]

The solvent isotope effect (k_{D_2O}/k_{H_2O}) of 1.3 for the isomerization of 3-methyl-3-cyclohexen-1-one is consistent with a rate-determining enolization and is in agreement with that observed by Malhotra and Ringold[3] (1.6) for this reaction. On the other hand, the solvent isotope effect of 0.2 for 3-cyclohexen-1-one is inconsistent with this mechanism. One is tempted to attribute this result to the direct protonation route, but this interpretation is clearly at odds with the comparatively rapid rate observed. In order to estimate the rate for the direct protonation route, we have interpolated the data of Beishline[18,19] for the protonation (hydration) of propylene in aqueous perchloric acid to the temperature and acidity of our experiments. Using the additional data of Taft[19,20] for the effect of substituents on the protonation (hydration) of 3-substituted isobutenes to estimate the effect of the presence of the carbonyl group, we estimate that the observed rate of isomerization of 3-cyclohexen-1-one is more than 1000 times faster than that predicted for a direct protonation of the olefin. This large difference more than compensates for any weakness in the analogies.

We conclude then that the isomerization of cyclohex-3-en-1-one also follows the lower-energy enolization route, but that the protonation of the enol has become the rate-limiting step (7). When enol formation is nearly at equilibrium (*i.e.*, relatively fast), it is little affected by the medium, and the observed solvent isotope effect is due for the most part to the slower rate of deuteration of the enol in D_2SO_4–D_2O. In general, proton transfers are slower in deuterated media; solvent isotope effects of 0.3–0.4 for the protonation of a series of enol ethers[21] and of 0.3 for acetone's enol[22] have been measured.



(7)

We have confirmed that exchange is indeed much faster than isomerization in an nmr experiment. The nmr spectrum of cyclohex-3-en-1-one in D_2O had multiplets at about 1.5 and 1.8 ppm upfield from the HDO absorbance. Presumably the former is due to the hydrogens on C-2. In the D_2SO_4–D_2O–dioxane mixture these absorbances occurred at 2.6 and 3.0 ppm upfield from HDO. The first spectrum was completed about 3 min after the substrate was added to the acid solution. At this point the absorbance due to the hydrogens at C-2 was nearly half gone. Within another 10 min no absorbance was discernible at its position. On the other hand, an absorbance appears upfield from the other absorbances at 3.4 ppm upfield from HDO, due to the C-5 hydrogens of 2-cyclohexen-1-one, which are no longer allylic after isomerization. However, about 1.5 hr were required for this peak to reach half of its final height. Thus the rate of exchange (enolization) is about 50 times the rate of isomerization; *i.e.*, the protonation of the enol at the γ position is the rate-determining step.

In the complete mechanism of the acid-catalyzed double-bond migration in unsaturated ketones shown

(17) L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, **61**, 2791 (1939). G. Archer and R. P. Bell, *J. Chem. Soc.*, 3228 (1959). C. G. Swain and A. S. Rosenberg, *J. Amer. Chem. Soc.*, **83**, 2154 (1961).

(18) R. R. Beishline, Ph.D. Thesis, Pennsylvania State University, University Park, Pa., 1962.

(19) P. B. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, London, 1966, p 26.

(20) R. W. Taft, Jr., Office of Naval Research Project NR055-295 Final Report, University Park, Pa., Sept 1960. The authors are grateful to Professor Taft for copies of this report.

(21) A. J. Kresge, D. S. Sagatys, and H. L. Chen, *J. Amer. Chem. Soc.*, **90**, 4174 (1968).

(22) J. E. Dubois and J. Toullec, *Chem. Commun.*, 478 (1969).

in eq 3–6, either step 4 or step 5 will be rate-limiting depending on the relative values of the rate constants k_{-2} and k_3. Both the literature and this work confirm the role of alkyl substitution at the β carbon in determining this ratio. In those cases where this carbon is tertiary ($\Delta^{5(6)}$-3-keto steroids,[3] 3-ethoxycholesta-3,5-diene,[3] and 3-methyl-3-cyclohexen-1-one), protonation of the enol or ether occurs preferentially at the γ carbon. In those cases where the β carbon is secondary (2-hydroxyhexa-2,4-diene[23] and 3-cyclohexen-1-one), protonation at the α carbon dominates.

In the systematic study by Rogers and Sattar,[24] the acid-catalyzed hydrolysis of several conjugated enol ethers showed protonation at the α and/or γ carbon as indicated by the formation of the corresponding β,γ or α,β unsaturated ketone, respectively. Their data clearly indicate that substitution at the β carbon enhances γ over α protonation. On the other hand, substitution at the α or the γ carbon inhibits protonation at that carbon. These results are consistent with the well-known effects[25] of substitution on olefin protonation.

We conclude that in general one may expect the acid-catalyzed isomerization of β,γ unsaturated ketones to α,β unsaturated ketones to occur *via* enol intermediates. The enolization step will be rate-determining if the α carbon is primary, but the protonation of the enol will be rate-limiting if the β carbon is secondary. These two situations will be distinguishable in general by the solvent isotope effect, although intermediate cases[7] may occur.

Registry No.—3-Cyclohexen-1-one, 4096-34-8; 3-methyl-3-cyclohexen-1-one, 31883-98-4; 2-cyclohexen-1-one, 930-68-7; 3-methyl-2-cyclohexen-1-one, 1193-18-6.

(23) H. Morrison and S. R. Kurowsky, *Chem. Commun.*, 1098 (1967).
(24) N. A. J. Rogers and A. Sattar, *Tetrahedron Lett.*, 1471 (1965).
(25) Reference 19, p 43.

The Mechanism of the Acid-Catalyzed Double-Bond Migration in 4-Methyl-4-penten-2-one and 2-Cyclohexen-1-yl Methyl Ketone[1]

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The solvent–isotope effect (k_{D_2O}/k_{H_2O}) of about 1.4 observed in the acid-catalyzed isomerization of 4-methyl-4-penten-2-one to 4-methyl-3-penten-2-one in aqueous sulfuric acid demonstrates that this reaction occurs through a rate-determining enolization. The isomerization of 2-cyclohexen-1-yl methyl ketone to 1-cyclohexen-1-yl methyl ketone has a solvent–isotope effect of 1.0, and the rate of hydrogen exchange (enolization) at the α carbon is faster than the rate of isomerization; thus this reaction occurs through a rate-limiting protonation of the enol. These results are in agreement with previous results showing the role of substitution at the carbon β to the carbonyl in determining the nature of the rate-limiting step.

The acid-catalyzed isomerization of β,γ- to α,β-unsaturated ketones occurs *via* an enol intermediate. Malhotra and Ringold[3] have shown by the solvent isotope effect (k_{D_2O}/k_{H_2O}) of 1.6 that the isomerization of $\Delta^{5(6)}$- to Δ^4-3-keto steroids occurs *via* a rate-determining formation of the enol. Similarly,[4] we have concluded from the solvent isotope effect (k_{D_2O}/k_{H_2O}) of 1.3 that the isomerization of 3-methyl-3-cyclohexen-1-one to 3-methyl-2-cyclohexen-1-one also occurs by a rate-determining enolization. On the other hand, the isomerization of 3-cyclohexen-1-one to 2-cyclohexen-1-one shows a reversed solvent isotope effect (k_{D_2O}/k_{H_2O}) of 0.2, indicating a rate-limiting protonation of the enol. We concluded that, in general, β,γ unsaturated ketones with a tertiary β carbon will isomerize *via* a rate-determining enolization, while those with a secondary β carbon will isomerize *via* a rate-limiting protonation of the enol.

We describe here the results obtained for the acid-catalyzed isomerizations of 4-methyl-4-penten-2-one and 2-cyclohexen-1-yl methyl ketone. In both cases the rate of appearance of the conjugated isomer shows complex kinetic behavior, as monitored by uv measurements. A complete kinetic analysis has been carried through, and the results are consistent with the above generalization.

Experimental Section

1-(Acetoxyethylidenyl)-2-cyclohexene.—Following the method of House and Trost,[5] 5 ml of 70% perchloric acid was added to a mixture of 500 ml of carbon tetrachloride, 150 g of acetic anhydride, and 25 g of 1-cyclohexen-1-yl methyl ketone under nitrogen. After stirring for 2 hr, the solution was neutralized with a saturated solution of sodium bicarbonate. Two ether extracts of the neutral mixture were combined, washed with a saturated solution of sodium chloride, and dried with magnesium sulfate. The solvent was removed by rotary evaporation after the drying agent was removed by filtration. The 31.2 g of crude material resulting showed 84% conversion to the enol ester by gas chromatography (Carbowax 20M on Chromosorb W). Because distillation [bp 71–72° (1.2 mm)] resulted in large amounts of pot residue, analytical samples were obtained by gas chromatography: ir (CCl_4) 1750, 1670, and 1220 cm^{-1}; nmr (CCl_4) δ 1.5–2.4 (m, 6), 1.8 (s, 3), 2.0 (s, 3), 5.6 (m, 1), and 6.1 ppm (m, 1).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.09; H, 8.26.

1-Cyclohexen-1-yl Methyl Ketone.—Prepared by the rearrangement of 1-ethynylcyclohexanol according to the procedure of Newman,[6] a small sample was purified by gas chromatography (Carbowax 20M on Chromosorb W), $\lambda_{max}^{H_2O}$ 239 nm (ϵ 12,000).

2-Cyclohexen-1-yl methyl ketone was prepared by the addition of the conjugated enol acetate, 1-(acetoxyethylidenyl)-2-cyclohexene, to methyllithium according to the method of House and

(1) Supported in part by grants from the National Science Foundation, GP-1572 and GP-6133X.
(2) National Institutes of Health Predoctoral Fellow, 1966–1968, GM-30, 162.
(3) S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, **87**, 3228 (1965).
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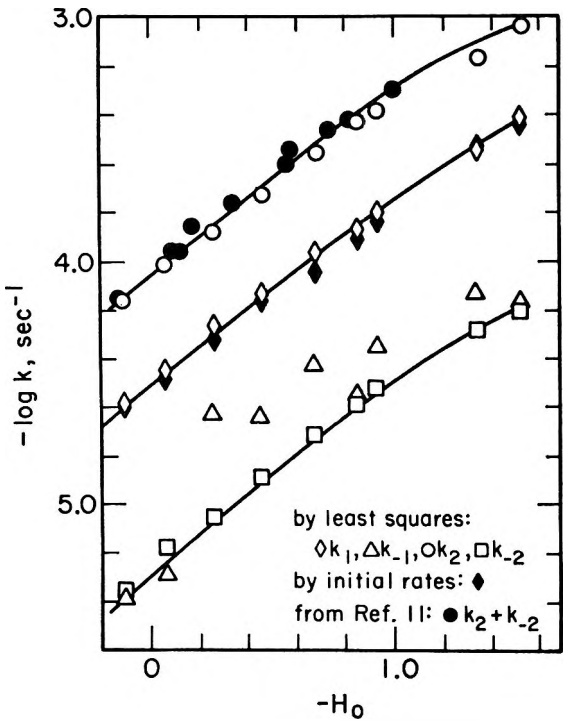


Figure 1.—Rate constants for 4-methyl-4-penten-2-one in aqueous sulfuric acid. Scheme of eq 1.

Trost.[5] Gas chromatography (Carbowax 20M on Chromosorb W) indicated 92% conversion and afforded a pure sample: ir (CCl_4) 1710 cm^{-1}; nmr (CCl_4) δ 1.6–2.1 (m, 6), 2.1 (s, 3), 3.0 (m, 1), and 5.8 ppm (s, 2).

Anal. Calcd for $C_8C_{12}O$: C, 77.37; H, 9.74. Found: C, 77.11; H, 9.99.

2-Cyclohexen-1-yl-1-*d* Methyl Ketone.—This compound was prepared by the same method as its undeuterated counterpart except that the lithium enolate was quenched with a 10% solution of acetic acid-*O*-*d* in deuterium oxide. The product was purified by preparative gas chromatography, and was shown by mass spectroscopy to contain 93.7% deuterium (at C-1) according to isotopic abundances in the fragments).

4-Methyl-4-penten-2-one.—Distillation (spinning-band column containing about 30 theoretical plates, reflux ratio about 50:1) of commercial 4-methyl-3-penten-2-one (mesityl oxide) plus *p*-toluenesulfonic acid as a catalyst[7] resulted in a mixture containing about 30% 4-methyl-4-penten-2-one. Three refractionations (without catalyst) yielded material which was 96% pure. Small amounts of pure substance were obtained as needed from this mixture by gas chromatography (tricresyl phosphate on Chromosorb P): ir (CCl_4) 1720 cm^{-1}; nmr (CCl_4) δ 1.7 (s, 3), 2.0 (s, 3), 3.0 (m, 2), 4.8 (m, 1), and 4.9 ppm (m, 1).

Kinetic Procedures.—With the exceptions of the nmr and mass spectrometer experiments described below, the results here were obtained from the time-dependent behavior of the uv absorbances of the conjugated isomers. We have described the solutions and the apparatus used in the accompanying paper.[4]

The pseudo-first-order rate constants for the isomerizations of 2-cyclohexen-1-yl methyl ketone in H_2SO_4–H_2O and of 2-cyclohexen-1-yl-1-*d* methyl ketone in D_2SO_4–D_2O were determined by the use of the computer program LSKIN1.[8]

The uv data for 4-methyl-4-penten-2-one and for 2-cyclohexen-1-yl methyl ketone in D_2SO_4–D_2O exhibited non-first-order behavior, and they were treated in terms of eq 1 and 2. The integrated kinetic expressions for the conjugated isomers were obtained from the sets of differential rate equations for these schemes using matrix algebra methods which are described elsewhere.[9] The rate constants were computed from a nonlinear least-squares fit of the data to these expressions using a computer program based on Newton's method.[10]

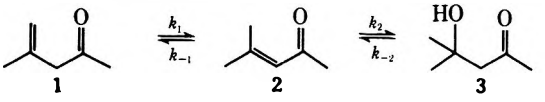
As noted, some rate constants were estimated from the initial rates, *i.e.*, by dividing the limiting slope of the absorbance *vs.* time curve at time zero by the initial concentration of the unconjugated isomer.

In qualitative kinetic experiments with 4-methyl-4-penten-2-one followed by nmr, about 0.2 g of substrate was diluted to 10 ml with 5–10% H_2SO_4. An nmr tube was filled with a portion of the solution and placed in the probe at 30–35°. The concentrations of the three species of this system (4-methyl-4-penten-2-one, 4-methyl-3-penten-2-one, and 4-hydroxy-4-methylpentan-2-one) were monitored by the distinct absorbances due to their C-4 methyl groups.

In the measurement of the rate of exchange of 2-cyclohexen-1-yl methyl ketone in heavy water, about 0.1 g of 2-cylcohexen-1-yl methyl ketone was dissolved in 50 ml of 3% aqueous deuteriosulfuric acid. The solution was placed in a serum-capped flask in a constant-temperature bath at 25.0°. At 5-min intervals 5-ml aliquots were withdrawn by hypodermic syringe and quenched by addition to 50 ml of pentane and 25 ml of water containing about 0.75 equiv of sodium bicarbonate in a separatory funnel. The pentane layer was washed with a saturated aqueous solution of sodium chloride and reduced to about 100 μl with a rotary evaporator. The solution was separated by gas chromatography (SE-30 on Chromosorb W at 120°) and the 2-cyclohexen-1-yl methyl ketone was collected. Low-voltage (30 eV) mass spectral analysis was used to calculate the fraction deuterated from peak heights. Each of the nine points (extending from 8 to 70% reaction) was the average of five or more spectra. High-voltage (70 eV) spectra confirmed that incorporation was in the 1 position: the ratio of the *m/e* 43 to the *m/e* 44 peaks for the acetyl fragment showed natural isotopic abundance, while the ratio of the *m/e* 81 to the *m/e* 82 peaks for the cyclohexenyl fragment was the same as that for the molecular ion.

Results and Discussion

4-Methyl-4-penten-2-one.—The kinetic solutions of 4-methyl-4-penten-2-one (1) in aqueous sulfuric acid showed a comparatively rapid initial increase in absorbance due to the formation of 4-methyl-3-penten-2-one (2). The absorbance reached a maximum which corresponds to about 20 mol % of the total organic material and then slowly decreased to about 6–7%. By comparing the time-dependent nmr spectra of reacting solutions with the spectra of the known materials, it was apparent that as 2 formed it was hydrated to 4-hydroxy-4-methylpentan-2-one (**3**).[11] Therefore, it was felt that the data should be analyzed in terms of the kinetic scheme in eq 1.



(1)

The four pseudo-first-order rate constants were determined at several acidities from a least-squares fit of the integrated rate equation for 2 to the uv data. The results are listed in Table I and are displayed in Figure 1. The last column of this table lists k_1 as determined from the initial rates of appearance of 2. The results show a somewhat larger than desirable scatter. Improved results would have been expected by fixing k_2 and k_{-2} as independently determined by Bell, Preston, and Whitney.[11] However, we chose to allow all constants to be determined by the analysis. The concordance of our values for k_2 and for k_{-2} with those of Bell, *et al.*,[11] is gratifying.

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TABLE I

RATE CONSTANTS FOR 4-METHYL-4-PENTEN-2-ONE IN AQUEOUS SULFURIC ACID.[a] RATE SCHEME OF EQ 1

H_2SO_4, %	$-H_0$	10^4k,[b] sec^{-1} k_1	k_{-1}	k_2	k_{-2}	10^4k_1,[c] sec^{-1}
4.87	−0.11	2.57	0.404	6.85	0.423	2.53
6.54	0.06	3.57	0.510	9.85	0.645	3.28
8.68	0.24	5.36	2.40	13.3	0.895	4.84
11.21	0.46	7.26	2.34	19.1	1.28	6.84
14.27	0.68	11.0	3.79	28.1	1.95	9.14
16.82	0.85	14.1	2.87	37.7	2.63	12.6
18.02	0.93	16.3	4.43	42.0	2.98	14.9
23.98	1.34	29.0	7.41	68.6	5.25	29.8
26.47	1.52	38.8	6.29	96.4	6.96	36.5

[a] Temperature, 25.0°. [b] Determined by least-squares analysis. [c] Determined from initial rate of isomerization.

Results of similar experiments in D_2SO_4–D_2O media are given in Table II. These results show clearly that

TABLE II

RATE CONSTANTS FOR 4-METHYL-4-PENTEN-2-ONE IN D_2SO_4–D_2O. RATE SCHEME OF EQ 2[a]

D_2SO_4, %	$-D_0$	10^4k,[b] sec^{-1} k_1	k_{-1}	k_2	k_{-2}	10^4k_1,[c] sec^{-1}	$k_1^{D_2O}/k_1^{H_2O}$[d]
14.5	0.76	19.2	6.94	5.35	0.369	18.0	1.5
16.0	0.87	22.1	8.99	6.46	0.570	23.8	1.7
17.6	0.99	23.8	12.4	7.75	0.535	21.4	1.3
19.1	1.10	30.6	13.8	8.13	0.645	27.7	1.4
20.1	1.17	30.4	17.2	9.27	0.585	26.5	1.2
21.2	1.24	37.2	17.0	9.66	0.740	32.4	1.2

[a] Temperature, 25.0°. [b] Determined from least-squares analysis. [c] From initial rates. [d] $k_1^{D_2O}$ from column 7, this table; $k_1^{H_2O}$ interpolated from column 7, Table I.

the solvent isotope effect (k_{D_2O}/k_{H_2O}) is greater than one (column 8); therefore, the reaction occurs *via* a rate-determining enolization, as is also the case for other β,γ unsaturated ketones with trisubstituted β carbons which have been studied, $\Delta^{5(6)}$-3-keto steroids,[3] and 3-methyl-3-cyclohexen-1-one.[4]

2-Cyclohexen-1-yl Methyl Ketone.—The rate of formation of 1-cyclohexen-1-yl methyl ketone (**5**) from 2-cyclohexen-1-yl methyl ketone (**4**) showed first-order behavior; the rate constants are listed in Table III. On the other hand, the formation of **5** from **4**

TABLE III

RATE CONSTANTS FOR FORMATION OF 1-CYCLOHEXEN-1-YL METHYL KETONE FROM 2-CYCLOHEXEN-1-YL METHYL KETONE IN AQUEOUS SULFURIC ACID[a]

H_2SO_4, %	$-H_0$	10^4k, sec^{-1}	H_2SO_4, %	$-H_0$	10^4k, sec^{-1}
1.67	−0.62	0.137	17.3	0.88	3.78
2.96	−0.35	0.234	20.8	1.13	5.84
3.92	−0.23	0.342	21.8	1.18	5.86
4.72	−0.13	0.428	26.6	1.53	10.4
6.51	0.06	0.774	28.9	1.70	13.2
9.25	0.31	1.25	32.4	1.96	19.2
13.13	0.60	2.24			

[a] Temperature, 25.0°.

in D_2SO_4–D_2O was monotonic, but not first order. The reason for this became apparent when the rate of exchange of the C-1 hydrogen of **4** was measured to be 3.21×10^{-4} sec^{-1} in 3.01% D_2SO_4 (D_0 = 0.36). This is nearly ten times more rapid than the rate of isomerization as determined from the initial rate of formation

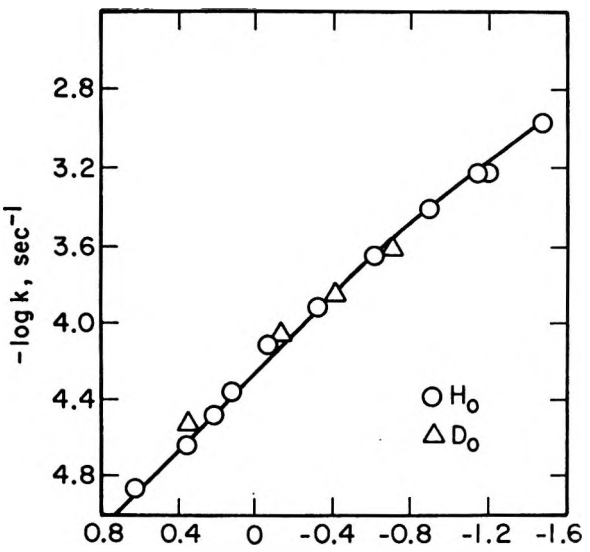


Figure 2.—Solvent isotope effect for formation of 1-cyclohexen-1-yl methyl ketone from 2-cyclohexen-1-yl methyl ketone.

of **5** (see Table V, column 7). Therefore, the exchanged compound, 2-cyclohexen-1-yl-*1-d* methyl ketone (**6**), must be considered a kinetically significant species. The isomerization rates for the two media are compared in Figure 2. Within experimental error there is no solvent effect for the isomerization reaction.

When compound **6** was prepared and then isomerized, first-order behavior was observed; the rate constants are listed in Table IV. By interpolation of these data

TABLE IV

RATE CONSTANTS FOR FORMATION OF 1-CYCLOHEXEN-1-YL METHYL KETONE FROM 2-CYCLOHEXEN-1-YL-*1-d* METHYL KETONE IN D_2SO_4–D_2O[a]

D_2SO_4, %	$-D_0$	10^4k, sec^{-1}
7.0	0.16	2.02
10.3	0.45	3.49
15.0	0.80	6.62

[a] Temperature, 25.0°.

and comparison with the initial rate data from Table V, an isotope effect ($k_{C\text{-}1\ H}/k_{C\text{-}1\ D}$) of 4.5 was calculated for

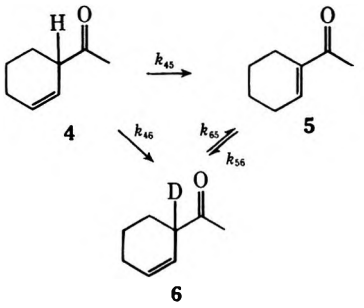
TABLE V

RATE CONSTANTS FOR 2-CYCLOHEXEN-1-YL METHYL KETONE IN D_2SO_4–D_2O. KINETIC SCHEME 2[a]

D_2SO_4, %	$-D_0$	10^4k,[b] sec^{-1} k_{45}	k_{46}	k_{65}	k_{56}	10^4k_{45},[c] sec^{-1}	$k_{C\text{-}1\ E}/k_{C\text{-}1\ D}$ isom[d]
2.94	0.36	2.45	20.4	.383	0.0541	3.04	
6.72	0.13	8.45	66.0	1.27	0.274	8.7	4.5
9.49	0.40	16.8	145	3.00	0.498		
9.75	0.42	18.7	153	3.05	0.518	14.8	4.8
12.9	0.66	37.9	279	6.49	1.21		
13.7	0.71	34.9	301	6.41	1.24	24.2	4.4
17.0	0.94	80.8	692	15.0	3.21		

[a] Temperature, 25.0°. [b] Determined by least-squares analysis. [c] From initial rates. [d] $k_{C\text{-}1\ D}$ interpolated from Table IV.

the isomerization reaction. Thus it was felt that the total behavior of the formation of **5** from **4** in D_2SO_4–D_2O could be accounted for in terms of kinetic scheme 2. Table V lists the rate constants determined for this model by a nonlinear least-squares regression on the uv data for the formation of **5**.



(2)

In summary, we have found that in D_2SO_4–D_2O 2-cyclohexen-1-yl methyl ketone exchanges the hydrogen at C-1 (*i.e.*, enolizes) about ten times faster than it isomerizes to 1-cyclohexen-1-yl methyl ketone. Since the C-1 D compound isomerizes at a rate which is $^1/_{4.5}$th of that of the C-1 H compound, the former compound accumulates, and the formation of the conjugated isomer shows non-first-order behavior. Because enolization is faster than isomerization, we conclude that protonation of the enol has become rate-limiting in the isomerization process, as we have observed previously for 3-cyclohexen-1-one.[4]

Because the medium can be expected to affect the enolization process and the protonation of the enol to form either the α-deuterated β,γ-unsaturated ketone or the α,β-unsaturated ketone, the observed solvent isotope effect is a complex combination of the effects on these individual processes. For enol formation we expect the usual effect (k_{D_2O}/k_{H_2O}) of about 1.4.[4] If we take the effect which has been observed on the protonation of enol ethers[12] or of acetone's enol[13] as a model, we can expect effects of 0.3–0.4 on the protonations of the enol (at the α carbon to form α-deuterated 2-cyclohexenyl methyl ketone and at the γ carbon to form γ-deuterated cyclohexenyl methyl ketone), contributing to the total observed effects on the rate of isomerization in opposing directions. Apparently in this case these contributions result in the total observed effect of 1.0. This is in contrast to the result for 3-cyclohexen-1-one, where the rate of exchange is so much faster than the rate of isomerization that the enolization process is virtually at equilibrium, which is affected comparatively little by the medium. In that case the medium effect on the protonation of the enol leading to isomerized product clearly dominates the observed solvent isotope effect.

Registry No.—**1**, 3744-02-3; **4**, 29372-98-3; **5**, 932-66-1; 1-(acetoxyethylidenyl)-2-cyclohexene, 32958-83-1.

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Photoreduction of 2,4-Dimethyl-3-oxo-3,5,6,7,8,8a-hexahydro-1,8a-butanonaphthalene, a Nonphotorearranging Cross-Conjugated Cyclohexadienone

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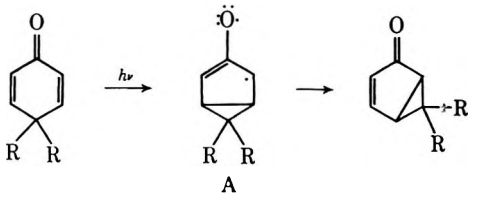
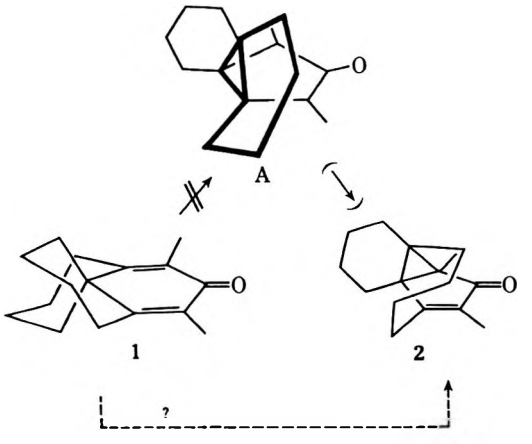
The title substance (1) was prepared from an (iodobutyl)tetrahydronaphthol by internal displacement. Failure of 1 to undergo type A photorearrangement was observed, and a low quantum efficiency for photodecomposition was noted. In 2-propanol solvent, photoreduction of one of the double bonds of 1 was achieved. Nmr examination of 1 and its di- and tetrahydro derivatives allowed stereochemical structure assignments to be made. The mechanism of photoreduction is considered to be a proton abstraction (radical) from solvent by excited 1, followed by a disproportionation.

Recent reports[1,2] examining the influence of steric factors in the type A photorearrangement of 2,5-cyclohexadienones have prompted us to record the synthesis and limited photochemical reactivity of a novel tricyclic dienone (1). Our original intent in preparing the ring system of **1** was to attempt to disprove the mechanistic proposals for the type A photoisomerization of cyclohexadienones advocated by Zimmerman.[3] A key intermediate in the latter scheme involves bridging between β and β' positions of the conjugated system (A). It will be observed that due to the geometric constraints imposed by the tetramethylene bridges of the spiro ring system of 1 the intermediate (containing as it would a trans-fused norcarane ring—bold face bonds) may not





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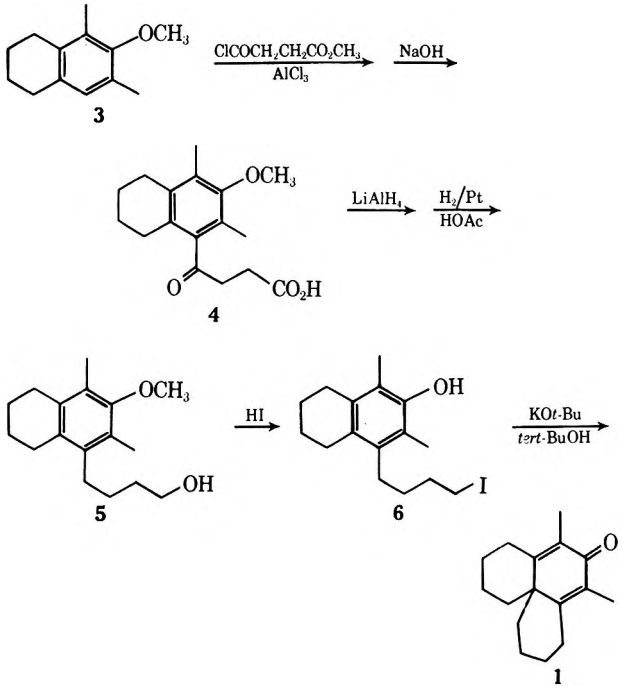
be easily formed from **1**. However, the ultimate product of a type A rearrangement (**2**) appears to be capable of existence by examination of molecular models.[4] Consequently, were the photorearrangement to proceed and to yield the normal product (**2**), a full-fledged intermediate such as that previously proposed (A) would have to be discounted and alternatives (*e.g.*, perhaps a concerted mechanism) would receive support. On the other hand, should an abnormal product arise, further insight into the properties of the excited species produced by irradiation of cyclohexadienones might be gained.

Results

Synthesis of Dienone 1.—A representative of the desired ring system was prepared from 7-methoxy-6,8-dimethyl-1,2,3,4-tetrahydronaphthalene[5] (**3**) by the sequence shown. Friedel–Crafts condensation of β-carbomethoxypropionyl chloride with **3** followed by saponification gave **4**. This was exhaustively reduced,



first with lithium aluminum hydride and then catalytically with hydrogen and platinum in acetic acid in order to convert some residual intermediate aryl carbinol to **5**. Treatment with aqueous hydriodic acid then simultaneously converted the methyl aryl ether to a phenol and the primary alcohol function on the side chain to an iodide, yielding **6**. Upon treatment with potassium *tert*-butylate in *tert*-butyl alcohol, **6** gave, probably through an Ar_2^--6-assisted[6] ionization, a low conversion to the target structure **1**, mp 148°, which was isolated by column chromatography.

Photolysis in Isooctane.—When **1** was submitted to intense irradiation in degassed isooctane solution (*ca.* 0.003 *M*) at wavelengths (254 nm, from low-pressure mercury lamps) corresponding to its ultraviolet absorption, relatively slow photochemical decomposition was observed. No characterizable photolysis product could be isolated from solution after or during irradiation. A brown residue formed on the walls of the reaction vessel and had to be removed periodically, since it suppressed further photoconversion of **1**. Examination of this material revealed only tars. At the conclusion of irradiation no ultraviolet-absorbing species remained in solution.

In view of the negative preparative results obtained, a brief examination of the efficiency of the photodecomposition of **1** was undertaken. The photoreduction of benzophenone in 2-propanol is known to proceed with a quantum yield near unity,[7] and this reaction may therefore be used for crude actinometry. Qualitative experiments comparing the rate of photodisappearance of benzophenone (degassed 2-propanol) against the rate for **1** (isooctane) under otherwise identical conditions such that all incident light was absorbed in each case, indicated that **1** disappeared from solution at least 20 times more slowly than did benzophenone. It follows that the quantum efficiency for photoreaction of **1**, by whatever mechanism, must be less than 0.05.

Similar photochemical behavior for **1** was observed when it was intensively purified by sublimation–recrystallization (to remove possible adventitious quenchers), when it was irradiated in other inert (purified) solvents, when it was irradiated selectively at the $n \rightarrow \pi^*$ transition, or when photosensitization (acetophenone) was attempted. In no case was a photorearrangement product obtained.

Photoreduction of 1 in 2-Propanol.—In an effort to gain some indication of the photochemical fate of **1**, irradiation in 2-propanol was attempted.[1] Slow disappearance of dienone was again observed, but when the reaction was interrupted short of completion a new crystalline ketone, **7** (mp 123°), could be isolated by column chromatography. This was demonstrated to be a reduction product by mass spectroscopy, which revealed the addition of two atomic weight units over that of starting dienone. Additional spectroscopic evidence (ir 1655, 1615 cm^{-1}; uv 251 nm) indicated a cyclohexenone structure. Examination of the nmr spectrum revealed that the resonance from one of the methyl groups in the dienone had become split (J = 7 Hz) and had moved to higher field, as if the carbon to which it were attached had become quaternized by addition of a hydrogen nuclei. On this evidence and reasonable mechanistic considerations, the new substance appeared most probably to have resulted from the addition of a molecule of hydrogen (actually derived from the dehydrogenation of 2-propanol) across one of the double bonds of **1**.

However, some form of concurrent rearrangement could not be excluded, and therefore an independent synthesis of the new material was thought desirable. Controlled catalytic reduction of **1**, such that only 1 equiv of hydrogen was absorbed, yielded a new substance which was demonstrably *different* (tlc behavior)

(4) The double bond of **2** should be relatively free of torsional strain since its trans substituent positions are linked by a seven-atom chain at worst: J. A. Marshall and H. Faubl, *J. Amer. Chem. Soc.*, **92**, 948 (1970); J. R. Wiseman and W. A. Pletcher, *ibid.*, **92**, 956 (1970).

(5) W. Cocker, *J. Chem. Soc.*, 36 (1946).

(6) R. Baird and S. Winstein, *J. Amer. Chem. Soc.*, **84**, 788 (1962); see also S. Masamune, *ibid.*, **86**, 288 (1964); E. J. Corey, N. N. Girotra, and C. T. Mathew, *ibid.*, **91**, 1557 (1969); T. G. Crandall and R. G. Lawton, *ibid.*, **91**, 2127 (1969).

(7) J. N. Pitts, Jr., R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Recktenwald, and R. B. Martin, *ibid.*, **81**, 1068 (1959); see also W. M. Moore and M. D. Ketchum, *J. Phys. Chem.*, **68**, 214 (1964); M. J. Gibian, *Tetrahedron Lett.*, 5331 (1967); N. Filipescu and F. L. Minn, *J. Amer. Chem. Soc.*, **90**, 1544 (1968); S. G. Cohen and J. I. Cohen, *Israel J. Chem.*, **6**, 757 (1968). With rigorous exclusion of oxygen Φ may approach 2 for this system.

from the photoreduction product, plus a substantial amount of recovered dienone 1. The nonidentity of the reduction products was not particularly surprising, since the catalytic procedure would be expected to yield a cis hydrogenation product, which models indicate to be sterically congested and therefore not to be the thermodynamically favored isomer. The new substance was partially separated by column chromatography; the material obtained proved to be an oil which apparently contained a small amount of unreduced 1. In view of its noncrystallinity, the reduction product could not be assumed to be a homogeneous substance. Consequently, an attempt was made to convert it to a more easily characterizable compound, which it was hoped would turn out to be 7. The oil was refluxed in trifluoroacetic acid, whereupon it was isomerized cleanly to a new material (8) which had properties (tlc behavior) quite similar to 7. However, upon purification (column chromatography) and characterization, the new substance (mp 92°) was shown to be a *saturated* cyclohexanone (see Experimental Section). Apparently, reduction of the intermediate cyclohexenone was more facile than reduction of the dienone 1;[8] this fits with the observation that roughly an equivalent amount of unreduced dienone 1 was recovered in the reduction even though a full mole of hydrogen was absorbed.

At this point a chemical correlation had not been established with respect to the photoreduction product 7. However, a thorough nmr investigation of the materials in hand was undertaken at this juncture, with the result that a complete stereochemical assignment could be made for 7 as well as for the tetrahydro substance produced by catalytic reduction (8). This required use of high-field strength 250 MHz instrumentation in conjunction with the lanthanide shift reagent $Eu(THD)_3$[9] and spin decoupling. Consideration of the spectral data upon which the structures were based is deferred to the Discussion.[10]

Discussion

Lack of Photorearrangement of 1.—The failure of the cross-conjugated cyclohexadienone 1 to photoisomerize was until recently without precedent.[1] Negative results of the sort here obtained are open to numerous interpretations. Insofar as possible we shall avoid concocting an explanation for the failure of 1 to yield rationalizable rearrangement product. However, we do feel that some significance may be attached to the low quantum efficiency (<0.05) for the disappearance of 1 from solution. This should be contrasted with unconstrained cyclohexadienones which undergo type A photorearrangement with quantum efficiencies near unity.[1,3] While the actual mode of deactivation of photoexcited 1 remains undetermined, it is clear that type A photoisomerization has been greatly retarded, if not prevented altogether, by the tetramethylene bridges of 1. This is entirely consistent with Zimmerman's mechanism for the latter process, in which β,β' bonding may be a requisite first step. As indicated in the introduction, access to such a mode of reactivity is effectively denied to 1 by steric considerations. Hence, our result might be taken as negative evidence in support of Zimmerman's scheme. However, regarding our original objective, the type A photoproduct (*e.g.*, 2) is itself characteristically photolabile,[11] and therefore cannot be excluded as an intermediate which does not accumulate due to the relatively low efficiency of its formation. With this in mind it is worthwhile taking a closer look at the steric constraint upon type A photorearrangement imposed by the ring system of 1. The extra ring strain (beyond that of a cyclopropane ring) induced upon β,β' bonding in 1 (*i.e.*, the intermediate A) would be comparable to that in *trans*-cycloheptenone, which can be produced by photoisomerization of *cis*-cycloheptenone.[12] Hence, the type A process must be regarded as feasible.[13] Consequently, for 1 the conclusions must be drawn either that (a) the driving force for β,β' bonding, etc., upon electron promotion is sufficiently powerful to overcome this steric prohibition only <5% of the time (and that the product 2 is further degraded), or (b) that the driving force is insufficient and some other mechanism operates in this specific case to give a different product. Although speculations may be drawn about other plausible modes of photoreaction, among them dimerizations, reductive hydride transfer (see later) and various types of fragmentation, we decline to do so here.

We should like to note that the photochemical inertness of 1 does allow further inference to be drawn regarding the nature of the intermediates within Zimmerman's generalized scheme. There is still some question as to whether the structure of the type A intermediate possesses a finite lifetime or whether it is merely a formalism which does not have a discrete existence within the scope of a concerted process. In the latter case, α,γ bonding would be synchronous with β,β' bonding (and with β',γ bond rupture). The conceptual alternatives are represented pictorially in the figures as path A_1 and path A_2, respectively. The geometrical distinction between the two is an exiguous one, but it has to do with the motion of the $RC_\gamma R$ group. In path A_1 this group translates to a symmetrical position above the ketone-containing ring (this corresponds to the type A intermediate) and then undergoes a transposition with rotation to give the final product. In path A_2 rotation commences immediately as the $RC_\gamma R$ group

(8) Alternatively, it may be that the intermediate cyclohexenone was simply not desorbed from the catalyst; the stereochemistry of the double reduction is consistent with this interpretation (see Discussion).

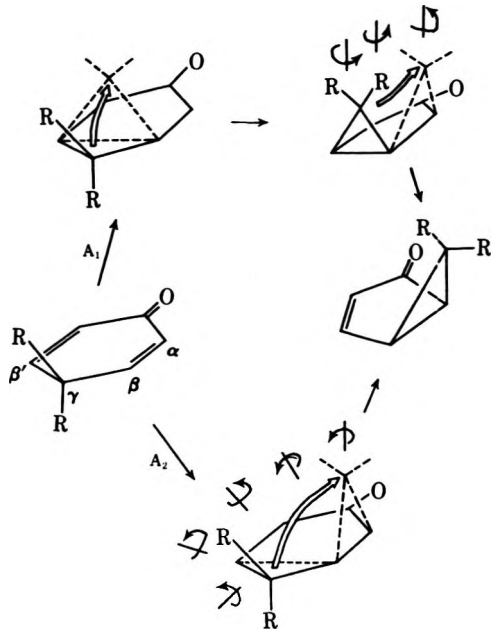
(9) Tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium.

(10) It might appear that a chemical correlation would still be feasible by catalytic hydrogenation of the photoreduction compound 7 to the corresponding saturated ketone, with subsequent comparison (after isomerization) with the tetrahydro substance (8). However, it is not obvious that the same stereochemistry would be obtained in the hydrogenation of 7, since the configuration produced for the methyl group in photoreduction of 7 is the opposite to that expected for catalytic cis monohydrogenation of 1 (see Discussion). Hence, there is no reason to expect 7 to be adsorbed cleanly on the catalyst on the same face of the molecule as the intermediate in the hydrogenation of 1 (which ultimately gives 8). Due to this uncertainty and to a shortage in the quantity of available 7, and because there is considered to be no ambiguity in structural assignments, this reduction was not examined.

(11) H. E. Zimmerman, R. Keese, J. Nasielski, and J. S. Swenton, *J. Amer. Chem. Soc.*, **88**, 4895 (1966); F. Frei, C. Ganter, D. Kägi, K. Kocsis, M. Miljkovic, A. Siewinski, R. Wenger, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **49**, 1049 (1966).

(12) E. J. Corey, M. Tada, R. LaMahieu, and L. Libit, *J. Amer. Chem. Soc.*, **87**, 2051 (1965); P. E. Eaton and K. Lin, *ibid.*, **87**, 2052 (1965). The presumption that strain in a trans cycloalkene, $(CH)_2(CH_2)_n$, approximates that in the corresponding *trans*-bicyclo[$(n-1).1.0$] ring system has justification in fact: W. Kirmse and C. Hase, *Angew. Chem., Int. Ed. Engl.*, **7**, 891 (1968); P. G. Gassman, F. J. Williams, and J. Seter, *J. Amer. Chem. Soc.*, **90**, 6893 (1968); A. J. Ashe, III, *Tetrahedron Lett.*, 523 (1969); K. E. Wiberg and A. de Meijere, *ibid.*, 519 (1969).

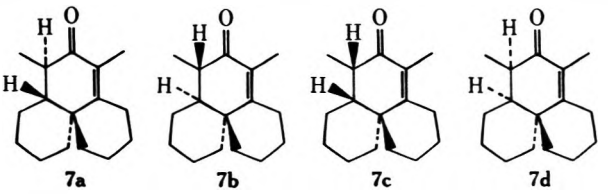
(13) There is an initial input of 75–90 kcal of excitation energy (assuming triplet manifold).



leaves the plane of the cyclohexadienone ring and continues in the course of a concerted reaction to give the product.[14] Of course, there may be a continuum of reaction paths between these conceptual extremes. The pertinent observation is that **1** would accommodate itself better to path A_2 than to path A_1, since in the former the trans-fused norcarane structural feature (introduction) tends to be avoided. From the photochemical inertness of **1** it is possible to infer that path A_1 more accurately describes the course of the *normal* type A process, and that an intermediate with a finite lifetime is required (perhaps to achieve spin inversion and electron demotion). However, this is offered as a suggestion only, since it is based upon negative evidence.[15]

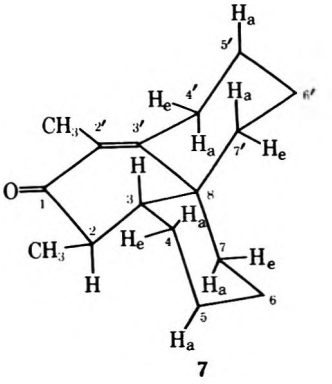
Since we were chiefly interested in reactions which might be competitive with the normal type A isomerization, and especially in view of the elegant substantiation of Zimmerman's mechanism provided in his examinations of dienone photoreactivity since the inception of this work, we have not probed further into the photobehavior of this ketone in nonparticipating solvents. We have limited our discussion to the steric aspects of the molecule **1**, since electronic considerations have been adequately presented elsewhere.[1,3,14] Particular attention should be drawn to a sterically constrained system devised by Zimmerman which also failed to rearrange.[1] The latter study complements ours, since the constraint in that system was designed to prevent the second step in path A_1 (above). As noted, ours was designed to inhibit the first step. The similarity in the photochemical behavior of the two systems is probably not coincidental, since they additionally give related (but different) photoreduction products (subsequent sections).

Structure of 7 and 8.—As previously indicated, the new ketone obtained in low yield upon photolysis in 2-propanol appeared to be a reduction product resulting from the transfer of two hydrogen atoms from the solvent to one of the double bonds of **1**. It must be realized, however, that a number of diastereomers can result from this operation. Of the four possibilities depicted, only the first (**7a**) is consistent with the nmr



7a **7b** **7c** **7d**

evidence. The normal (60 MHz, CCl_4 solution) spectrum consists of a broad envelope upon which is superimposed, as the only recognizable functionalities, a singlet (δ 1.77) arising from the methyl group remaining on a double bond and a doublet (δ 1.05, J = 7 Hz) arising from the other methyl group. Upon the addition of increments of $Eu(THD)_3$,[9] these (and other resonances) are progressively shifted strongly downfield, until at saturation the methyl groups appeared to have suffered an induced shift of *ca.* 9.7 ppm relative to TMS (δ_{Eu} 11.3 and 10.8, respectively).[16] Even more strongly affected was a single-proton multiplet which ultimately was shifted to δ_{Eu} 15.0 downfield from TMS.[16] This must be assigned[18] to H-2, adjacent to the carbonyl



7

group and on C-2 bearing the methyl group. Less strongly affected was a one-proton *doublet*, δ_{Eu} 8.8 (J = 12 Hz), which was shown to be coupled to H-2 by irradiation of the latter signal. Coupling of this magnitude indicates a trans diaxial vicinal relationship for this proton (H-3) and H-2 as shown in the perspective view. Of most significance, however, is the observation that H-3 is not further coupled. It is therefore concluded that this proton must have a gauche relationship with *both* protons of the adjacent methylene group ($H_{a,e}$-4). This is only feasible for the stereochemical relationship depicted; the fusion of the C-4–C-7 annelated ring is therefore fixed as being cis relative to the octalone portion of the rest of the molecule. While trans fusion is

(14) A variation of this is to have the primary photochemical process be a twisting of one of the double bonds in the dienone. See ref 1 for a discussion on this point. See also R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed Engl.*, **8**, 781 (1969), Section 6.2, for orbital symmetry aspects of the concerted pathway.

(15) Moreover, see ref 1 for contrary arguments.

(16) The chemical shifts designated by δ_{Eu} in this paper are those measured for the particular samples used in this study in which carbon tetrachloride solutions saturated with $Eu(THD)_3$ were examined. Since the induced shift is highly concentration dependent the usual meaning of δ (extrapolation to infinite dilution) should not be inferred for these measurements. For this study ΔEu values[17] were not derived, since for the majority of protons sufficient resolution was not obtainable until the end of the shifting process, when the spectrum was examined at 250 MHz; extrapolated values in the absence of shift reagent were thus not calculable. Due to the line broadening effect of the reagent, couplings of less than 2–3 Hz were not observable.

(17) P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *J. Amer. Chem. Soc.*, **92**, 5734, 5737 (1970).

(18) For purposes of discussion the positions are numbered nonsystematically according to the figures given. Full names are given in the Experimental Section.

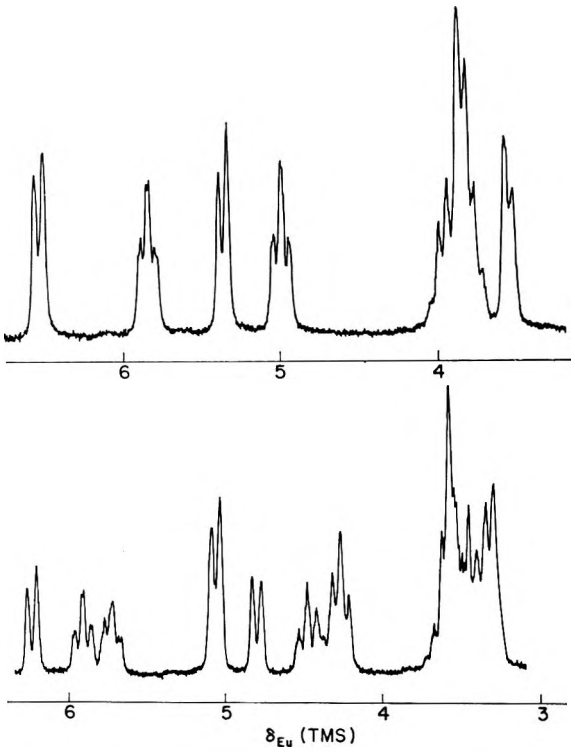
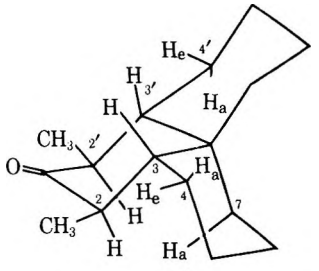


Figure 1.—Portions of Eu(THD)$_3$ shifted spectra of 1 (upper) and 7 (lower). See text and footnote 16 for interpretation.

stereochemically feasible (**7b**, above) it would definitely produce a trans diaxial relationship which should further split H-3.

However, failure to observe further coupling for the β proton (H-3) of **7** is negative evidence. It would be desirable to have an analogous structure wherein the alternative stereochemical relationship could be examined to substantiate the nmr interpretation. The saturated cyclohexanone **8**, produced by



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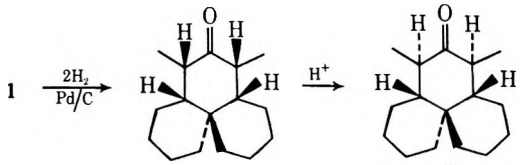
catalytic hydrogenation and acidic isomerization, fulfills this objective excellently. For this substance there are of course several more configuration possibilities than for **7**. Those which potentially contain a twofold rotation axis (as does **1**), etc., may be immediately excluded by the nmr observation that the unshifted methyl groups (δ 0.86 and 0.93, J = 7 Hz) are nonequivalent. Of the remaining isomers, only that depicted in perspective is considered to be consistent with the known relative thermodynamic stability of **8** and the Eu(THD)$_3$ shifted spectrum of this material at 250 MHz. For **8** the methyl groups undergo an induced shift of nearly the same magnitude as in **7** when a carbon tetrachloride solution is saturated with Eu(THD)$_3$ (both δ_{Eu} 9.1). Similarly, the α protons (which are also nonequivalent) are shifted to δ_{Eu} 11.7 and 12.3 (H-2 and H-2′, relative assignments undetermined) as was the corresponding proton of **7**. In addition, the β protons were found to be shifted to a similar relative position as in **7**. However, in this case one of these protons, δ_{Eu} 7.8, was a *triplet* (coupling *ca.* 12 Hz) whereas the other was a *doublet*, δ_{Eu} 7.4 (J = 10 Hz). We find this uniquely consistent with the structure pictorially represented. The latter resonance (doublet) arises from H-3, which is coupled only to H-2, since it bears a gauche relationship with both protons of the C-4 methylene group as in **7**. The triplet resonance, ascribed to H-3′, is coupled to both H-2′ and the axial proton (H_a-4′) of the adjacent methylene group, to both of which it bears a trans diaxial vicinal relationship (and hence experiences an equivalent coupling). The feasible structural alternatives for **8** (*i.e.*, other than that shown) either do not possess trans diaxial orientation between the α and β protons (H-2,-H-3 and H-2′,H-3′) and/or fail to display acceptable relationships between the β and γ protons (H-3,H_{ae}-4 and H-3′,H_{ae}-4′). Accordingly, the course of the catalytic hydrogenation must be as depicted (**1** → **8**).



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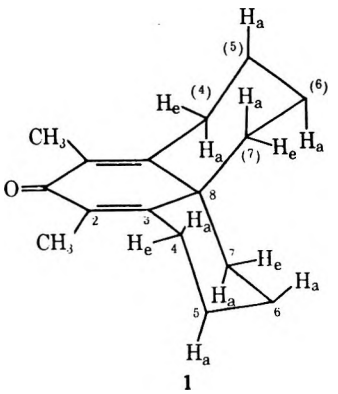
The preceding paragraphs have outlined the nmr spectral features which allow assignment of structure to **7** and **8**. In the case of the photoproduct, however, a reservation must be made that there is no proof that carbon skeleton rearrangement has not taken place. One should consider the possibility that **7** in fact possesses a different ring system. We have two reasons for discounting this prospect. One is that we are unable to formulate an isomeric structure which is consistent with the data cited. Secondly, additional features of the nmr spectrum of **7** lend confidence to the assumption that a common carbon framework is shared by all of the substances which we have identified; specifically, the annelated tetramethylene bridges are part of cyclohexane rings which in each case are *locked into chair conformations*. The 250-MHz spectrum of the dienone **1** in the presence of Eu(THD)$_3$ was also recorded and is partially presented in Figure 1. In addition to the substantial shift of the methyl groups (δ_{Eu} 12.1, not shown), four additional resonances were sufficiently moved that their coupling patterns could be discerned. It was evident that these arose from the methylene protons on C-4 and C-7. There were two



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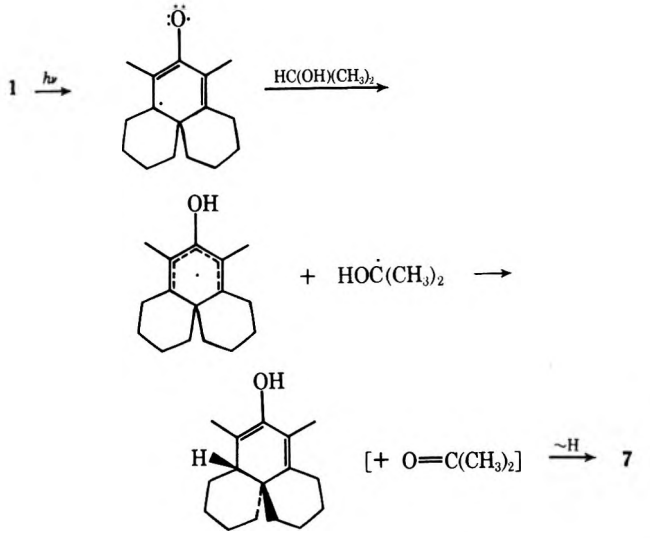
doublets (δ_{Eu} 6.6, J = 14 Hz and δ_{Eu} 5.4, J = 14 Hz) which must be assigned to positions equatorial to six membered rings (H_e-4 and H_e-7), where they experience only geminal coupling. The axial protons to which they are coupled (δ_{Eu} 5.9 and 5.0, respectively) are *triplets* (coupling *ca.* 13 Hz). This latter splitting is interpreted as the resultant of reciprocal geminal coupling to the equatorial protons *plus* trans diaxial vicinal coupling of the same magnitude to one other proton in each case. Suitable stereochemistry for this latter pattern is found for both the axial proton H_a-4 (adjacent to the double bond) and the axial proton H_a-7 (adjacent to a quaternary center); the other axial protons (H-5, H-6) should exhibit further coupling (however, they are buried in an eight-proton multiplet, δ_{Eu} 3.5–4.1). There is no internal evidence to allow relative assignments of the described resonances to the C-4 or C-7 methylene positions. (However, see the discussion of **7** which follows.)

The point of describing the nmr spectrum of **1** is that correlations may be drawn to the corresponding resonances observed in **7**, lending credence to the assumption that skeletal rearrangement has not taken place in the photoreduction. Of course, the symmetry of **1** has been destroyed in **7**, such that the tetramethylene bridges are no longer equivalent. It is apparent (Figure 1) that the downfield doublet and triplet of **1** have been split into four resonances in **7**. Furthermore, it was confirmed by spin decoupling that the furthest downfield doublet in **7** (δ_{Eu} 6.2, J = 14 Hz) is geminal to the second triplet upfield (δ_{Eu} 5.7), whereas the adjacent triplet (δ_{Eu} 5.9) is coupled to a single proton doublet 0.9 ppm upfield (δ_{Eu} 4.8, J = 14 Hz). It is our feeling that the large difference in the chemical shifts found in the equatorial protons indicates that the downfield resonances in **1** and **7** arise from the C-4 (C-4′) methylene hydrogens which are (were) adjacent to a double bond. The other methylene groups described in the spectrum of **1** are little effected by saturation of one of the double bonds. A two-proton doublet, δ_{Eu} 5.1 (J = 13 Hz, equatorial protons), in the same region of the spectrum as in the case of **1** was shown by spin decoupling to be geminal to an apparent two-proton quartet (δ_{Eu} *ca.* 4.5) which we feel is best interpreted as overlapping (axial proton) triplets. As before, these resonances are regarded as arising from C-7 (C-7′) methylene groups. It will be noted that an additional two-proton triplet (or, more likely, overlapping pair of doublets) has been shifted selectively downfield (δ_{Eu} *ca.* 4.3) from the six-proton multiplet arising from the rest of the hydrogens in the molecule (δ_{Eu} 3.1–3.8). No assignment is offered for these resonances; by irradiation they appeared to be coupled only to the high-field multiplet. The correlations which we have pointed out strongly support the conclusion that there are tetramethylene bridges existing in chair conformation cyclohexane rings in **7** (as in **1**).

The region of the spectrum exhibited in Figure 1 (and just discussed) was also examined in the Eu(THD)$_3$ shifted spectrum of the saturated ketone **8**. While resonances were observed in the same places, extensive overlapping precluded analysis of the sort given for **1** and **7**. However, one proton was selectively shifted proportionately further downfield. This resonance (δ_{Eu} 6.0) was a triplet (coupling *ca.* 13 Hz), suggesting it to be one of the axial hydrogens previously discussed. From inspection of models we believe it to be H_a-7 (see perspective representation of **8**), which is located over the cyclohexanone ring and in close proximity to the α protons (C-2, C-2′) which are strongly deshielded.

In discussing the induced shift results we have avoided speculation as to the mode of action of the europium chelate, which probably operates through coordination with the carbonyl group. We have not given a more quantitative evaluation of the magnitude of the shifts, since extrapolated ΔEu values[17] were not easily obtainable[16] and because the mechanism by which the europium nucleus accomplishes its effects is presently incompletely established.[19] Trial calculations using formulae which have been suggested[17,19,20] and which might have unambiguously settled the question of structure in **7** (or led to firm assignments of the C-4 and C-7 methylene group protons) were not fruitful, since the results depended grossly upon the orientation assumed for the carbonyl-O to Eu coordination and since the Eu to H distances were all approximately the same for the critical protons.[21]

Mechanism of Photoreduction of 1.—Clearly a hydrogen abstraction step is involved in the production of **7**, and based upon precedent, the sequence given is



considered most probable. Purely on the basis of analogy,[1,3] the photochemically active state of **1** we believe to be the n → π^* triplet, although preparatively the irradiation was absorbed by the $\pi \rightarrow \pi^*$ band. Intersystem crossing is generally more than sufficiently facile to account for the observed quantum efficiency.[1,3] Moreover, hydrogen abstraction to give ketyl radicals is characteristic of the n → π^* state.[1,7] The next step is formulated as disproportionation of the radical pair to give acetone and the enol of **7**. (We disfavor the possibility that the radical from **1** abstracts another hydrogen from solvent 2-propanol, since this would seem to be an endothermic step. Disproportionation of two mole-

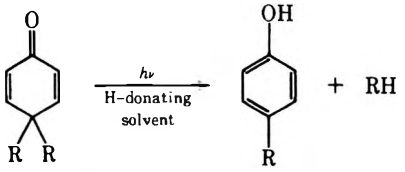
(19) In addition to the pseudocontact interaction the possibility of a contact interaction operating through the π system cannot be excluded. For pertinent references see C. C. Hinckley, M. R. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, **93**, 2417 (1971).

(20) J. Briggs, F. A. Hart, and G. P. Moss, *Chem. Commun.*, 1506 (1970); A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5149, 5153 (1970).

(21) Z. W. Wolkowski, *Tetrahedron Lett.*, 821 (1971); T. H. Siddall, III, *Chem. Commun.*, 452 (1971).

cules of the radical from 1 is also reasonable.) This second proton appears to enter into the less hindered site of the molecule; the product which would ultimately result from attack upon the opposite (more hindered) position of the π electronic system is inconsistent with the nmr spectral evidence, as cited in the previous section.[22] The final step of the mechanism is ketonization of the enol, which preferentially should produce the substance in which a trans hydrogenation of one of the double bonds in 1 has been achieved, since this configuration is clearly the most stable (equatorial methyl group).

Finally, we would point out that this photoreduction appears to be unique among cyclohexadienones. In those few cases in which type A photorearrangement (or the diversion of intermediates therefrom) is not the exclusive reaction path, formation of a phenol by expulsion of one of the ring substituents has been the alternative reaction course.[1,23] We were able to detect



only a trace of material which may have been phenolic[1] in the reductive photolysis of 1. It is not unreasonable that the annelated rings attached to the cyclohexadienone nucleus of 1 might suppress this mode of reactivity, especially if the expulsion step were a reversible radical fragmentation.[24,25] Alternatively, it may be that the fragmentations also proceed from the type A intermediate, and that transient β,β' bonding may be obligatory in those cases as well.

Experimental Section

Preparation of 4.—To a stirred solution of 109.75 g (0.58 mol) of 3[5] and 132 g (0.88 mol) of β-carbomethoxypropionyl chloride[26] in 300 ml of benzene maintained at 0–6.5° was added slowly 132 g (1.0 mol) of aluminum chloride. After stirring for 16 hr at room temperature the mixture was decomposed with ice and diluted with hydrochloric acid. The oily product was extracted into ether and dried with anhydrous sodium sulfate. The residue obtained upon removal of the ether solvent was distilled at reduced pressure. There was obtained 145 g of crude methyl ester of 4, bp 180–186° (0.01 mm), which solidified on standing. Spectral evidence indicated that the ester was impure; therefore it was saponified to the carboxylic acid. The distillate was dissolved in 500 ml of dioxane and was added to a solution of 50 g of sodium hydroxide in 1.0 l. of water. The mixture was warmed and stirred until a homogeneous solution was obtained and then was allowed to stand for 1 hr. Upon acidification a substance precipitated which was collected and recrystallized from 2.0 l. of toluene. There was obtained 123 g (73%) of β-(2,4-dimethyl-3-methoxy-5,6,7,8-tetrahydro-1-naphthoyl)propionic acid (4), mp 182–183°.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.23; H, 7.73.

Preparation of 5.—To a solution of 80.8 g (0.28 mol) of 4 in 500 ml of tetrahydrofuran was added portionwise 10.0 g of lithium aluminum hydride and the mixture was refluxed for 3 hr. An additional 5.0 g of lithium aluminum hydride was then added and refluxing was continued for 2 hr. Excess hydride was destroyed with methanol and the solvent was removed under vacuum. The residue was treated with dilute hydrochloric acid and the mixture so obtained was extracted with ether. After drying over anhydrous sodium sulfate, the solvent was removed. The product at this stage was a mixture of a cyclic ether, a diol, and a hydroxy ketone, which could be separated by column chromatography. For preparative purposes, the unresolved mixture was hydrogenolyzed to 5. Adams catalyst was prepared by reducing 0.5 g of platinum oxide in 100 ml of acetic acid. To this was added the mixture from the hydride reduction in 200 ml of acetic acid; hydrogen uptake proceeded for 24 hr under several atmospheres pressure. The filtered solution was then added to excess sodium hydroxide solution (hot) and stirred to saponify any ester which may have formed. The chilled basic solution was then extracted with ether and, after drying, the extracts were evaporated to give a residue which solidified upon standing. Recrystallization from hexane gave 34 g (46%) of 2,4-dimethyl-1-(4-hydroxybutyl)-3-methoxy-5,6,7,8-tetrahydronaphthalene (5), mp 66–67°.

Anal. Calcd for $C_{172}H_6O_2$: C, 77.82; H, 9.99. Found: C, 78.41; H, 10.06.

Preparation of 6.—A mixture of 20.0 g (0.076 mol) of 5 and 200 ml of 50% hydriodic acid was refluxed for 1.5 hr. The cooled solution was diluted with water and the insoluble oil was extracted into methylene chloride. The extracts were washed with water, saturated sodium bicarbonate solution, and saturated sodium chloride solution. After drying, the solvent was removed and the residue was recrystallized from 100 ml of hexane to give 19.9 g (73%) of 1,3-dimethyl-4-(4-iodobutyl)-5,6,7,8-tetrahydro-2-naphthol (6), mp 87–88°. This substance decomposed on standing.

Anal. Calcd for $C_{16}H_{23}IO$: C, 53.64; H, 6.47. Found: C, 54.06; H, 6.64.

Preparation of 1.—To a solution of 10.0 g (0.028 mol) of 6 in 150 ml of *tert*-butyl alcohol was added 10.0 g of commercial potassium *tert*-butylate and the solution was stirred until homogeneous. Upon heating a precipitate (KI) formed. After 15 min at reflux the mixture was poured into 500 ml of cold water and extracted with ether. After washing with water and saturated sodium chloride solutions, the extracts were evaporated to give a residual oil. This was submitted to column chromatography on 80 g of silicic acid with chloroform eluent. First eluted was a yellow oil, followed by 1 and then by another yellow oil. The chromatographic fractions containing 1 were combined and purified by recrystallization from 20 ml of hexane followed by sublimation at 100° (0.1 mm). A final recrystallization from hexane gave 0.77 g (12%) of 2,4-dimethyl-3-oxo-3,5,6,7,8,8a-hexahydro-1,8a-butanonaphthalene (1): mp 147.5–148°; ir ν_{max}^{KBr} 1650 and 1610 cm^{-1}; mass spectrum m/e 230; $\lambda_{max}^{n\text{-hexane}}$ 247 nm (ϵ 16,000), 321 sh (26), 331 (32), 343 (31), 357 (20), and 371 sh (8); $\lambda_{max}^{i\text{-PrOH}}$ 253.5 nm; nmr $\delta_{max}^{CCl_4}$ 1.85 (d, J = 0.8 Hz, CH_3 coupled across double bond to one methylene proton) and 0.8–3.0 ppm (m, CH_2) (see also text).

Anal. Calcd for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.27; H, 9.45.

Photoreduction of 1.—A solution of 600 mg (2.6 mmol) of 1 in 550 ml of distilled 2-propanol was irradiated (Vycor flask) at 40–50° with a bank of 16 low-pressure mercury arcs (Rayonet photochemical reactor) for 185 hr, at which time the absorbance at *ca.* λ 250 nm had decreased by >60%. Solvent was removed by distillation and evaporation on a rotary evaporator and the oily residue was submitted to column chromatography on 50 g of silicic acid with carbon tetrachloride–chloroform gradient elution. Fractions were collected periodically and evaporated to dryness. From later fractions was obtained after recrystallization from hexane 106 mg of starting material dienone 1. More rapidly eluted was a new substance which was recrystallized from hexane to give 55 mg (9% based on unrecovered 1) of 2,*cis*-4-dimethyl-3-oxo-*cis*-3,4,4a,5,6,7,8,8a-octahydro-1,8a-butanonaphthalene (7): mp 123–123.5°; ir ν_{max}^{KBr} 1655 and 1615 cm^{-1}; mass spectrum m/e 232; λ_{max}^{EtOH} 251 nm (ϵ 10,500); nmr (see text).

Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.77; H, 10.52.

No product could be isolated following relatively slow photodegradation in the following solvents: CH_3CN, *i*-C_8H_{18}, *n*-C_6H_{14}, $(C_2H_5)_2O$, and *tert*-C_4H_9OH.

(22) The steric discrimination is between one or two 1,3-diaxial interactions in the transition state.

(23) K. Schaffner, *Advan. Photochem.*, **4**, 81 (1966).

(24) We note that in the parallel study of Zimmerman previously cited,[1] explusion of a methyl group was the reaction course which was observed.

(25) The mechanism we suggest is closer to that proposed by Zimmerman[1] than to the alternative originally postulated by Schuster: D. I. Schuster and D. J. Patel, *J. Amer. Chem. Soc.*, **87**, 2515 (1965); D. I. Schuster and C. J. Polowczyk, *ibid.*, **88**, 1722 (1966); however, see D. I. Schuster and D. J. Patel, *ibid.*, **90**, 5145 (1968).

(26) J. Cason, "Organic Syntheses," Collect. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 169.

Catalytic Hydrogenation of 1.—A solution of 233 mg (1.0 mmol) of 1 in 15 ml of ethyl acetate was added to a prereduced mixture of 24 mg of catalyst (10% palladium on carbon) in 5 ml of ethyl acetate in a conventional (1 atm pressure) hydrogenation apparatus. After stirring for 45 min, *ca.* 24 ml of hydrogen had been absorbed and the reduction was interrupted. Catalyst was removed by filtration and solvent was evaporated under reduced pressure. The residue was submitted to column chromatography on 17 g of silicic acid with chloroform eluent. Product was eluted first, followed by 83 mg of recovered 1. Since the new substance could only be obtained as an oil contaminated with 1, it was directly isomerized. Chromatographic fractions containing reduced material were combined and dissolved in *ca.* 1 ml of trifluoroacetic acid and the solution was refluxed for 1.5 hr. After removal of solvent the residue was submitted to column chromatography as before. After combination of appropriate chromatographic fractions and recrystallization from hexane, there was obtained 66 mg of *cis*-2,*cis*-4-dimethyl-3-oxo-*cis*-perhydro-*trans*-1,8a-butanonaphthalene (8): mp 91.5–92.5°; ir ν_{max}^{KBr} 1700 cm^{-1}; mass spectrum *m/e* 234; nmr (see text).

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.01; H, 11.23.

Registry No.—1, 32670-24-9; 4, 32670-25-0; 5, 32670-26-1; 6, 32670-27-2; 7a, 32653-54-6; 8, 32653-55-7.

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Hydride Reduction of *N*-Cyclopropylimines

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The fate of intermediates generated by hydride addition to the carbon atom of *N*-cycloalkylimines was studied to determine the stability of species which have a negatively charged nitrogen atom adjacent to a small ring. When sodium aluminum hydride or lithium aluminum hydride was used as the hydride source, cleavage of the three-membered ring accompanied reduction of the carbon–nitrogen double bond. However, only the imine group was reduced when sodium borohydride, lithium borohydride, or hydrogen and platinum were employed. Results are rationalized in terms of isomerizations analogous to the cyclopropylcarbinyl allylcarbinyl anion conversion.

The proclivity for cyclopropylcarbinyl anions to undergo ring opening to give the isomeric allylcarbinyl anions is well known.[2] For example, reactions[3,4] of cyclopropylcarbinyl Grignard and lithium reagents, Wolff–Kishner reduction[2] of certain cyclopropyl aldehydes, treatment of cyclopropylcarbinyl quaternary salts with sodium amide,[2] and addition of isopropyllithium[5] to substituted vinyl cyclopropanes all lead to products which involve ring opening of a cyclopropylcarbinyl species having some carbanoid character. In like manner, cyclopropoxides rearrange to carbonyl compounds.[6]

To determine the stability of intermediates which have a negatively charged nitrogen atom adjacent to the small ring, we examined the consequence of adding hydride to the carbon atom of a number of *N*-cycloalkylimines. The imines studied included *N*-(3-phenylpropylidene)cyclopropylamine (1), *N*-benzylidenecyclobutylamine (2), *N*-benzylidene(*trans*-2-phenylcyclopropyl)amine (3), *N*-(3-phenylpropylidene)benzylamine (4), and *N*-benzylidenecyclopropylamine (5). Lithium aluminum hydride, sodium aluminum hydride, lithium borohydride, and sodium borohydride were employed as hydride sources. The course of catalytic hydrogenation was also investigated.

In previous work, Kaiser, Burger, and coworkers[7] observed that reduction of *N*-(2-phenylcyclopropyl)-formamide with lithium aluminum hydride gave not the expected *N*-methylamine but *N*-methyl-3-phenylpropylamine. In addition, 2-phenylcyclopropylamine was found to be unstable to lithium aluminum hydride. Our results are in accord with theirs and also establish the requirements for ring opening in a variety of *N*-cycloalkylimine–hydride reductions.

Results

Condensation reactions between the appropriate amines and aldehydes provided the desired imines. These preparations are summarized in Table I.

Imine reductions were accomplished by refluxing an ether or tetrahydrofuran (THF) solution approximately 0.05–0.5 *M* in the imine with an excess of the complex hydride. Reactions were quenched by addition of a 1:1 mixture of 10% sodium hydroxide and ethanol or 10% hydrochloric acid and methanol and the products were isolated by distillation and characterized by nmr analysis and in some cases by independent synthesis. Results are collected in Tables II and III.

Discussion

The results in Table III may be divided into two groups: those reactions in which reduction of the carbon–nitrogen bond is accompanied by ring cleavage (runs 1, 2, 5, 7, 8, 10, 11) and those examples in which reduction leaves the small ring intact (runs 4, 13–19). The aluminum-containing reagents belong to the former group, the borohydrides and catalytic hydrogenation to the latter.

Runs 1 and 5 show that ring opening is not a function of the group attached to the imine carbon atom, and run 4 demonstrates that ring cleavage is unimportant in the case of *N*-cyclobutyl compounds.

Ring-opened products can be accounted for by a scheme involving isomerization of intermediate I to

(1) NASA Fellow.

(2) C. L. Bumgardner and J. P. Freeman, *Tetrahedron Lett.*, 737 (1964).

(3) M. S. Silver, P. R. Shafer, J. E. Nordlander, C. Ruchardt, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 2647 (1960).

(4) P. T. Lansbury and V. A. Pattison, *ibid.*, **85**, 1886 (1963).

(5) J. A. Landgrebe and J. D. Shoemaker, *ibid.*, **89**, 4465 (1967).

(6) C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

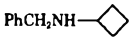
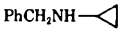
(7) C. Kaiser, A. Burger, L. Zirngibl, C. S. Davis, and C. L. Zirkle, *J. Org. Chem.*, **27**, 768 (1962).

TABLE I
IMINES

Compd	$R_1CH{=}NR_2$ R_1	R_2	Bp, °C (Torr)	$n^{25}D$	Yield, %	Nmr,[a] δ (ppm)
1[b]	$PhCH_2CH_2$ a		75.8 (0.5)	1.5502	62	7.72 (vinyl), 7.15 (phenyl), 2.72 (benzyl), 2.50 (a) 0.90 (cyclopropyl)
2[b]	Ph		128–130 (0.5)	1.5885	42	8.07 (vinyl), 7.70, 7.32 (phenyl), 3.13, 2.16, 1.90 (cyclobutyl)
3[b]	Ph		135–137 (0.5)	1.5950	45	8.38 (vinyl), 7.66, 7.30 (phenyl), 3.15, 2.50, 1.70 (cyclopropyl)
4[b]	$PhCH_2CH_2$ c b		75–76 (0.5)	1.5598	73	7.70 (vinyl), 7.17 (phenyl), 4.50 (a), 2.83 (c), 2.60 (b)
5[b]	Ph		56–58 (0.5)	1.5750	60	8.40 (vinyl), 7.69, 7.38 (phenyl), 3.00, 0.91 (cyclopropyl)

[a] Ratios of signals were in agreement with assigned structures. Spectra were run as approximately 5% by volume solutions in deuteriochloroform with the probe temperature at 25°. [b] Satisfactory analytical data (±0.4%) for C, H, and N were reported: Ed.

TABLE II
AMINES

Compd	Structure[a]	Bp, °C (Torr)	$n^{25}D$	Nmr,[b] δ (ppm)
6[c]	$PhCH_2CH_2CH_2NHCH_2CH_2CH_3$ f e d c b a	71–73 (0.5)	1.5094	7.16 (phenyl), 2.55 (f, d, c), 1.77 (e), 1.43 (b), 0.98 (amine), 0.90 (a)
7[d]	$PhCH_2NHCH_2CH_2CH_3$	57–59 (0.5)	1.5068	7.13 (phenyl), 3.72 (benzyl), 2.52, 1.48, 0.90 (propyl), 1.18 (amine)
8[d]	$PhCH_2NHCH_2CH_2CH_2Ph$ d c b a	145–147 (0.5)	1.5732	7.25, 7.17 (phenyl), 3.75 (d), 2.62 (c, a), 1.79 (b), 1.29 (amine)
9[d]		81–82 (0.3)	1.5248	7.19 (phenyl), 3.55 (benzyl), 3.17, 2.10, 1.56 (cyclobutyl), 1.31 (amine)
10[d]		53 (0.2)	1.5309	7.26 (phenyl), 3.77 (benzyl), 2.07, 0.45 (cyclopropyl), 1.85 (amine)

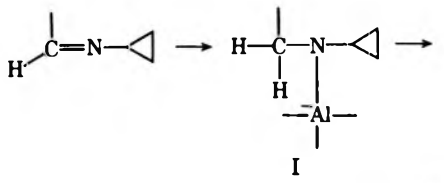
[a] The infrared and mass spectra were consistent with assigned structures. [b] Ratios of signals were in agreement with assigned structures. Spectra were run as approximately 5% by volume solutions in deuteriochloroform with the probe temperature at 25°. [c] *Anal.* Calcd for $C_{12}H_{19}N$: C, 81.29; H, 10.80; N, 7.90. Found: C, 80.68; H, 10.16; N, 8.40. [d] Satisfactory analytical data (±0.4%) were reported: Ed.

TABLE III
IMINE REDUCTIONS

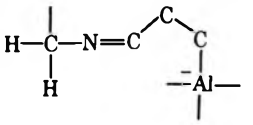
Run no.	Imine	Reducing agent	Solvent	Time, hr	Products	Product ratios[a]	Yield, %	Ring opening
1	1	$LiAlH_4$	Ether[a]	12	6		43	Yes
2	3	$LiAlH_4$	Ether[a]	12	8		85	Yes
3	4	$LiAlH_4$	Ether[a]	12	8		85	
4	2	$LiAlH_4$	Ether[a]	12	9		45	No
5	5	$LiAlH_4$	Ether[a]	12	7		80	Yes
6	5	$LiAlH_4$	Ether[b]	4	10		59	No
7	5	$LiAlH_4$	THF[b]	12	7		50	Yes
8	5	$LiAlH_4$	THF[b]	4	7 + 10	9:1	58	Yes
9	5	$NaAlH_4$	Ether[b]	12				
10	5	$NaAlH_4$	THF[b]	24	7 + 10	1:1	47	Yes
11	5	$NaAlH_4$	THF[b]	12	7 + 10	1.5:8.5	60	Yes
12	5	$NaAlH_4$	THF[b]	4	10		30	No
13	5	$LiBH_4$	Ether[b]	12	10		45	No
14	5	$LiBH_4$	THF[b]	12	10		47	No
15	5	$LiBH_4$	THF[b]	24	10		52	No
16	5	$NaBH_4$	Ether[b]	12	10		42	No
17	5	$NaBH_4$	THF[b]	12	10		57	No
18	5	$NaBH_4$	THF[b]	24	10		67	No
19	5	H_2/Pt	EtOH[c]	12	10		72	No
20	10[e]	$LiAlH_4$	Ether	12	7 + 10	2:8	49	Yes

[a] 200 ml ether, 0.10 mol imine, 0.12 mol $LiAlH_4$. [b] 100 ml solvent, 0.0050 mol imine, 0.0070 mol of the complex metal hydride. [c] 100 ml ethanol, 0.050 mol imine, 30 psig H_2. [d] Based on nmr analyses. [e] Amine.

intermediate II, in analogy with carbon (and oxygen) derivatives which tend to transfer by ring cleavage the negative center from the cyclopropylcarbinyl to an allylcarbinyl site.

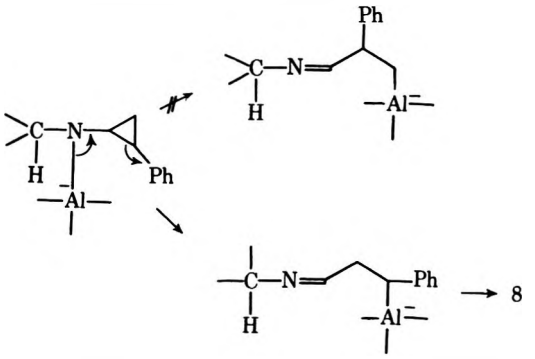


I



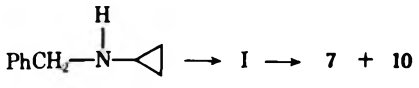
II

Consistent with this picture are runs 2 and 3, which show that phenyl substitution on the small ring results in unidirectional cleavage to give only the 3-phenylpropylamine and not the isomeric 2-phenylpropyl compound. The low-energy path should be the one leading to an intermediate having a partial negative charge adjacent to the phenyl ring.



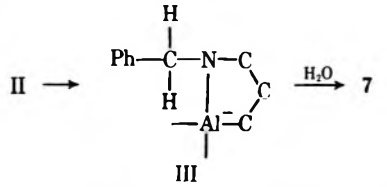
Catalytic hydrogenation (run 19), which presumably does not involve highly polar intermediates such as I, does not yield ring-opened products. Similarly, runs 13–18, which probably proceed through intermediates having nitrogen bound to the small, nonmetallic boron atom, do not result in ring cleavage.

The fact that the ratio of amine **7** to amine **10** is time-dependent (runs 5–8, 10–12) indicates that intermediate I is present and capturable, *i.e.*, that conversion of starting material into II is not concerted. Additional support for the role of intermediate I is available from run 20. This reaction, starting with *N*-benzylcyclopropylamine and lithium aluminum hydride, provides another route to intermediate I and the products **7** and **10**.



Even under conditions where some starting imine was recovered, no *N*-propylidene derivatives (expected from hydrolysis of intermediate II) were isolated. Intermediate II may undergo, as previously suggested,[7] rapid conversion into the five-membered cyclic intermediate III,[8] hydrolysis of which yields the final saturated acyclic product.

In any event, we conclude from the results summarized in Table III that intermediates having a negatively charged nitrogen atom adjacent to a three-membered ring are not stable and isomerize readily *via* ring opening.



III

Experimental Section[9]

General.—The following materials were used: benzaldehyde (N.F.) (Baker), benzylamine (Matheson Coleman and Bell), cyclobutylamine (Ash-Stevens), cyclopropylamine (Columbia Organic Chemicals), hydrocinnamaldehyde (Practical) (Matheson Coleman and Bell), *trans*-2-phenylcyclopropylamine (Aldrich), lithium aluminum hydride (Metal Hydrides), sodium borohydride (Metal Hydrides), lithium borohydride (Alfa Inorganics), sodium aluminum hydride (Alfa Inorganics).

Preparation of Imines.—To approximately 0.1 mol of the amine in an ice bath, approximately 0.1 mol of the aldehyde was slowly added with stirring. After 90 min 3 g of ground KOH was added to remove water; 30 min later the solution was extracted with five 10-ml portions of ether. The decanted ether layers were combined and dried over magnesium sulfate. The ether was removed on a rotary vacuum apparatus and the remaining imine was distilled under reduced pressure using a Vigreux column. A viscous red residue remained after distillation.

Physical constants, yields, and analyses of the distillates are recorded in Table I.

Imine Reduction with $LiAlH_4$ and $NaAlH_4$.—The imine was added with stirring to the hydride in either tetrahydrofuran or ether and the mixture was refluxed for 4–24 hr (Table III). After removing the heat, 20 ml of a 1:1 mixture (by volume) of 10% NaOH and 95% ethanol was added. The ether was decanted and the residue was washed with ether. (When THF was used as the solvent, it was removed on a rotary vacuum apparatus and the residue was mixed with 50 ml of ether.) The combined ether layers were extracted with five 10-ml portions of 10% HCl. The acid solution was made basic with aqueous NaOH and extracted with five 10-ml portions of ether. The combined ether layers were dried over magnesium sulfate and the ether was removed on a rotary vacuum apparatus. Distillation through a Vigreux column under reduced pressure separated the amines from a small amount of a viscous red residue.

Physical constants and analyses of the distillates are listed in Table II. Yields and product ratios are collected in Table III.

Imine Reduction with $NaBH_4$ and $LiBH_4$.—The procedure for imine reduction with $NaBH_4$ and $LiBH_4$ was identical with that for imine reduction with $LiAlH_4$ and $NaAlH_4$ except that the hydride was destroyed with 25 ml of a 1:1 mixture (by volume) of 10% HCl and methanol instead of a 1:1 mixture of 10% NaOH and 95% ethanol.

For physical constants and analysis of the products see Table II. For yields and product ratios see Table III.

Imine Reduction by Catalytic Hydrogenation.—Approximately 0.05 mol of the imine in 100 ml of 95% ethanol was reduced at room temperature in a Parr pressure apparatus with 0.09 g of platinum oxide under hydrogen at 30 psig.

Results are recorded in Tables II and III.

Registry No.—**1**, 32861-45-3; **2**, 32861-46-4; **3**, 22783-18-2; **4**, 32861-47-5; **5**, 3187-77-7; **6**, 28031-50-7; **7**, 2032-33-9; **8**, 32861-51-1; **9**, 32861-52-2; **10**, 13324-66-8; $LiAlH_4$, 16853-85-3; $NaAlH_4$, 13770-96-2; $LiBH_4$, 16949-15-8; $NaBH_4$, 1333-73-9; H_2, 1333-74-0; Pt, 7440-06-4.

Acknowledgment.—We are grateful to the National Science Foundation for financial support.

(8) For a possible oxygen analog of III, see W. T. Borden, *J. Amer. Chem. Soc.*, **92**, 4900 (1970).

(9) Boiling points are uncorrected. Nuclear magnetic resonance spectra were obtained using either a Varian T-60 or A-100 high-resolution spectrometer using tetramethylsilane as an internal standard. Infrared spectra were determined with a Perkin-Elmer infrared spectrophotometer Model 521 with a sodium chloride prism. Mass spectra were obtained using an Associated Electronics Model MS-12 mass spectrometer. Elemental analyses were performed on a F & M Scientific CHN Analyzer Model 185.

Photodifluoramination of Cycloalkanes

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Received August 31, 1971

Irradiation (253.7 nm) of cyclobutane, cyclopentane, and cyclohexane with tetrafluorohydrazine in the gas phase gives in high yield the corresponding difluoraminocycloalkanes. In contrast, similar treatment of cyclopropane results in a complex mixture including $F(CH_2)_3NF_2$, $F(CH_2)_2NF_2$, FCH_2NF_2, and $F(CH_2)_2CN$. Possible processes by which these products arise and the role of excited intermediates are examined.

Irradiation (253.7 nm) of tetrafluorohydrazine (N_2F_4) and acyclic saturated hydrocarbons in the gas phase leads to substitution of a hydrogen atom by an NF_2 moiety.[2] If the hydrocarbon reactant is unsaturated, addition of the elements of NF_3 across the multiple bond also becomes an important process.[2] To extend the scope of these reactions to cycloalkanes, we examined the photodifluoramination of cyclohexane, cyclopentane, cyclobutane, and cyclopropane. All of these compounds, with the notable exception of cyclopropane, smoothly undergo substitution. In contrast, addition and novel fragmentation occur in the case of the three-membered ring.

Results and Discussion

Results are summarized in Tables I, II, and III.

Table I shows that cyclobutane, cyclopentane, and cyclohexane all undergo substitution of hydrogen by NF_2, a reaction previously found[2] to be characteristic of acyclic alkanes. This substitution process is believed to involve the following steps (1–4).[2]

$$N_2F_4 \longrightarrow 2NF_2 \quad (1)$$

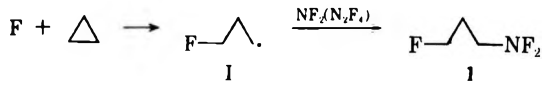
$$NF_2 \xrightarrow{h\nu} NF + F \quad (2)$$

$$RH + F \longrightarrow HF + R \quad (3)$$

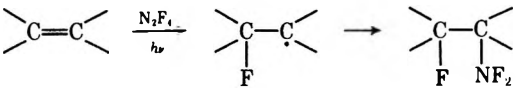
$$R + NF_2(N_2F_4) \longrightarrow RNF_2 \quad (4)$$

As shown by the first three entries in Table I, difluoraminocycloalkanes were isolated in high yield and no ring cleavage or isomerization of the intermediate cycloalkyl radical was detected. These observations in the case of cyclobutane provide additional evidence, this time from a gas-phase reaction at 25°,[3] that the cyclobutyl radical is stable with respect to isomerization to cyclopropylcarbinyl and allylcarbinyl forms.

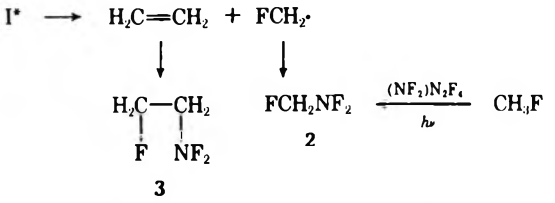
On the other hand, entry 4, Table I shows that the only C_3 products isolated from the cyclopropane reaction are acyclic, suggesting that F attacks at a C–C bond to give intermediate I.



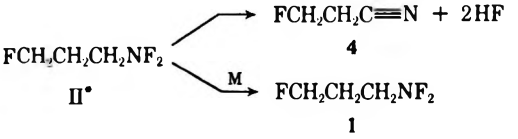
Capture of intermediate I by an NF_2 group would lead to 1-difluoramino-3-fluoropropane (1) in analogy with addition reactions of alkenes,[2] alkynes, and other unsaturated substrates.[4]



Formation of the unusual C_1 and C_2 fragments[5] given in Table I may be rationalized in terms of intermediate I also. If this radical is chemically activated, I*, it may undergo unimolecular decomposition to ethylene and the fluoromethyl radical. The latter intermediate



would be expected to be converted readily to difluoraminofluoromethane (2), which was independently synthesized by photolysis of NF_2 with methyl fluoride. Since ethylene is known to yield 1-difluoramino-2-fluoroethane (3) under the reaction conditions, finding this adduct in Table I is understandable once a source of ethylene is provided.[6] Generation of I in an excited state seems plausible, since rupture of the highly strained ring accompanies formation of the very strong C–F bond.[7] Also, if intermediate II is produced "hot," II*, dehydrofluorination to give 1-cyano-2-fluoroethane (4) can compete with deactivation steps



(1) NASA Fellow.

(2) (a) C. L. Bumgardner, E. L. Lawton, K. G. McDaniel, and H. Carmichael, *J. Amer. Chem. Soc.*, **92**, 1311 (1970); (b) for a general review, see W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969, pp 206–228.

(3) In the liquid phase at 0°, chlorination of cyclobutane gives cyclobutyl chloride free of allylcarbinyl chloride and 1,4-dichlorobutane: C. Walling and P. S. Fredricks, *J. Amer. Chem. Soc.*, **84**, 3326 (1962).

(4) C. L. Bumgardner and M. Lustig, *Inorg. Chem.*, **2**, 662 (1963); M. Lustig, C. L. Bumgardner, and J. K. Ruff, *ibid.*, **3**, 917 (1964); C. L. Bumgardner and K. G. McDaniel, *J. Amer. Chem. Soc.*, **91**, 1032 (1969); C. L. Bumgardner and G. P. Crowther, Abstracts, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969.

(5) The general process $RCH_2CH_2\cdot \rightarrow R\cdot + H_2C{=}CH_2$, although common in hydrocarbon pyrolyses [C. Walling in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 440] would not be expected to be facile at room temperature. Furthermore, radicals of the type FCH_2CH_2CHR generated by hydrogen abstraction during photodifluoramination do not fragment (ref 2).

(6) C. L. Bumgardner, *Tetrahedron Lett.*, 3683 (1964).

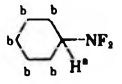
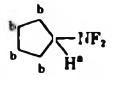
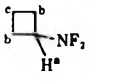
(7) The energy initially associated with I* is the sum of the translational energy of the reacting F and cyclopropane, the activation energy, and the enthalpy of the reaction. This last value should be substantial since the strain energy of the cyclopropane ring is estimated to be 46 kcal/mol [J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1965, p 113] and the C–F bond strength is in the neighborhood of 110 kcal/mol [J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," Wiley, New York, N. Y., 1966, p 824.]

TABLE I
PHOTODIFLUORAMINATION OF CYCLOALKANES

Entry	Starting material	Product	Yield,[a] %	Type of process
1	Cyclohexane	Difluoraminocyclohexane	70	Substitution
2	Cyclopentane	Difluoraminocyclopentane	62	Substitution
3	Cyclobutane	Difluoraminocyclobutane	56	Substitution
4	Cyclopropane	1-Difluoramino-3-fluoropropane (1)	*b*	Addition and fragmentation
		1-Difluoramino-2-fluoroethane (3)		
		Difluoraminofluoromethane (2)		
		1-Cyano-2-fluoroethane (4)		

[a] Based on the equation $2RH + 2N_2F_4 \rightarrow 2RNF_2 + N_2F_2 + 2HF$. [b] Depends on pressure; see Experimental Section and Table III.

TABLE II
CHARACTERIZATION OF PHOTOPRODUCTS[a]

Entry	Starting material	Products	Registry no.	Chemical shift[b] ϕ	Chemical shift[b] δ	Coupling constant, Hz	Ir, cm^{-1}
1	Cyclohexane		14182-78-6	-43.2 (NF_2)	3.29 (t in m, CH^a) 1.10–2.10 (m, CH_2^b)	$J_{FH^a} = 26$	2950 (CH) 2860 (CH) 965 (NF_2) 843 (NF_2)
2	Cyclopentane		14182-80-0	-53.2 (NF_2)	3.93 (t in m, CH^a) 1.60–2.30 (m, CH^b)	$J_{FH^a} = 23$	2950 (CH) 930 (NF_2) 840 (NF_2)
3	Cyclobutane		32979-58-1	-44.6 (NF_2)	4.20 (t in m, CH^a) 2.67 (m, CH^b) 2.28 (m, CH^b) 1.99 (m, CH_2^c)		2950 (CH) 950 (NF_2) 915 (NF_2) 850 (NF_2)
4	Cyclopropane	$^aFCH_2{}^bCH_2{}^cCH_2{}^dNF_2{}^e$	20575-36-4	$+221.7$ (t in t, CF) -54.4 (NF_2)	4.50 (d in t, CH_2^b) 2.05 (d in m, CH_2^c) 3.70 (t in t, CH_2^d)	$J_{F^aH^b} = 48$ $J_{F^aH^c} = 25$ $J_{H^bH^c} = 6$ $J_{F^eH^d} = 28$ $J_{H^cH^d} = 6$	2960 (CH) 1129 (CF) 1070 (CF) 935 (NF_2) 845 (NF_2)
		$^aFCH_2{}^bCH_2{}^cNF_2{}^d$	3732-68-1	$+224.3$ (t in t, CF) -54.3 (NF_2)	4.64 (d in t, CH_2^b) 3.75 (t in d, in t, CH_2^c)	$J_{F^aH^b} = 48$ $J_{F^aH^c} = 23$ $J_{F^dH^c} = 25$ $J_{H^bH^c} = 5$	2950 (CH) 1060 (CF) 868 (NF_2) 860 (NF_2)
		$^aFCH_2NF_2{}^b$	3732-65-8	$+202.8$ (t, CF) -27.6 (NF_2)	5.15 (d in t, CH_2)	$J_{F^aH} = 48$ $J_{F^bH} = 22$	2950 (CH) 1130, 1125 (CF) 929, 860, 845, 940, 935 (NF_2)
		$FCH_2{}^aCH_2{}^bCN$	504-62-1	$+216.8$ (t in t, CF)	4.52 (d in t, CH_2^a) 2.65 (d in t, CH_2^b)	$J_{FH^a} = 45$ $J_{FH^b} = 22$ $J_{H^aH^b} = 5$	2990, 2920 (CH) 2260 (CN) 1080 1040 (CF) 1010

[a] Mass spectra and satisfactory combustion analyses (±0.4% for C, H, N) were obtained for new compounds in entries 2–4: Ed. The data recorded in entry 1 for difluoraminocyclohexane agree with those reported by K. Baum, *J. Org. Chem.*, **32**, 3648 (1967), and by C. M. Sharts, *ibid.*, **33**, 1008 (1968), who prepared this compound by different routes. [b] Spectra were run as approximately 5% by volume solutions in deuteriochloroform with the probe temperature at 25°. Fluorine (^{19}F) chemical shifts (ϕ) are in parts per million relative to fluorotrichloromethane as an external reference. Proton (^1H) chemical shifts (δ) are in parts per million downfield relative to tetramethylsilane as an internal reference. Ratios of signals agreed with assigned structures.

TABLE III
PRESSURE DEPENDENCE OF PRODUCTS FROM IRRADIATION OF CYCLOPROPANE AND N_2F_4

Inert gas (CF_4)	Mmol of product: −33° Trap FCH_2CH_2CN	−86° trap FCH_2CH_2-CH_2NF_2	−86° trap FCH_2-CH_2NF_2	−126° Trap FCH_2NF_2
None	0.25	Trace	0.08	0.60
310 Torr	0.15	0.06	0.07	0.63

which yield a ground state molecule. Photodifluoramination of methane is known to give mixture of CH_3NF_2 and HCN, the latter product arising from decomposition of excited CH_3NF_2.[8] Therefore, the partitioning of I* between **1** and the fragments (Table

(8) C. L. Bumgardner, E. L. Lawton, and H. Carmichael, *Chem. Commun.*, 1079 (1968).

I) and the ratio of **4** to **1** should be pressure dependent.[9]

Table III indicates that increasing the pressure by addition of inert CF_4 does favor production of **1** at the expense of **4**. Interestingly, though, the amounts of **2** and **3** remain unchanged so that fragmentation of I* is unaffected. This difference in quenchability between I* and II* may be attributed to the higher energy of the former.[10]

The results in Table I contrast with those from photochlorination of cyclopropane, which yields mainly the substitution product, chlorocyclopropane, in the gas phase below 100° and the addition product, 1,3-dichloropropane, in the liquid phase at 0°.[11] Moreover, Fettis, Knox, and Trotman-Dickenson[12] observed that cyclopropane and fluorine, in the temperature range −60 to 20°, react to give fluorocyclopropane (substitution) and a fluoropropene, which presumably comes about *via* isomerization of the small ring fluoride. In our study the failure to observe any difluoraminocyclopropane, the simple substitution product, is puzzling. Since the yield of volatile products from the cyclopropane reaction was small, the possibility exists that difluoraminocyclopropane was produced, but was removed by secondary decompositions resulting in high-molecular-weight materials (see Experimental Section). In any event, formation of **1** from cyclopropane appears to be a clear case of radical addition to the small ring and **2** and **3** obviously arise from C–C cleavage unprecedented in the chemistry of cyclopropane.

Experimental Section[13]

Caution: Tetrafluorohydrazine and derivatives should be handled with care. The reactions and isolation operations were conducted routinely behind shields.

Starting Materials.—Cyclohexane (Matheson Coleman and Bell, spectral grade), cyclopentane (Columbia Organic Chemicals, 99%), cyclopropane (Matheson, 99%), methyl fluoride (Matheson, 99%), and carbon tetrafluoride (Matheson, 99.7%), were used as received except for cyclopentane, which was redistilled prior to use. Cyclobutane was synthesized from cyclobutyl bromide (Ash Stevens, 99%) by the method described by Pomerantz, *et al.*[14] Tetrafluorohydrazine of the (mol %) composition 99.3% N_2F_4, 0.1% N_2O, 0.4% NO, 0.1% N_2, 0.1% NF_3, and 0.02% N_2F_2 was kindly supplied by the Gorgas Laboratory of the Redstone Research Division of the Rohm and Haas Co., Huntsville, Ala.

Photodifluoramination of the Cycloalkanes.—Results are summarized in Table I. The reaction of cyclopropane is described as an example. A high-vacuum system was used to transfer reactants to a 650-ml Pyrex glass reaction vessel. Kel-F90 fluorocarbon grease was used on all joints and stopcocks. The lamp employed in the photolyses was a low-pressure cold cathode mercury resonance lamp (Hanovia 2537) housed in a spiral Vycor 791 glass envelope of sufficient thickness to filter all radiation below 210 nm and to transmit approximately 60% of the 253.7-nm radiation. A 5000-V AC transformer (Nester-Faust NFUV-400) served as the power supply. The immersion lamp was sealed into the center of the reaction vessel. Photolyses were conducted at room temperature. The reaction mixture, consisting of a 1:1 molar ratio of hydrocarbon to tetrafluorohydrazine at 270 Torr total initial pressure, was irradiated for 90 min.

Difluoraminoalkanes were separated from the other products,[15] SiF_4, N_2F_2, oxides of nitrogen, and unchanged starting material, by trap-to-trap distillation on the vacuum line through −33, −86, −126, and −197° traps in series. The contents of each trap were purified further by chromatography on a Barber and Coleman Model 5000 gas chromatograph using a QF-1 column and a Bendix Model 12 Time-of-Flight mass spectrometer as a detector. In those cases where the vacuum line fractions consisted of mixtures, the composition was determined by analysis of the ^1H nmr spectrum. Pure compounds were isolated by collecting samples as they were eluted from the chromatographic column. In order to obtain sufficient material for characterization (Table II), fractions from four successive runs were combined.

To determine product variation with pressure, the reaction described above was repeated with the addition of 310 Torr of the inert gas, CF_4. Results are recorded in Table III.

Of the 15 mmol of carbon atoms introduced in the 5 mmol of cyclopropane charged, only 3 mmol of carbon atoms were accounted for as products or recovered starting material. The remainder appeared in the form of a brown residue coating the walls of the reaction vessel. Such residues were not obtained when cyclohexane, cyclopentane, or cyclobutane was the reactant.

Cyclopropane (135 Torr) was irradiated alone for 60 min in the apparatus described to determine the photolytic stability of the hydrocarbon. No decomposition was detected by infrared or mass spectroscopy.

Registry No.—N_2F_4, 10036-47-2; cyclohexane, 110-82-7; cyclopentane, 287-92-3; cyclobutane, 287-23-0; cyclopropane, 75-19-4.

Acknowledgment.—We are grateful to the National Science Foundation for generous support of this work and to the National Aeronautics and Space Agency for a fellowship for E. L. L.

(9) Another possible route to cyanide **4** involves secondary decomposition of **1** *via* radical attack at the carbon atom bearing the NF_2 group. This

$$FCH_2CH_2CH_2NF_2 \xrightarrow[-HF]{F} FCH_2CH_2CHNF_2 \xrightarrow[-HF]{-F} \mathbf{4}$$

explanation is unattractive, however, for no bisdifluoramines such as $FCH_2CH(NF_2)CH_2NF_2$ were found. Photodifluoramination of difluoraminoethane, for example, not only yields acetonitrile but 1,2-bisdifluoraminoethane (ref 2).

(10) According to RRK theory [S. W. Benson and G. Haugen, *J. Phys. Chem.*, **69**, 3898 (1965)], the rate constant, k_e, for unimolecular decomposition of a "hot" molecule is given by

$$k_e = A[(E - E_1)/E]^{s-1}$$

A and E_1 are the Arrhenius parameters for decomposition of a thermalized molecule, E is the energy of the vibrationally excited species, and s is the number of effective oscillators.

(11) J. D. Roberts and P. H. Dirstine, *J. Amer. Chem. Soc.*, **67**, 1281 (1945). See also references cited in footnote 3.

(12) G. C. Fettis, J. H. Knox, and A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1064 (1960).

(13) Proton nuclear magnetic resonance, fluorine nuclear magnetic resonance, infrared, and mass spectra were obtained using the following instruments, respectively: Varian HA-100 high-resolution spectrometer, Varian DA 60 high-resolution spectrometer, Beckman IR-5A-spectrophotometer, and either a Consolidated Model 620, Bendix Model 12, or Associated Electronic Model MS 902 mass spectrometer.

(14) P. Pomerantz, A. Fookson, T. W. Mears, S. Rothberg, and F. L. Howard, *J. Res. Nat. Bur. Stand.*, **52**, 59 (1954).

(15) Identified by their infrared and mass spectra.

The Cyclic Addition of Hetero Radicals. II. Cyclic Additions of Alkoxy Radicals in Alkenes[1]

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A series of alkenyl nitrite esters were photolyzed to study the cyclic additions of the resulting alkoxyl radicals. The photolysis of 4-pentenyl-1 nitrite ester resulted in a high yield of tetrahydrofurfural oxime. The apparent preference for formation of five-membered rings over six-membered rings is discussed. Cyclic addition of the 5-hexenyl alkoxy radical only occurs in the presence of iodine. The importance of the photolysis of the nitroso monomer intermediate is discussed. The use of various radical traps as well as quantum yields for cyclic addition *vs.* Barton reaction is also discussed.

Intermolecular addition of radicals to olefins results in the most stable radical intermediate,[3] *e.g.*, the classical example of anti-Markovnikov addition of hydrogen bromide to a double bond. Many free-radical cyclic addition reactions violate this principle. Pyrolysis of 6-heptenoyl peroxide (**1**) resulted in methylcyclopentane (**2**), not the expected cyclohexane (eq I).[4]

$$\left(CH_2{=}CH(CH_2)_4CO_2\right)_2 \xrightarrow{\text{heat}} \text{methylcyclopentane} \qquad \text{(I)}$$

1 **2**

Other studies[5-10] have also noted a definite preference for the formation of five-membered ring in the cyclic addition of carbon radicals. Julia[11] has made one of the more thorough studies of the problem and has provided an excellent review.

Capon and Rees[12] have suggested that five-membered ring formation is favored because the addition of the radical to a double bond is so fast that the radical attacks the first termus of the double bond presented to it and that there are simply more conformations presenting the carbon five termus than the carbon six termus.

Surzur and coworkers[13] found the five-membered ring to be preferred to the six by a four to one ratio in the cyclic addition of nitrogen radicals, but in the cyclic addition of sulfur radicals the six-membered ring was generally preferred.[14,15] However, they were able to show conclusively that the addition of the sulfur radical was reversible.

In this paper, we present some of our observations on the cyclic addition of alkoxy radicals generated by the photolysis of nitrite esters.

(1) For part I of this series, see R. D. Rieke and Ned A. Moore, *Tetrahedron Lett.*, 2035 (1969).

(2) NASA Fellow, 1966–1969; Allied Chemical Fellow, 1969–1970.

(3) W. A. Pryor, "Introduction to Free Radical Chemistry," Prentice Hall, Englewood Cliffs, N. J., 1966, p 23.

(4) R. C. Lamb, P. W. Ayers, and M. K. Toney, *J. Amer. Chem. Soc.*, **85**, 3483 (1963).

(5) C. Walling and M. S. Pearson, *ibid.*, **86**, 2263 (1964).

(6) N. O. Brace, *ibid.*, **86**, 524 (1964).

(7) N. O. Brace, *J. Org. Chem.*, **31**, 2879 (1966).

(8) N. O. Brace, *J. Org. Chem.*, **32**, 2711 (1967).

(9) R. F. Garwood, C. J. Scott, and B. C. L. Weedon, *Chem. Commun.*, **14** (1965).

(10) R. C. Lamb, J. C. Pacifici, and R. W. Ayers, *J. Org. Chem.*, **30**, 3099 (1965).

(11) M. Julia, *Pure Appl. Chem.*, **15**, 167 (1967).

(12) B. Capon and C. W. Rees, *Ann. Rep. Chem. Soc. (London)*, **61**, 261 (1964).

(13) J. M. Surzur, P. Tordo, and L. Stellay, *Bull. Soc. Chim. Fr.*, 111 (1970).

(14) J. M. Surzur, M. P. Crozet, and C. DuPuy, *C. R. Acad. Sci.*, 264 (1967).

(15) Some of our preliminary results on the oxidation of unsaturated Bunte salts indicate that the initial ring closure may strongly favor the five-membered ring product.

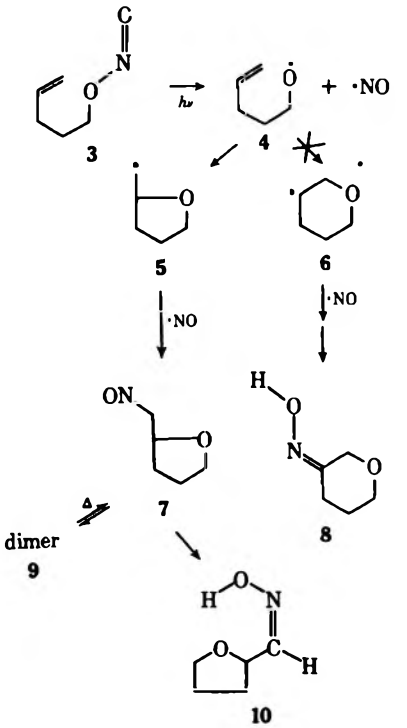
Results

Preparation of the Nitrite Esters.—The nitrite esters of *n*-pentanol, 5-hexan-1-ol, and 4-penten-1-ol were prepared[16] (crude yields from 72 to 93%). All of these nitrite esters proved to be stable when protected from light and stored in a deep freeze.

The nitrites were readily identified by their very characteristic series of low intensity peaks from 310 to 385 mμ in the uv and by their characteristic doublet at 1650 and 1610 cm^{-1} in the ir.[17] Nmr indicated that no migration of terminal double bonds occurred during synthesis. All nitrites were checked for purity by vpc prior to their photolysis, and thick film ir was used to check for the presence of any alcohol in the nitrite.

4-Pentenoxy Radical.—Irradiation of 4-pentenyl-1 nitrite (**3**, Scheme I) yielded as the major product tetrahydrofurfural oxime (**10**).

SCHEME I



Compound **10** was identified by its ir, mass spectrum, and nmr. Nmr was most definitive. Due to the syn and anti isomers, the trigonal carbon proton exhibited

(16) L. Hunter and J. H. Marriott, *J. Chem. Soc.*, 281 (1936).

(17) P. Kabasakalian and E. R. Townley, *J. Amer. Chem. Soc.*, **84**, 2711 (1962).

TABLE I
COMBINED RESULTS OF VARIOUS 4-PENTENYL-1 NITRITE IRRADIATIONS

Type	Concn	Wt loss,[a] %	% oxime in mixture	% oxime, theory	4-Penten-1-ol	Unknown III, %	Unknown IV, %	Unknown V, %
Normal	8.52×10^{-3}	13.2	62	54	Trace	Trace	8.6	7.3
Normal	7.52×10^{-2}	0	68	68	3.3	Trace	4.3	10
Normal	7.87×10^{-1}	20	61	48	[b]	[b]	[b]	[b]
O_2	8.80×10^{-2}	7.5	35	33	6.5	5.8	8.5	18.8
Filter A	7.54×10^{-2}	[c]	71	[c]	5.1	3.4	Trace	Trace

[a] Weight loss is actually greater than this since some benzene is always present in the mixture recovered after stripping. [b] Additional unknowns appeared. [c] Not irradiated to completion.

two chemical shifts, each a doublet. In DMSO, the oxime proton also exhibited two chemical shifts due to the syn and anti isomers. A 3 to 7 anti to syn ratio was indicated. This procedure was developed by Kleinspehn and coworkers.[18] Compound **10** was also converted into its *p*-nitrophenylhydrazone derivative, which had the same melting point as reported in the literature.[19]

The highest yield, 68% of **10** was obtained when a 7.5×10^{-2} *M* solution of the nitrite ester **3** was irradiated. Four other products were indicated by vpc. One of these, 3.3%, was identified as 4-penten-1-ol. Mass spectral analysis indicated that two of these, totaling 14.3%, were not monomeric. The fourth was only present in a trace amount at this concentration.

A definite concentration effect was observed. Both increasing and decreasing the concentration of nitrite ester by a factor of ten resulted in a decreased yield of the oxime **10**. Results are tabulated in Table I.

The intermediate carbon radical in the Barton reaction has been trapped with various free-radical trapping agents.[20] Similar experiments were tried in the photolysis of the nitrite esters.

A 1.5:1 atomic ratio of iodine to nitrite **3** resulted in a 61% yield of the one major product, 2-iodomethyltetrahydrofuran (**1**), and a 2.5% yield of oxime. Uv indicated no nitroso dimer formation. The pentenyl nitrite **3** proved to be quite stable when stirred in the dark with iodine. Compound **11** was identified by infrared comparison to a known sample prepared by the method of Staninets and Shilov.[21]

Photolysis of the pentenyl nitrite **3** in carbon tetrachloride resulted in a 52% yield of oxime **10**, a 3% yield of 4-penten-1-ol, and only a 7% yield of 2-chloromethyltetrahydrofuran (**12**) which was identified by infrared comparison to a known sample.[22]

The photolysis of a 40:1 molar ratio of bromotrichloromethane to pentenyl nitrite **3** through a sodium nitrate filter solution resulted in a blue solution and no nitroso dimer formation. The sodium nitrate filter solution was used to prevent the photochemical addition of bromotrichloromethane to the carbon–carbon double bond.[23] The blue color, indicating the presence of nitrosotrichloromethane,[20] stripped over with the benzene. A 51% yield of the one major product, 2-bromomethyltetrahydrofuran (**13**), was found. Compound **13** was identified by infrared comparison to a known sample of **13** prepared by the method of Paul.[24] Only a 1% yield of oxime **10** was found.

Effect of Oxygen.—Kabasakalian and Townley[17] noted during their study of the photolysis of *n*-octyl nitrite that in the presence of oxygen *n*-octyl nitrate was the major product and there was no nitroso dimer formation. The photolysis of pentenyl nitrite **3** in a solution that had been purged with oxygen and under an atmosphere of pure oxygen resulted in definite nitroso dimer formation and a 33% yield of tetrahydrofurfural oxime (**10**). Results are tabulated in Table I.

Possible Photolysis of the Nitroso Monomer Intermediate.—In 1935 Anderson and coworkers[25] found that, in the case of tertiary nitroso compounds, light caused the elimination of HNO to form a double bond. Their tertiary nitroso compounds exhibited a broad absorption band from 580 to 740 mμ with maximum absorption at 695 mμ. A filter solution blocking transmission in this region but allowing photolysis of the nitrite ester was prepared. The transmission spectrum of this solution is given in Table II (Experimental Section).

A photolysis, using the filter solution of pentenyl nitrite **3** at the concentration normally resulting in the best yield of tetrahydrofurfural oxime (**10**) was found to result in 10% decrease in the yield of **10**. A similar photolysis at lower concentration resulted in a 4% increase in the yield of **10**. Results, including minor products, are tabulated in Table I.

5-Hexenoxy Radical.—We were unable to isolate any cyclic addition product from the photolysis of the hexenyl nitrite **14** and were only able to separate and identify the corresponding alcohol, 5-hexen-1-ol, in low yield. Similar results have been reported by Surzur and coworkers,[26] who suggested that this was the result of the Barton reaction producing an allyl radical. Our efforts indicate that neither oximes or isoxazolines, both of which could be expected to result from the Bargon reaction, were formed in any significant amount.[27]

Quantum Yield Studies.—It was decided to compare the quantum yield of 4-pentenyl-1 nitrite (**3**) to that

(18) G. C. Kleinsphen, J. A. Jung, and S. A. Studniarz, *J. Org. Chem.*, **32**, 460 (1967).

(19) A. Gerrecs and L. Somolyi, *Acta Chim. Acad. Sci. Hung.*, **24**, 73 (1960).

(20) M. Akhtar, D. H. R. Barton, and P. G. Sammes, *J. Amer. Chem. Soc.*, **87**, 4601 (1965).

(21) V. I. Staninets and E. A. Shilov, *Ukr. Khim. Zh.*, **31**, 1286 (1965).

(22) A sample of 2-chloromethyltetrahydrofuran was generously provided by Dr. Burgess Cooke of this laboratory.

(23) C. Walling and E. S. Huyser, *Org. React.*, **13**, 91 (1963).

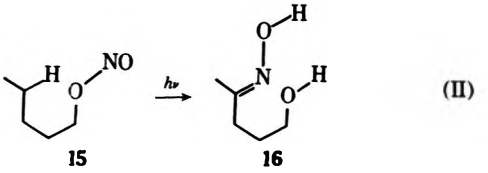
(24) M. R. Paul, *Ann. Chim. (Paris)*, **18**, 303 (1932).

(25) K. D. Anderson, C. J. Crumpler, and D. L. Hammick, *J. Chem. Soc.*, 1679 (1935).

(26) J. M. Surzur, M. P. Bertrand, and R. Nouguier, *Tetrahedron Lett.*, 4197 (1969).

(27) The photolysis of 5-hexenyl nitrite (**14**) in the presence of iodine yielded 42% of 2-iodomethyltetrahydropyran and 14% of 5-hexen-1-ol. Bromination of the stripped off benzene yielded 10% 2-(1,2-dibromo)-ethyltetrahydrofuran. Details of this reaction and other attempts to trap the 5-hexenoxy radical will appear immediately following this article in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

of a suitable saturated nitrite, which should undergo the Barton reaction. *n*-Pentyl nitrite (**15**, eq II)



(II)

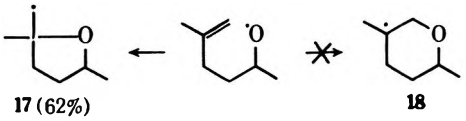
15 **16**

was chosen because it has a secondary hydrogen available for abstraction and because Kabasakalian and coworkers[28] had reported it to undergo the Barton reaction nicely as indicated by a strong nitroso dimer formation. They did not, however, isolate and identify any of the products. For this reason, and in order to determine a flame ionization detector correction factor for use in its quantum yield determination,[29] compound **15** was irradiated in a benzene solution. Ir indicated the major product to be the expected γ-hydroxypropyl methyl ketoxime (**16**), and vpc analysis indicated a 47% yield.

The quantum yields of both the pentenyl nitrite **3** and *n*-pentyl nitrite were run at the same time under the same conditions. A quantum yield of 0.71 was indicated for the unsaturated nitrite based on the appearance of tetrahydrofurfural oxime (**10**), while a quantum yield of 0.25 was indicated for the saturated nitrite based on the appearance of γ-hydroxypropyl methyl ketoxime (**16**).

Discussion

The pentenoxy radical apparently undergoes cyclic addition to form a five-membered ring with little or no six-membered ring compounds. This result parallels the carbon radical work but is somewhat surprising for the following two reasons. First of all, the five-membered ring product yields the thermodynamically less stable primary radical. Second, the Barton reaction, though admittedly a different type of reaction, requires exclusively a six-membered transition state.[17] Similar results have been reported on the cyclic addition of pentenoxy radical by Surzur and coworkers.[26] Furthermore, Surzur[26] found only five-membered ring cyclization *via* the primary radical **17**, even when cyclic addition *via* a six-membered ring would have resulted in the tertiary radical **18** (eq III).



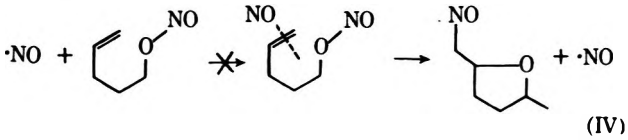
(III)

17 (62%) **18**

Thus, it appears that the observed product is the kinetically controlled product. A possible explanation for the lower energy of activation for the five-membered transition state is a more favorable activation entropy. The kinetic preference of five-membered transition states over six-membered transition states is a frequently observed occurrence in organic reactions.[30,31]

We can conclude that the cyclization observed is the result of photolysis and not thermolysis of the nitrite ester. Both 4-pentenyl-1 nitrite and 5-hexenyl-1 nitrite proved to be stable to refluxing benzene for up to 24 hr. Furthermore, the quantum yield is too low to allow the existence of a free-radical chain.

Also, there does not appear to be any interaction of nitric oxide with the double bond of another 4-pentenyl 1-nitrite involved in the cyclization. Such involvement would appear to require a chain mechanism (eq IV),



(IV)

and, as Surzur and coworkers[26] have suggested, such participation by nitric oxide should result in cyclization in the 5-hexenyl-1 nitrite system. Cyclization does not appear to occur in this system.

However, the best evidence that there is no interaction between nitric oxide and the double bond of another nitrite molecule is the fact that cyclic addition occurs even with other radical traps present. It would appear that there is no way such participation could have resulted in **11** with iodine as a trap and **12** when bromotrichloromethane was used as a trap.

At the same time, the addition of a bromine radical to the double bond of a nitrite molecule can be eliminated because this would require that the trichloromethyl radical, rather than a bromine, be abstracted when using bromotrichloromethane as a trap. It also seems unlikely that the addition of an iodine radical to the double bond of a nitrite molecule is involved in the formation of **11** because the addition of an iodide radical to a double bond is endothermic by 7 kcal[32] and because the nitrite was completely stable when stirred in the dark with iodine.

It is not unexpected that the use of carbon tetrachloride as a trap was largely unsuccessful. It is not a very efficient transfer agent. The bond energy of the C–Cl bond is 68 kcal compared to only 49 kcal for the C–Br bond of bromotrichloromethane.[33]

Possible Photolysis of the Nitroso Monomer Intermediate.—Unfortunately, filter solution A also reduced transmission in the region of the nitrite ester at the same time it blocked transmission in the nitroso monomer region. This makes it difficult to compare the results using the filter solution to those obtained with no filter solution. Use of the filter resulted in longer photolysis times. This means that at any given time there is going to be a lower concentration of reaction intermediates, and a concentration effect was observed in the photolysis of the pentenyl nitrite **3**.

At the concentration normally producing the best yield of oxime **10**, an 8% reduction in yield was observed when the filter solution was used. This was presumably due to the increased photolysis time. On the other hand, the use of the filter solution resulted in a 4% increase in yield at lower concentration.

It would be expected that at lower concentration the photolysis of the nitroso monomer intermediate **7**

(28) P. Kabasakalian, E. R. Townley, and M. D. Yudis, *J. Amer. Chem. Soc.*, **84**, 2716 (1962).

(29) H. M. McNair and J. Bonelli, "Basic Gas Chromatography," Varian Aerograph, Walnut Creek, Calif., 1967, p 124.

(30) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964), and references cited there n.

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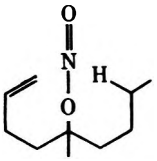
(32) D. H. R. Barton, J. M. Beaton, L. E. Seller, and M. M. Pechet, *J. Amer. Chem. Soc.*, **81**, 80 (1959).

(33) C. J. M. Stirling, "Radicals in Organic Chemistry," American Elsevier, New York, N. Y., 1965, p 167.

should be a greater problem because at lower concentration it should have a longer lifetime. Thus it would appear that, under certain conditions, slight increases in yield may be achieved by protecting the nitroso monomer from photolysis but, in general, it does not appear to be a major problem.

Cyclic Addition *vs.* the Barton Reaction.—The addition of an alkoxyl radical to a double bond is far more exothermic than is the abstraction of a hydrogen atom, 20 kcal as opposed to 8.5 kcal.[34] Also, the formation of the five-membered transition state required for cyclic addition should be faster than the formation of the six-membered transition state required for the Barton reaction. For these reasons, it would be expected that cyclic addition should be faster than the Barton reaction. The evidence indicates that this is indeed the case.

Surzur and coworkers[26] irradiate a molecule (**19**) that was capable of undergoing both cyclic addition and the Barton reaction. They found only the cyclic addition present even though they apparently looked very carefully for the Barton reaction product.



19

Kabasakalian and Townley[17] found the Barton reaction to be completely blocked by the presence of oxygen during their study of the photolysis of *n*-octyl nitrite. They found that the major product was *n*-octyl nitrate, presumably formed *via* reactions V, VI, and VII originally suggested by Hanst and Calvert.[35]

$$CH_3(CH_2)_6CH_2ON{=}O \xrightarrow{h\nu} CH_3(CH_2)_6CH_2O\cdot + \cdot NO \quad (V)$$

$$2\cdot NO + O_2 \longrightarrow 2\cdot NO_2 \quad (VI)$$

$$CH_3(CH_2)_6CH_2O\cdot \longrightarrow CH_3(CH_2)_6CH_2ONO_2 \quad (VII)$$

However, the presence of oxygen does not block cyclic addition during the irradiation of pentenyl nitrite **3**. This suggests that cyclic addition is faster than the oxidation of the nitrite to the nitrate and, hence, faster than the Barton reaction.[36]

Perhaps most conclusive is the large difference in quantum yields for these two processes. The quantum yield for formation of oxime **10** *via* cyclic addition of the pentenoxyl radical is 0.71. This number represents a minimum quantum yield for the cyclic addition process as the primary carbon radical is also most likely involved in the unidentified products. Since the per cent yield of the oxime **10** is about 70%, it is quite likely that the quantum yield for cyclic addition may be close to unity. The quantum yield for the Barton reaction product (**16**, eq II) from the photolysis of *n*-pentyl nitrite was only 0.25 with an observed yield of **16** of 48%. This would place a maximum value of the quantum yield for proton abstraction in the Barton reaction of 0.50 which is still substantially lower than the minimum quantum yield for cyclic addition. The measurement of quantum yields for the disappearance of the two nitrite esters proved to be experimentally too difficult to determine in our hands. Thus, if we make the assumption that the quantum yield for the initial cleavage of the two nitrite esters to the alkoxyl radicals is the same,[37] it would appear that the overall higher quantum yield for cyclic addition can only be explained in terms of a faster forward rate. In the case of the Barton reaction, the slower forward rate would allow more recombination of the alkoxyl radical with nitric oxide to give starting nitrite ester and a lower quantum yield.

Photolysis of 5-Hexenyl-1 Nitrite.[38]—Unfortunately, the results of the photolysis of hexenyl nitrite **14** are somewhat confusing and it is difficult to draw many definite conclusions from them. It is clear that the direct photolysis of the 5-hexenyl-1 nitrite does not yield any monocyclic nonpolymeric products. The results of the photolysis in the presence of radical trapping agents is less clear. The photolysis of the 5-hexenyl-1 nitrite in the presence of iodine is discussed in terms of a separate mechanism.[27]

Conclusions.—The cyclic addition of the 4-pentenoxyl radical has been shown to yield exclusively the five-membered ring product. The controlling factor in yielding a kinetically controlled product rather than a thermodynamically controlled product appears to be a more favorable activation entropy. It was demonstrated that the primary carbon radical resulting from the cyclic addition of the alkoxyl radical can be trapped with several radical traps. The effects of oxygen on the reaction and the quantum yield indicated that the cyclic addition was faster than the Barton reaction. It was demonstrated that the photolysis of the intermediate nitroso monomer was relatively unimportant. Finally, it was shown that the 5-hexenyl alkoxyl radical does not cyclize.

Experimental Section

Ir spectra were recorded on a Perkin-Elmer 237B, uv on a Unicam SP800B, and nmr on a Varian A-60. Quantitative analysis was accomplished using a Perkin-Elmer 881 vpc equipped with flame ionization and using a $^1/_8$ in. × 8 ft column of 5% SE-30 on Chromosorb G. Flame ionization correction factors[29] were determined in all cases unless specified otherwise. Vpc separations were accomplished on a Hewlett-Packard 5750 using thermal detectors and a 0.25 in. × 6 ft column of 10% SE-30 on Chromosorb P. Boiling and melting points are uncorrected.

4-Pentenyl-1 Nitrite.—4-Penten-1-ol (8.5 ml, Aldrich) was added to 8.65 g of sodium nitrite dissolved in 81 ml of water and stirred for 15 min in an ice bath. Concentrated hydrochloric acid (3.8 ml) was then injected with a hypodermic needle into the aqueous layer with stirring. The solution immediately turned a cloudy blue-gray, which rapidly faded to yellow. After 1 hr of vigorous mechanical stirring in the ice bath, a second 3.8-ml portion of acid was injected. Stirring was maintained for an

(34) P. Williams and A. Williams, *Chem. Rev.*, **59**, 239 (1959).

(35) P. L. Hanst and J. G. Calvert, *J. Phys. Chem.*, **63**, 2071 (1959).

(36) The possibility remains that the difference between the effect of oxygen on the photolysis of *n*-octyl nitrite and the photolysis of pentenyl nitrite **3** lies in the interaction of oxygen with the excited nitrite ester, not with the effect of oxygen on the radical species after cleavage.

(37) Within the limits of the methods used, the uv spectrum and the extinction coefficient of the saturated and the unsaturated nitrite esters were the same.

(38) The photolysis of 5-butenyl-1 nitrite should provide an interesting comparison between cyclic addition to form a five-membered ring and β scission to form an allyl radical. However, Surzur and coworkers[26] reported finding only polymer. We undertook the photolysis of this nitrite with iodine present as a trap and found at least nine different products, no one of which could be called major. This would seem to indicate that there is no one major pathway available to the 3-butenoxy radical. We will endeavor to report on these products in the future.

additional 3 hr. The mixture was protected at all times from direct light. The crude yellow nitrite (8.7 g, 91%) was separated and vacuum distilled while protected from light: bp 53–55° (130 mm); ir (film) 1650, 1610 cm^{-1} (nitrite); uv (95% ETOH) low intensity peaks from 310 to 385 nm, λ_{max} 357 nm (ϵ 100); nmr (neat) τ 5.0 (m, 1 H), 5.7 (m,2 H), 6.0 (t, 2 H), 8.75 (m, 4 H).

Photolysis Precedure.—Irradiations were performed in a 350-ml capacity photolysis flask into which was slipped a quartz, water-jacketed immersion well containing a 450-W medium-pressure Hanovia mercury lamp. The lamp was surrounded by a Pyrex sleeve. Solvents were dried by refluxing over magnesium sulfate prior to their use and all apparatus, with the exception of the immersion well, was oven dried prior to use.

The solution was purged for 1 hr prior to photolysis with a stream of vanadate scrubbed nitrogen to remove all oxygen. If a radical was to be used, nitrogen flow was maintained during photolysis to sweep out as much nitric oxide as possible. If no trap was to be used, nitrogen flow was stopped and the system was sealed during photolysis. Magnetic stirring was used throughout both purging and photolysis.

All nitrites were checked for purity prior to photolysis by vpc and for the presence of alcohols by thick film ir. The disappearance of the nitrite could be followed by uv, and the formation of any nitroso dimer could be monitored by its characteristic peak at 294 nm.[17]

Photolysis of 4-Pentenyl-1 Nitrite.—Nitrite (3.08 g) was added to 350 ml of benzene, purged, and irradiated for 45 min. The solution turned to a deep yellow during photolysis and was stripped to 3.053 g of a viscous oil, which was injected directly into the vpc to reveal a 68% yield of **10**. The heat of the injector, 150°, was sufficient to break down all nitroso dimer into oxime.

Tetrahydrofurfural Oxime (10).—The above oil recovered from the photolysis of 4-pentenyl-1-nitrite was heated for 14 hr at 45° to cleave all nitroso dimer and isomerize it to the oxime. The disappearance of the dimer was followed by uv. Compound **10** was isolated by placing the mixture on a slurry packed column of Florisil activated at 500°F using chloroform as an eluent: ir ($CHCl_3$) 3300 (OH), 1640 (C=N), and 1050 cm^{-1} (CO); uv (95% ETOH) λ end absorption 210 nm (ϵ 1500); nmr (CS_2) 0.5 (s, 1 H, C=NOH), 2.75 (d, 0.7, J = 7 cps, syn CH), 3.3 (d, 0.3 H, J = 5 cps, anti CH), 5.9 (m, 3 H), 8.3 (m, 4 H); mass spectrum m/e 115 (M^+, 3%), 71 (C_4H_7O, 85%).

***p*-Nitrophenylhydrazone Derivative of 10.**—The method of Gerecs and Somobyi[19] was used, mp 146–147° (lit. 145–146°).

Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.56; N, 17.86. Found: C, 56.41; H, 5.39; N, 18.09.

Photolysis of 4-Pentenyl-1 Nitrite in the Presence of Oxygen.—Nitrite (0.92 g) was added to 90 ml of benzene and the solution purged with oxygen for 30 min. The solution was then irradiated for 45 min with the oxygen turned off and the system sealed. Uv indicated that all nitrite was gone and indicated strong nitroso dimer absorption. Vpc analysis indicated a 34% yield of **10**.

Photolysis of 4-Pentenyl-1 Nitrite Using a Filter Solution.—Filter solution A consisted of 93 g of $Co(NO_3)_2 \cdot 3H_2O$, 131 g of $CoSO_4 \cdot 7H_2O$, 76 g of $Cr_2(SO_4)_3 \cdot 18H_2O$, and 97 g of $CuSO_4 \cdot 5H_2O$ per liter of water. The transmission spectrum of filter solution A is given in Table II. A pump circulated the filter solution through the immersion well and a cooling coil which was immersed on an ice bath.

Nitrite (3.08 g) was added to 350 ml of benzene. After 3 hr and 45 min of photolysis, uv indicated all nitrite had disappeared and that nitroso dimer had been formed. Vpc indicated a 60% yield.

Photolysis of 4-Pentenyl-1 Nitrite with Iodine.—Nitrite (2.44 g) was added to 350 ml of benzene in which 3.9 g of iodine had been dissolved. After 4.5 hr of irradiation, uv indicated no remaining nitrite ester and no nitroso dimer formation. Excess iodine was removed with a 10% aqueous solution of sodium thiosulfate. 2-Iodomethyltetrahydrofuran (**11**) was separated by preparative vpc and identified by ir comparison to a known sample prepared by the method of Staninets and Shilov:[21] ir ($CHCl_3$) 1060 cm^{-1} (CO); nmr ($CDCl_3$) τ 6.1 (m, 3 H), 6.75 (d, 2 H) 8.1 (m, 4 H). Vpc indicated a 61% yield of **11**, and nmr intergration of the mixture indicated a 2.5% yield of oxime.

Photolysis of 4-Pentenyl-1 Nitrite with Bromotrichloromethane.—A filter solution consisting of 120 g of sodium nitrite per liter of water was prepared and circulated through the immersion well and a cooling coil.

Nitrite (1.289 g) was added to a solution of 308 ml of benzene and 42 ml of bromotrichloromethane. After 25 min of irradiation, uv indicated no remaining nitrite and no nitroso dimer formation. The solution was a deep blue. This blue stripped over with the benzene and excess bromotrichloromethane.

2-Bromomethyltetrahydrofuran (**13**) was separated by preparative vpc and identified by ir comparison to a known sample prepared by the method of Paul.[24] Vpc analysis indicated a 51% yield of **13** and 1% yield of **10**.

Photolysis of 5-Hexenyl-1 nitrite.—Nitrite (3.286 g) was added to 350 ml of benzene and irradiated for 45 min. Uv indicated no remaining nitrite and nitroso dimer formation. The solution turned yellow during photolysis and became cloudy. The cloudiness cleared after sitting a few minutes. A very viscous red-brown oil settled out of solution, was taken up in methanol, and stripped to 0.77 g.

An oily material (2.81 g) was recovered after stripping off the benzene, but only trace amounts of material would come through the vpc. Only 5-hexen-1-ol was identified by comparison to a known sample.

The recovered oil was heated until uv indicated no remaining nitroso dimer, but all separation attempts, including preparative vpc, Florisil chromatography, paper chromatography, and extraction techniques, failed. Ir (film) of the mixture indicated no peaks in the vicinity of 1725 cm^{-1} (isoxazoline) and nmr in deuterated DMSO indicated no peak in the vicinity of τ 0 (oxime).

Photolysis of *n*-Pentyl Nitrite.—Nitrite (3.388 g) was added to 350 ml of benzene and irradiated for 1 hr. Uv indicated no remaining nitrite and nitroso dimer formation. A small amount of a brown oil settled out of solution and was taken up in methanol and combined with the benzene solution prior to stripping.

The major product was separated by preparative vpc. Ir indicated it to be the expected γ-hydroxypropyl methyl ketoxime (**16**), and vpc indicated a 47% yield: ir (film) 3400 (very strong, OH), 1665 cm^{-1} (C=N).

Quantum Yields.—4-Pentenyl-1 nitrite (**3**) and *n*-pentyl nitrite were irradiated in a merry-go-round apparatus at the same time and the same concentration, using a medium pressure mercury lamp and filters to isolate the 3660-Å line. The samples were sealed in Pyrex ampoules after three freeze-pump-thaw cycles using liquid nitrogen and a maximum pressure of 10^{-4} nm, and ferric oxalate actinometry was used. Half the tubes were irradiated for 5 min and half for 10 min. Blank tubes were made up and carried through the entire process for both nitrites.

Vpc analysis indicated a quantum yield of 0.71 for the unsaturated nitrite **3** based on the appearance of the aldoxime **10** and a quantum yield of 0.25 for the saturated nitrite **15** based on the appearance of the ketoxime **16**. No significant difference was noted between the tubes irradiated for 5 min and those irradiated for 10 min.

TABLE II

TRANSMISSION SPECTRUM OF FILTER SOLUTION A[a]

Before photolysis		After 1.5 hr of photolysis	
mμ	% T	mμ	% T
190–320	0.0	190–320	0.0
330	10.6	330	10.3
348	30.7	348	25.0
360	10.6	360	10.4
384–434	0.0	385–432	0.0
466	10.6	466	10.7
485	23.0	485	23.0
506	10.6	506	10.7
548–640	0.0	554–620	0.0
656	1.2	655	2.3
665–850	0.0	696–850	0.0

[a] The per cent transmission has been corrected to the 0.5-cm path length of the immersion well.

Registry No.—**3**, 29668-65-3; **4**, 23127-65-3; *anti*-**10**, 20728-36-3; *syn*-**10**, 23247-31-6; 5-hexenoxy radical, 32730-57-7; 5-hexenyl-1 nitrite, 32730-59-9.

Acknowledgment.—Financial support of this investigation by a National Science Foundation Grant and by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. Helpful discussions with Professor D. G. Whitten are gratefully acknowledged.

The Mechanism of the Rearrangement of Bis(diphenylphosphinyl) Peroxide[1]

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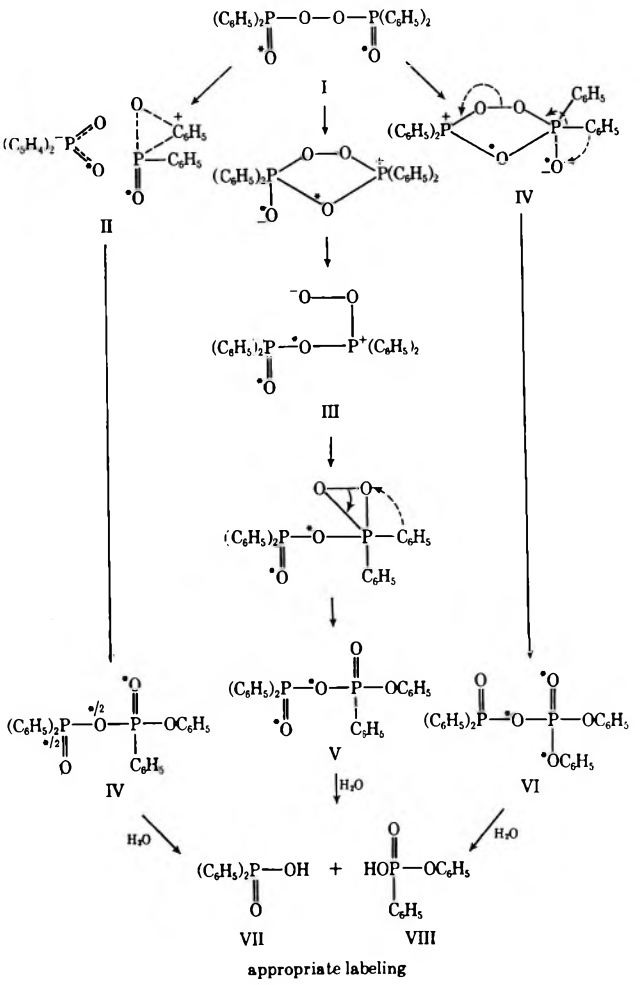
The thermal decomposition of bis(diphenylphosphinyl-^{18}O) peroxide in chloroform solution has been found to produce an unsymmetrical anhydride [$Ph_2P(=O)OP(=O)OPh_2$] in which all of the oxygen-18 label remains in the oxo oxygens. Only a concerted process or an ion pair so intimate as to prevent scrambling of the label is consistent with this labeling of the rearrangement product. In contrast, photolysis of the labeled peroxide in chloroform results in a much more rapid first-order decomposition which yields the same anhydride but with scrambling of the oxygen-18 label. This scrambling of the label corresponds to a free-radical intermediate for the photolytic process.

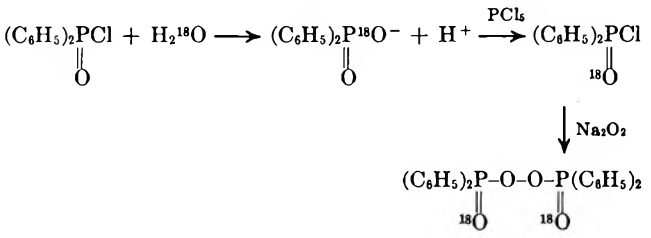
The thermal decomposition of bis(diphenylphosphinyl) peroxide (I) has been found[4] to yield, after hydrolysis of the reaction mixture, diphenylphosphinic acid (VII) and phenyl hydrogen phenylphosphonate (VIII). Evidence was presented that the reaction was ionic in nature and the following three alternative mechanisms (Chart I) were proposed. The present work was planned to establish whether one of these three mechanisms can be operative by labeling the oxo oxygens of the peroxide with oxygen-18 and determining the labeling in the product. The decomposition of the peroxide was also reported[4] to be accelerated by light and in the present work it was proposed, in addition, to elucidate this photolytic mechanism by oxygen-18 labeling experiments.

CHART I



Results and Discussion

Labeling of the Peroxide.—Labeling of the peroxide was accomplished by the following sequence of reactions. Since the phosphinyl peroxide is thermally too unstable to pass through a mass spectrometer, the incorporation of oxygen-18 in the oxo oxygen of the peroxide was assumed to be identical with that in the precursor phosphinyl chloride. Measurement of the oxygen-18 content of the diphenylphosphinyl chloride itself was found to be impractical, for the only peaks observed in the mass spectrometer corresponded to the chlorine cation (*m/e* 35, 37). However, treatment of the acid chloride with methanol gave the methyl ester which in the mass spectrometer produced a series of useful ions (Table I). The parent peaks (*m/e* 232, 234) were initially chosen for the analysis and, from the peak heights of multiple runs applying the statistical isotope occurrence formulas of Beynon,[5] the oxo oxygen enrichment with oxygen-18 above natural abundance was 5.3%. The base line at this portion of the spectrum was so poor and the correction for the m + 1 contribution of the 231 peak so large that the average



(1) Supported in part by National Science Foundation Grant No. GP-19018.

(2) Taken in part from the thesis of R. L. Waller, submitted in May 1971, to the Graduate School, Case Western Reserve University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Presented in part at the 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971.

(3) Preliminary work on this problem was performed at the American Cyanamid European Research Institute at Geneva, Switzerland.

(4) R. L. Dannley and K. R. Kabre, *J. Amer. Chem. Soc.*, **87**, 4805 (1965).

(5) J. H. Beynon, "Mass Spectrometry and Its Applications to Organic Chemistry," Elsevier, Amsterdam, 1960, p 296.

TABLE I
IONS OBTAINED FROM UNLABELED METHYL DIPHENYLPHOSPHINATE IN THE MASS SPECTROMETER

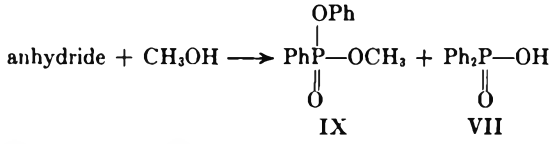
Ion	m/e	Relative peak heights
$(C_6H_5)_2POOCH_3^+$	232	54
$(C_6H_5)_2POCH_2^+$	231	100
$(C_6H_5)_2PO^+$	201	22
$C_6H_5POOCH_3^+$	155	29
$C_6H_5^+$	77	52

deviation was at least 0.4%. Therefore the analysis was repeated using multiple runs of the peaks at *m/e* 155, 157, where a satisfactory base line was obtained and there were no nearby peaks contributing. From the 155, 157 peaks, the enrichment of oxo oxygen with oxygen-18 was determined to be 4.6% with an average deviation of only 0.2%. The theoretical value from the enriched water (10.13% oxygen-18)[6] was 4.96%. The experimental value (4.6%) can be expected to be a little lower than the theoretical because of the inability to completely exclude atmospheric moisture during the synthesis. The labeled acid chloride was converted to the peroxide by the literature method.[4]

Identification of the Anhydride Product.—In the initial work with the phosphinyl peroxide,[4] it was concluded that the unsymmetrical anhydride (*e.g.*, V) was produced by thermal rearrangement of I because hydrolysis of the reaction mixture led to essentially quantitative yields of VII and VIII. All attempts in the initial and present work to isolate or synthesize an analytically pure sample of the anhydride have failed. The compound not only may be low melting but in addition probably has a tendency to partially disproportionate to symmetrical anhydrides.

However, in the present work, in the mass spectrum of the crude thermal rearrangement reaction mixture was found a principle peak (*m/e* 434) which corresponds to the molecular weight of the unsymmetrical anhydride. There is no other compound logically expected to be present with this molecular weight.

Also, treatment of the crude reaction mixture with methanol gave IX. This ester (IX) is the expected principal product from methanolysis of the anhydride because solvolytic attack should predominate where there is reduced electron density on the phosphonic



phosphorus as opposed to the phosphinic phosphorus. An anhydride structure must be present because the ester IX could not be obtained from the corresponding acid VIII under the experimental conditions.

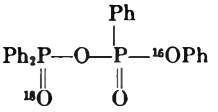
These two units of data therefore support the original conclusion that the unsymmetrical anhydride is the initial product of the rearrangement process.

Determination of the Labeling in the Anhydride Produced by Thermal Rearrangement of the Peroxide.—The labeled bis(diphenylphosphinyl) peroxide was thermally decomposed in chloroform solution and phenyl hydrogen phenylphosphonate (VIII) was isolated. This ester was cleaved with sodium naphthalene and the resultant phenol was transformed to the trimethylsilyl ether. Mass spectrometric analysis of this ether (Table II) disclosed that none of the oxygen-18 label was incorporated in the phenol oxygen.

Since the phenolic oxygen of VIII arises exclusively from the peroxidic oxygen of I, the rearrangement does not proceed through IV. Structures II and III are the only proposed intermediates consistent with these data.

In a preceding section of this paper an assumption was made that, in the conversion of the diphenylphosphinic chloride to the peroxide, there would be no scrambling of oxo and peroxidic oxygens. Such a scrambling to yield some oxygen-18 labeling of the peroxidic oxygens would necessarily produce some labeling of the phenolic oxygen of VIII. Therefore the absence of any oxygen-18 enrichment of the phenolic oxygen of VIII provides experimental proof that no scrambling of the label occurs during peroxide formation and this original assumption is experimentally confirmed.

To further elucidate the mechanism of the peroxide rearrangement, additional identification of the fate of the oxygen label was needed. The mass spectrum of a concentrated crude sample of the reaction products (Table III) provided two significant units of data. First, a principal peak (*m/e* 434) was observed which corresponds to the molecular weight of the unsymmetrical anhydride. The importance of this peak in the proof of the anhydride structure has already been discussed. The second unit of data obtained from the mass spectrum of the reaction mixture was the measurement of a peak of *m/e* 233 (Table II) corresponding to $PhOP(=O)PhO^+$. The comparison of this peak to the 235 peak showed an oxygen-18 enrichment in this ion corresponding to the incorporation of only one oxygen-18 (4.5% enrichment of one oxygen found; 4.6% theoretical). The other oxygen-18 must necessarily be present in the anhydride as $Ph_2P{=}O$. Some confirmation of this conclusion was obtained by comparing the 201 peak to the 203 peak which showed the enrichment of oxygen-18 in this ion to be 4.9% above the natural abundance. This peak cannot correspond to the $PhOPPh^+$ ion because the phenolic oxygen has been proved not to be oxygen-18 enriched. In the Ph_2PO^+ ion, the oxygen logically arises from the P=O linkage although the P—OP linkage as a source of this oxygen is not excluded. Therefore the labeling in both ions is in agreement with the following anhydride labeling.



To establish the labeling of the last two undesignated oxygens, it was necessary to subject the crude rearrangement product to methanolysis to give methyl phenyl phenylphosphonate (IX). The importance of this solvolysis in proof of the anhydride structure has been discussed already. Mass spectral analysis of the *m/e* 248 to the 250 peak of IX showed the presence of one labeled oxygen (3.8 ± 0.4% oxygen-18 enrichment found for one oxygen *vs.* 4.6% theoretical). The peak required for analysis was not a major peak (Table IV) and this accounts for the somewhat limited

(6) Analysis provided by the $H_2{}^{18}O$ source, Miles Laboratories.

TABLE II

ISOTOPE RATIOS FOR REAGENTS AND PRODUCTS FROM THERMAL AND PHOTOLYTIC REARRANGEMENTS OF I

Compd	Ion	Run	No. of scans	(M + 2)/M	Total ^{18}O, %	^{18}O enrichment, %
Methyl diphenylphosphinate[a]	$(C_6H_5)_2POOCH_3^+$	1	12	0.067 ± 0.0027	5.5[b]	5.3[b]
Methyl diphenylphosphinate[a]	$C_6H_5P(O)OCH_3^+$	1	10	0.0531 ± 0.0011	4.8[b]	4.6[b]
Phenyl trimethylsilyl ether[a]	$C_6H_5OSi(CH_3)_2^+$	1	10	0.0438 ± 0.0009	0.20	0
Phenyl trimethylsilyl ether[a]	$C_6H_5OSi(CH_3)_2^+$	2	10	0.0437 ± 0.0009	0.18	0
Unsymmetrical anhydride[a]	$C_6H_5OP(C_6H_5)OO^+$	1	6	0.0620 ± 0.0025	5.1[b]	4.5[b]
Unsymmetrical anhydride[a]	$(C_6H_5)_2PO^+$	1	1	0.060	5.1	4.9
Methyl phenyl phenylphosphonate[a]	$(C_6H_5)P(OC_6H_5)(O)(OCH_3)^+$	1	10	0.0542 ± 0.0043	4.4[b]	3.8[b]
Phenyl trimethylsilyl ether[c]	$C_6H_5OSi(CH_3)_2^+$	1	10	0.0628 ± 0.0025	2.1	1.9

[a] Thermal rearrangement product. [b] ^{18}O enrichment only in one oxygen. [c] Photolytic rearrangement product.

TABLE III

MASS SPECTRAL ANALYSIS OF DIPHENYLPHOSPHINIC PHENYLPHOSPHINIC ANHYDRIDE PHENYL ESTER

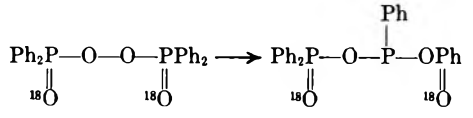
Ion	m/e	Relative peak heights (parent m/e as 100)
$(C_6H_5)_2POP(C_6H_5)OC_6H_5$	434	100
$(C_6H_5)_2POPOC_6H_5$	418	320
$(C_6H_5)_2POPOC_6H_5$	357	610
$C_6H_5POP(C_6H_5)_2$	341	1300
$OP(C_6H_5)OC_6H_5$	233	14
$P(C_6H_5)OC_6H_5$	217	210
$(C_6H_5)_2PO^+$	201	300

TABLE IV

MASS SPECTRAL ANALYSIS OF METHYL PHENYL PHENYLPHOSPHONATE

Ion	m/e	Relative peak heights (parent m/e as 100)
$(C_6H_5)(C_6H_5O)P(O)(OCH_3)^+$	248	100
$(C_6H_5)(C_6H_5O)P(O)(OCH_2)^+$	247	126
$(C_6H_5)(C_6H_5O)P(O)_2^+$	233	250
$(C_6H_5)(C_6H_5O)P^+$	201	194
$(C_6H_5O)P(O)(OCH_3)^+$	171	74
$(C_6H_5)P(O)(OCH_3)^+$	155	525
$(C_6H_5)P(OCH_3)^+$	139	115
$C_6H_5O^+$	93	7550
$C_6H_6^+$	77	7550

accuracy of this determination. The oxo oxygen must contribute this label, for the methoxy oxygen comes from the methanol and the phenoxy oxygen has been proved not to be labeled. The labeling pattern of the anhydride is now completely established. All three

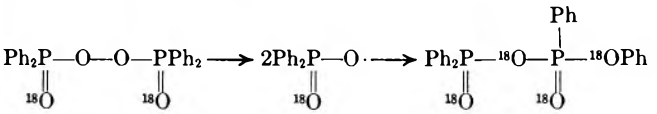


of the previously proposed[4] mechanisms are therefore incorrect. Instead there must be a concerted rearrangement or an ion pair similar to II so intimate that scrambling of the oxygen in the negative ion does not occur. A concerted rearrangement involves orbital symmetry restrictions which are difficult to evaluate because of the unsaturated groups adjacent to the reaction site.

Photolytic Rearrangement of I.—It has also been reported[4] that the rearrangement of I can be catalyzed by ultraviolet light. A free-radical mechanism was proposed for this rearrangement.

In the present work it was confirmed that the decomposition of I can be catalyzed by light because at 18° the half-life was only 7 min with the Hanovia lamp used, while without irradiation the half-life at this temperature was almost 10 hr. Obviously the photolytic mechanism differs from the thermal process. Previously[4] the photolytic process (with poor temperature control) was reported to be second order with respect to peroxide, but in the present work (with fairly good temperature control, 17 ± 1°) a good first-order plot was obtained.

Photolytic decomposition of I labeled with oxygen-18 as previously described has now been found to produce phenyl hydrogen phenylphosphinate in which the phenoxy group contains essentially one-half the enrichment (1.9 ± 0.4% above natural abundance) of oxygen-18 compared to the original oxo oxygen enrichment (4.6%). The 1.9 ± 0.4% compares favorably with the 2.3% predicted theoretically by complete oxygen scrambling in a free-radical intermediate.



The yields of rearrangement products were lower in the photolytic process than in the thermal reaction. Such low yields are often characteristic of free-radical intermediates.

Experimental Section

Diphenylphosphinic-^{18}O Chloride.—Diphenylphosphinic chloride (35.4 g, 0.15 mol) in benzene (100 ml) was refluxed for 1 hr with $H_2{}^{18}O$ (3 g, 0.16 mol). Diphenylphosphinic acid (35 g, 100% yield) was collected by filtration and dried to yield the pure acid, mp 188–190° (lit.[7] mp 190–191°). To the acid (17.6 g, 0.08 mol) mixed with phosphorus pentachloride (16.8 g, 0.08 mol) was added 1 ml of benzene and a vigorous reaction occurred. Vacuum distillation produced diphenylphosphinic-^{18}O chloride (15.7 g, 88%), bp 165° (0.17 mm) [lit.[8] bp 158–160° (0.1 mm)].

The mass spectrum[9] of this compound had peaks only at m/e 35 and 37.

Methyl Diphenylphosphinate-*oxo*-^{18}O.—A dry methanol (15 ml) solution of diphenylphosphinic-^{18}O chloride (0.2 g) was refluxed overnight. The excess methanol was removed using a rotary evaporator and the residue was distilled to yield a viscous liquid, bp 141–143° (0.34 mm) [lit.[10] bp 139–140° (0.34 mm)]. After several hours the liquid gave crystals, mp 59–62°, which gave ir and nmr spectra identical with those previously reported[10,11] for the ester.

Bis(diphenylphosphinyl-^{18}O) Peroxide.—Diphenylphosphinic-^{18}O chloride (15.5 g, 0.06 mol) in toluene (25 ml) was added slowly (45 min) at 0° to sodium peroxide (6.0 g, 0.077 mol) in water (100 ml). The mixture was stirred for 15 min after the addition was complete and the phosphinyl peroxide was then collected by filtration and washed first with cold (0°) water and then with small (2–5 ml) quantities of cold (0°) acetone. The crude peroxide was then dissolved in cold chloroform, heptane was added, and the mixture was cooled to give bis(diphenylphosphinyl-^{18}O) peroxide (6.1 g, 42%) which melted at 80° (lit.[4] mp 88°).

Decomposition of the Labeled Peroxide amd Analysis of the Product.—A solution of bis(diphenylphosphinyl-^{18}O) peroxide (6.1 g, 0.025 mol) in chloroform (75 ml) was stirred at room temperature overnight. The chloroform was evaporated *in vacuo* and the viscous residue was refluxed for 1 hr with a mixture of benzene (30 ml) and water (10 ml). The hot benzene layer was separated and evaporated. The crystalline residue was extracted with three 40-ml portions of boiling heptane. Cooling the combined heptane extracts precipitated phenyl hydrogen phenylphosphonate (2 g) which was collected by filtration and dissolved in tetrahyhrofuran (20 ml). Addition of sodium–naphthalene (0.03 mol) in tetrahydrofuran (20 ml) produced a vigorous reaction. When the reacton had subsided, the tetrahydrofuran was evaporated, the residue was dissolved in 0.1 *M* aqueous potassium hydroxide (20 ml), and the alkaline solution washed with three 30-ml portions of ether. The raffinate was acidified to pH 6 and extracted with three 40-ml portions of ether. The combined ether extracts were dried with magnesium sulfate and evaporated. The residue was refluxed for 1 hr with hexamethyldilazane (3 ml) and a trace of sand. Distillation yielded a liquid (1 ml) whose infrared spectrum was identical with that of authentic trimethylsilylphenyl ether. Mass spectral analysis of the ethers from two separate runs (Table II) using multiple scans of the m/e peaks 151 and 153, gave an oxygen-18 to oxygen-16 ratio for the phenolic oxygen of 0.0020 and 0.0018 (average 0.0019). Since the natural abundance is 0.0020, there was no oxygen-18 enrichment of the phenolic oxygen.

Methanolysis of Diphenylphosphinic Phenylphosphonic Anhydride Phenyl Ester Produced from the Thermal Decomposition of I in Chloroform.—A solution of I (2 g) in chloroform (100 ml) was stirred overnight at room temperature. An aliquot (10 ml) was added to anhydrous methanol (5 ml) and the resulting solution was refluxed overnight. Evaporation of this solution produced a viscous oil which was dissolved in ether (20 ml) and the ether solution was washed once with 5% aqueous sodium bicarbonate. Acidification of the basic extract produced diphenylphosphinic acid (0.85 g, mp 190°) which from the infrared spectrum appeared to contain small quantities of phenyl hydrogen phenylphosphonate. The ether raffinate was dried (Drierite) and evaporated to yield a viscous oil which gave infrared and nmr spectra identical with an authentic sample of methyl phenyl phenylphosphonate. In a control experiment, replacement of the aliquot with VIII gave no IX.

A second aliquot (10 ml) of the decomposition mixture was refluxed with methanol (5 ml) overnight, the mixture was concentrated by evaporating solvent, and the residue was subjected directly to mass spectral analysis.

A third aliquot of the reaction mixture was subjected directly to mass spectral analysis to observe the principal peak for the anhydride and the peaks corresponding to the ions produced by its fragmentation.

Kinetic Measurement of the Photolytic Decomposition of I.—The peroxide absorbs radiation at 275 mμ (ε 6300), 267 (7480), and 242 (15,900). A solution of bis(diphenylphosphinyl-^{18}O) peroxide (0.02 mol) in chloroform (1000 ml) was placed in a liquid-cooled immersion uv reactor. The system was irradiated with a mercury vapor lamp employing a Corex filter which prevented light below 260 ml from entering the reaction mixture. The temperature was maintained at 17 ± 1°. Aliquots were withdrawn at regular intervals and added to sodium iodide in 1:4 acetic acid–isopropyl alcohol, the resultant mixture was refluxed for 2 min, and the liberated iodine was titrated with standard sodium thiosulfate solution. With this photolytic apparatus, duplicate runs gave good first-order plots corresponding to a rate constant of $1.55 \pm 0.02 \times 10^{-2}$ sec^{-1}. The kinetic figures in minutes and $\ln a/(a - x)$ are, respectively, 3, 0.000; 5, 0.1750; 7, 0.3750; 9, 05871; 13, 1.000; 18, 1.3748; 22, 1.7437.

Photolytic Decomposition of Labeled I.—The above apparatus was utilized with I (6 g) in chloroform (1000 ml). The system was purged with nitrogen and then irradiated for 1 hr at 17°. The chloroform was distilled and the residue was refluxed for 4 hr with benzene (40 ml) and water (10 ml). The benzene layer was separated and evaporated. The residue was extracted with three 40-ml portions of boiling heptane. Cooling the combined heptane extracts gave VIII (0.6 g) which was cleaved with sodium naphthalene and converted to phenyl trimethylsilyl ether by the method already described. The ether was then subjected to mass spectral analysis.

Registry No.—Bis(diphenylphosphinyl) peroxide, 4250-08-2.

(7) A Michaelis and F. Wegner, *Ber.*, **48**, 316 (1915).

(8) N. T. Kurnath, Ph.D. Thesis, Case Western Reserve University, 1970.

(9) All the mass spectra were determined on a Varian M-66 mass spectrometer and are accurate to about ±5% for a major peak, but with ±10% for a minor peak or a poor base line.

(10) K. D. Berlin, T. H. Austin, and K. L. Stone, *J. Amer. Chem. Soc.*, **86**, 1787 (1964).

(11) K. D. Berlin, T. H. Austin, and M. Nagabhushanam, *J. Org. Chem.*, **30**, 1267 (1965).

Pyrolysis of N-[β-(N''-Phenylcarbamyl)ethyl]-N,N'-diphenylurea. Synthesis and Properties of the Decomposition Product, 2-Phenylimino-3-phenyloxazolidine and Its Analogs

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The pyrolysis of N-[β-(N''-phenylcarbamyl)ethyl]-N,N'diphenylurea proceeds by two simultaneous pathways. The major reaction is cyclization to 2-phenylimino-3-phenyloxazolidine with loss of aniline and carbon dioxide. The minor reaction is a dissociation into β-anilinoethyl N-phenylcarbamate and phenyl isocyanate. Further reactions of these intermediates lead to a complex mixture of other products. A simple and rapid method of synthesis of N,N'-disubstituted 2-iminooxazolidines consists in the acid cyclodehydration of N-(β-hydroxyethyl)-N,N'-diaryl- or -alkylarylureas. The 2-arylimino-3-aryloxazolidines are isomerized by heating with hydrobromic acid to 1,3-diaryl-2-imidazolidones. Other properties of the iminooxazolidines, including acid hydrolysis, reaction with aromatic amines, thermal isomerization, and polymerization, are reported.

Pyrolysis of N-[β-(N''-Phenylcarbamyl)ethyl]-N,N'-diphenylurea (1).—In line with our previous work on the thermal degradation of ethylene bis(N-phenylcarbamate),[1] it was expected that the pyrolysis of the urea carbamate **1** at 200–240° would give primarily carbon dioxide, aniline, and 1,3-diphenyl-2-imidazolidone by a one-step decomposition. However, a complex mixture of 11 products was found: carbon dioxide, aniline, 2-phenylimino-3-phenyloxazolidine (**2a**), 1,3-diphenyl-2-imidazolidone (**3a**), β-anilinoethyl N-phenylcarbamate (**4**), N,N'-diphenylpiperazine (**5**), N,N'-diphenylethylenediamine (**6**), N,N'-diphenylurea (**7**), 2-anilinoethanol (**8**), ethylene oxide (**9**), and 3-phenyl-2-oxazolidone (**10**) (Table I). All the products were completely identified by appropriate chemical reactions or by their melting points, ir spectra, nmr spectra, and comparison with authentic samples.

TABLE I
PYROLYSIS OF COMPOUND 1

Compd	Run 1, 1 hr, 200° (mmol)	Run 2, 2 hr, 200° (mmol)	Run 3, 2.5 hr, 210° (mmol)	Run 4, 1.5 hr, 230° (mmol)	Run 5, 2 hr, 240° (mmol)
Compound 1 submitted to pyrolysis	30.0	40.0	20.0	30.0	40.0
CO_2	22.3	27.7	15.4	25.0	33.7
Aniline	6.7	9.2	5.0	9.0	10.0
Compound 2a	16.3	24.9	14.0	19.3	15.3
1,3-Diphenyl-2-imidazolidone (3a)	0.7	2.5	2.2	4.3	12.0
Carbamate 4	4.1	2.8	0.3	0.0	0.0
N,N'-Diphenylpiperazine (5)	0.19	0.26	*a*	0.0	0.0
N,N'-Diphenylethylenediamine (6)	2.3	1.6	1.4	3.1	2.5
N,N'-Diphenylurea (7)	13.0	17.0	7.7	8.7	14.3
2-Anilinoethanol (8)	*a*	0.9	*a*	*a*	0.15
Ethylene oxide (9)[b]	*a*	*a*	*a*	*a*	*a*
3-Phenyl-2-oxazolidone (10)	0.6	1.7	1.0	1.0	2.5
Weight % recovered	89.5	92.1	95.4	91.2	92.8

[a] Isolated or detected but not determined quantitatively. [b] Detected by its reaction with KSCN, giving a characteristic pink color: W. Deckert, *Angew. Chem.*, **45**, 758 (1932).

The data in Table I indicate that the initial degradation of **1** occurs by two simultaneous pathways. The major reaction is cyclization to **2a** with loss of aniline and carbon dioxide. Its extent was calculated to be about 68 and 78% at 200 and 240°, respectively, from the data in expt 2 and 5. The minor pathway is a dissociation to the anilinoethyl carbamate **4** and phenyl isocyanate. Compounds **5–10** arise from further decomposition of **4** as shown by separate pyrolysis experiments (Table II). The main reactions are shown in Scheme I.

TABLE II
PYROLYSIS OF COMPOUND 4

Compd	Run 1, 2 hr, 200° (mmol)	Run 2, 2 hr, 240° (mmol)	Run 3,[a] 2 hr, 200° (mmol)
Compound 4 submitted to pyrolysis	10.0	10.0	10.0
CO_2	4.5	7.3	2.0
Aniline	3.5	7.0	*a*
1,3-Diphenyl-2-imidazolidone (3a)	0.3	0.4	0.17
Compound 4 (unreacted)	0.7	0.1	0.0
N,N'-Diphenylpiperazine (5)	1.5	3.5	0.17
N,N'-Diphenylethylenediamine (6)	1.3	1.2	1.9
N,N'-Diphenylurea (7)	2.0	0.8	5.2
2-Anilinoethanol (8)	0.7	0.4	3.9
Ethylene oxide (9)	*b*	*b*	*c*
3-Phenyl-2-oxazolidone (10)	2.8	0.7	1.9
Weight % recovered	93.6	91.3	

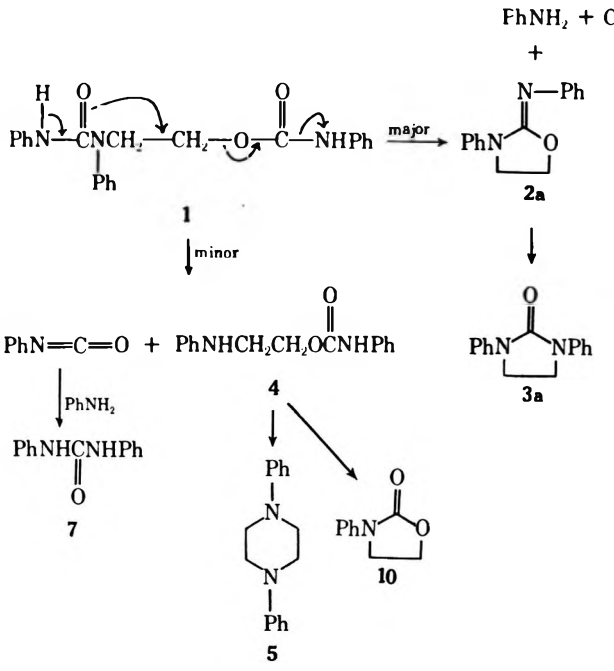
[a] 21.5 mmol of aniline added. [b] Detected qualitatively by its reaction with KSCN: W. Deckert, *Angew. Chem.*, **45**, 758 (1932). [c] Amount of ethylene oxide increasing very clearly as proved by a very deep pink color developed in the KSCN solution.

The parallel increase of imidazolidone **3a** and decrease of **2a** at progressively higher temperature indicate that isomerization of **2a** is the major source of **3a** in the decomposition of **1**. This was confirmed by the quantitative conversion of **2a** into **3a** at 200–240°. The small quantity of **3a** found in the pyrolysis of **4** may be due to the reaction of N,N'-diphenylethylenediamine (**6**) with N,N'-diphenylurea (**7**).[1]

N,N'-Diphenylpiperazine (**5**) probably arises from the intermolecular condensation of 2 mol of **4**. This reaction is suppressed to a large extent by dilution of **4** with aniline as shown by expt 3 (Table II). This

(1) H. C. Beachell and C. P. Ngoc Son, *J. Polym. Sci., Part A*, **2**, 4773 (1964).

SCHEME I



explains the very small amount of **5** found in the decomposition of **1**.

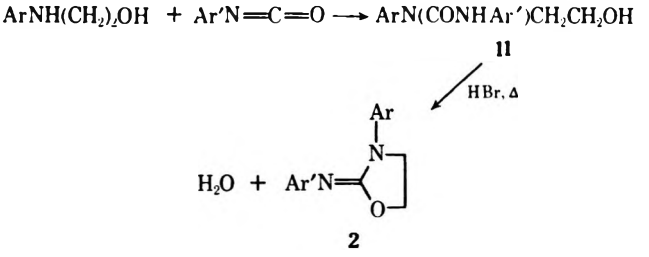
The diamine **6**, the urea **7**, 2-anilinoethanol (**8**), and ethylene oxide (**9**) are likely formed by the attack of aniline on **4** at the methylene adjacent to the oxygen[2,3] or at the carbonyl of the urethane function. This is supported by expt 3 (Table II), showing a net increase of these products in the pyrolysis of **4** in the presence of aniline. However, comparison of the data in Tables I and II shows that in the pyrolysis of **1**, the major portion of **7** must be formed from the reaction of aniline with phenyl isocyanate liberated during the partial dissociation of **1**. Compounds **6** and **7** may also be obtained from the reaction of aniline with **2a**; in fact, **2a** treated with an excess of aniline gave **6** and **7** in good yields.

Finally 3-phenyl-2-oxazolidone (**10**) would arise by the intramolecular cyclization of **4**.

Synthesis and Properties of *N,N'*-Disubstituted 2-Iminooxazolidines 2. A. Synthesis.—Although compound **2a** is one of the main decomposition products, it is not readily isolated from the reaction mixture. Various other time-consuming methods of synthesis of 2-arylimino-3-aryloxazolidines have been described such as the reaction of bis(β-anilinoethyl)-phenylphosphonite or ethyl bis(β-anilinoethyl)phosphite with 2 equiv of phenyl isocyanate,[4,5] and the cyclization of β-chloroethyl-*N,N'*-diarylureas in boiling water.[6]

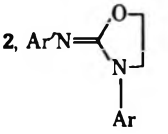
We found a very rapid and simple method of synthesis of compounds **2** which consists of the ring closure in acid medium of *N*-(β-hydroxyethyl)-*N,N'*-diarylureas **11**. The latter were quantitatively obtained by slow addition at room temperature of a dilute solution of aryl isocyanate into a dilute solution of 1 equiv of *N*-arylaminoethanol in dry benzene or dichloromethane as solvent (Scheme II).

SCHEME II



The cyclization must be carried out quickly to avoid further isomerization of **2** into 1,3-diaryl-2-imidazolidones **3**. In general, compounds **11** were heated in 48% HBr until dissolution, then reflux was continued for about 10 min. In most of the cases, the iminooxazolidines **2** were easily obtained with fairly good yields (65–75%) (Table III).

TABLE III[a]


(prepared from 11)

Compd	Ar	Ar'	Mp, °C	Yield, %
2a	C_6H_5	C_6H_5	115–116[b]	75
2b	C_6H_5	*p*-$CH_3C_6H_4$	95–96	70
2c	C_6H_5	*m*-$CH_3C_6H_4$	114–115	78
2d	C_6H_5	*p*-ClC_6H_4	143–144	61
2e	C_6H_5	*p*-$CH_3OC_6H_4$	91–92	72
2f	C_6H_5	*o*-$CH_3C_6H_4$	90–91	65
2g	C_6H_5	*p*-$NO_2C_6H_4$	164–166	27
2h	C_6H_5	*o*-$C_2H_5OC_6H_4$	105–106	40
2i	*p*-ClC_6H_4	*p*-ClC_6H_4	135–136	42

[a] Satisfactory analytical values (±0.40 for C, H, N) were reported for compounds listed in this table except for **2a** and **2c** (C found: 0.43 and 0.48 high) and **2b** (N found: 0.48 low): Ed. [b] Lit.[6] 115–116°.

Compounds **2** show characteristic infrared absorption around 1670 (C=N) and 1410 cm^{-1} (–N=CON<).[5] Their nmr spectra present two heptets centered around 4.2 ppm (A_2B_2 system).

B. Properties of 2. 1. Acid Hydrolysis and Isomerization.—In boiling 1.2 *N* aqueous HCl, all 2-arylimino-3-phenyloxazolidines are hydrolyzed to afford 3-phenyl-2-oxazolidone (**10**, yield 30–50%).

In boiling ≤8% HBr, hydrolysis does not occur; instead isomerization affords 1,3-diaryl-2-imidazolidones **3**, characterized by their ir spectra (C=O around 1690 cm^{-1}) and nmr spectra showing one singlet around 3.95 ppm (4 methylenic H). For example with **2a**, **2c**, **2g**, and **2i**, the corresponding imidazolidones were isolated with yields of 71, 75, 20, and 84%, respectively. The isomerization failed, however, with **2** having an ortho substituent on the ring of the aryl imino group.

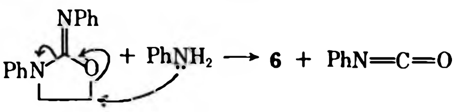
2. Nucleophilic Reaction of Aromatic Amines.—Primary aromatic amines react with **2** to give N,N'-disubstituted ureas and diamines.

For instance, a fourfold excess of aniline heated at reflux with **2a** yielded *N,N'*-diphenylethylenediamine

(2) E. Dyer and G. C. Wright, *J. Amer. Chem. Soc.*, **81**, 2138 (1959).
(3) C. P. Ngoc Son and T. T. Kim Lan, *Ann. Fac. Sci. Saigon*, 53 (1963–1964); Abstracts, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. V96.
(4) O. Mitsunobu, T. Ohashi, M. Kikuchi, and T. Mukaiyama, *Bull. Chem. Soc. Jap.*, **39**, 214 (1966).
(5) O. Mitsunobu, T. Ohashi, and T. Mukaiyama, *ibid.*, **39**, 708 (1966).
(6) H. Nohira, Y. Nishikawa, and T. Mukaiyama, *ibid.*, **37**, 797 (1964).

(6, 75%) and *N,N'*-diphenylurea (7, 80%). By analogy with the mode of attack of aromatic amines on 10[1,3] leading to its fragmentation into carbon dioxide and the corresponding diamine, the ring opening of 2a in the presence of aniline likely occurs at the methylene adjacent to the oxygen with subsequent formation of 6 and phenyl isocyanate. The latter reacts immediately with aniline in excess to yield 7 (Scheme III).

SCHEME III

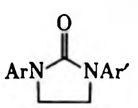


$$PhN{=}C{=}O + PhNH_2 \longrightarrow \mathbf{7}$$

Evidence for the proposed mechanism was the detection of phenyl isocyanate when 2a was treated with aniline at 190–210° in a 2-ml flask having a curved side arm. After a few minutes of heating, the isocyanate partly liberated from the reaction medium reacted with aniline to yield 7 on the upper part of the flask and in the side arm.

3. **Thermal Isomerization of 2.**—At high temperature (220–240°), under a nitrogen atmosphere, compounds 2 isomerize quantitatively to 3 (Table IV)

TABLE IV[a]

3,  (prepared from 2)

Compd	Ar	Ar'	Mp, °C	Yield, %
3a	C_6H_5	C_6H_5	210–212[b]	80
3b	C_6H_5	p-$CH_3C_6H_4$	188–189[c]	70
3c	C_6H_5	m-$CH_3C_6H_4$	136–137	73
3d	C_6H_5	p-ClC_6H_4	202–203[d]	82
3e	C_6H_5	p-$CH_3OC_6H_4$	211–212[e]	92
3f	C_6H_5	p-$NO_2C_6H_4$	208–209	80
3i	p-ClC_6H_4	p-ClC_6H_4	206–207	76

[a] Satisfactory analytical values (±0.40 for C, H, N) were reported for compounds listed in this table: Ed. [b] Lit.[1] 210–212°. [c] Lit.[6] 191–193°. [d] Lit.[6] 200–202°. [e] Lit.[6] 212–213°.

except 2f and 2h, which have an ortho substituent on the ring of the arylimino group. In the latter case,

$$\mathbf{2f} \xrightarrow{\Delta} (\text{-}\underset{\substack{|\\ C_6H_4\text{-}o\text{-}CH_3}}{N}CON(C_6H_5)CH_2CH_2\text{-})_n$$

polymerization occurs to give poly(ethylene-*N,N'*-diarylureas) characterized by elemental analyses and infrared spectra which display urea absorption around 1660 cm^{-1}. It appears that steric crowding of the ortho substituents plays an important role in the determination of the reaction pathways. Further investigations will help us to understand the mechanism of these reactions.

Experimental Section

Synthesis. A. Products of Degradation.—Aniline, *N,N'*-diphenylethylenediamine, and 2-anilinoethanol were commercially available from Eastman.

1,3-Diphenyl-2-imidazolidone (3a), mp and mmp 210–212°, ir (KBr) 1690 cm^{-1} (C=O), nmr ($CDCl_3$) 3.95 ppm (s, 4 methylenic H), *N,N'*-diphenylurea (7), mmp 242–243°, *N,N'*-diphenylpiperazine (5), mp 164–165° (lit.[7] 163–164°), nmr ($CDCl_3$) 3.5 ppm (s, 8 methylenic H), and 3-phenyl-2-oxazolidone (10), mp 119–120° (lit.[1] 120–121°), ir (KBr) 1750 cm^{-1} (C=O), were synthesized from known procedures.[1,7]

B. ***N*-[β-(*N''*-Phenylcarbamyl)ethyl]-*N,N'*-diphenylurea (1).**—Phenyl isocyanate (71.4 g, 0.6 mol) was added dropwise at reflux and under a nitrogen atmosphere to a solution of 2-anilinoethanol (41.1 g, 0.3 mol) in 150 ml of dry benzene. The solution was heated for 7 hr, then solvent was partially removed. Recrystallization from benzene–hexane afforded colorless needles: mp 137°; ir (KBr) 3300 (NH), 1706 (-NHCOO-), 1634 cm^{-1} (-NHCON<); yield 90%.

Anal. Calcd for $C_{22}H_{21}N_3O_3$: C, 70.40; H, 5.60; N, 11.20. Found: C, 70.35; H, 5.63; N, 11.22.

C. **β-Anilinoethyl *N*-Phenylcarbamate (4).**—β-Bromoethyl *N*-phenylcarbamate, mp 70° (24.4 g, 0.1 mol) (obtained by the reaction of 2-bromoethanol with an equimolar quantity of phenyl isocyanate in benzene solution), was treated with aniline (11.2 g, 0.12 mol) at reflux in dry benzene in the presence of pyridine for 5 hr. Pyridinium bromide was then removed and the solution was extracted with 1.2 *N* HCl. Neutralization of the aqueous layer with solid KOH at 0° yielded the carbamate 4 which was recrystallized from chloroform–hexane, mp 81–82°, yield 51%.

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.31; H, 6.25; N, 10.92. Found: C, 70.18; H, 6.25; N, 10.76.

D. **2-Arylimino-3-aryloxazolidines 2.**—All the compounds 2 were already recorded in Table III. A typical synthesis is described below.

E. **2-Phenylimino-3-phenyloxazolidine (2a).**—(β-Hydroxyethyl)-*N,N'*-diphenylurea, mp 83–84° (lit.[1] 82–83°), was first synthesized by a very slow dropwise addition of 1 equiv of phenyl isocyanate to 1 equiv of 2-anilinoethanol in very dilute benzene solution at room temperature and under a nitrogen atmosphere. A mixture of 5 g of the urea and 15 ml of 48% HBr was heated until complete dissolution occurred. Heating was continued for about 10 min, then the solution was diluted with distilled water and filtered. Neutralization of the filtrate with solid KOH at 0° provided 2a. Recrystallization from chloroform–hexane afforded colorless crystals: mp 115–116° (lit.[5] 116°); ir (KBr) 1670 cm^{-1} (C=N); nmr ($CDCl_3$) two symmetrical multiplets entered at 4.1 ppm; yield 75%.

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.63; H, 5.88; N, 11.76. Found: C, 75.20; H, 5.93; N, 11.85.

Reactions. A. Acid Hydrolysis of 2.—A typical reaction is described below.

A 1-g sample of 2a was heated with 10 ml of 1.2 *N* HCl at reflux for 3 hr and then cooled in the refrigerator. 3-Phenyl-2-oxazolidone (10) precipitated and was recrystallized from chloroform–hexane, mp 119–120°, yield 44%.

B. **Acid Isomerization of 2.**—The isomerization was performed with 48% HBr. With 2a, 1,3-diphenyl-2-imidazolidone (3a) precipitated during the reaction. Recrystallization from chloroform–hexane afforded yellowish crystals, mp and mmp 210–212°, yield 71%.

C. **Reaction of Aniline with 2a.**—A 1-g sample of 2a was treated with 3 ml of aniline for 1 hr at 200° and under a nitrogen atmosphere. The residue was extracted with cold ether. The insoluble fraction was impure *N,N'*-diphenylurea (80%) which was then recrystallized from chloroform–hexane, mp and mmp 242°. The filtrate was treated with 2 *N* HCl. Neutralization of the aqueous layer at 0° with solid KOH gave the diamine 6, mp 57–58°, yield 75%. Recrystallization from ether–hexane yielded pale yellow crystals, mp and mmp 62°.

D. **Thermal Isomerization of 2.**—General procedure: A 1-g sample of 2 was heated at 220–240° for 2 hr under a nitrogen atmosphere. The residue was washed with cold ether to eliminate the unreacted iminooxazolidine and recrystallized from chloroform–hexane to yield 3. All compounds 3 were recorded in Table IV.

From 2-*o*-tolylimino-3-phenyloxazolidine (2f), poly(ethylene-*N*-o-tolyl-*N'*-phenylurea) was obtained in 30% yield.

Anal. Calcd for $(C_{16}H_{16}N_2O)_n$: C, 76.03; H, 6.50; N, 11.01. Found: C, 76.18; H, 6.34; N, 11.11.

(7) H. W. Heine, B. L. Kapur, and C. S. Mitch, *J. Amer. Chem. Soc.*, **76**, 1173 (1954).

E. Pyrolysis of Compounds 1 and 4.—The pyrolysis of 1 and 4 was carried out in a 100-ml three-necked flask equipped with thermometer, nitrogen inlet, and condenser. The latter was connected to a $CaCl_2$ U-tube, a three-way stopcock carrying at each end an ascarite U-tube. The weighing of the latter at regular intervals of time permitted us to measure carbon dioxide liberated during the pyrolysis. The residue after the pyrolysis was partially dissolved in cold ether. The insoluble portion was composed of the compounds 2a, 3a, and 7. The filtrate contained aniline, and the products, 2a, 4, 5, 6, 8, 10, small amounts of 3a and 7 slightly soluble in cold ether. The degradation products were separated quantitatively by column chromatography on alumina of these two portions with hexane, benzene, chloroform, ethanol, and their mixtures as eluents.

Registry No.—1, 748-84-5; 2b, 32974-53-1; 2c, 32974-54-2; 2d, 32974-55-3; 2e, 32974-56-4; 2f, 13468-08-1; 2g, 32974-58-6; 2h, 32974-59-7; 2i, 32974-60-0; 3c, 32974-61-1; 3f, 32974-62-2; 3i, 5198-55-0; 4, 33020-71-2; 6, 150-61-8; 7, 102-07-8; β-bromoethyl *N*-phenylcarbamate, 32353-12-1; poly(ethylene-*N*-*o*-tolyl-*N*′-phenylurea), 33029-39-9.

The Transannular Neophyl Rearrangement[1,2]

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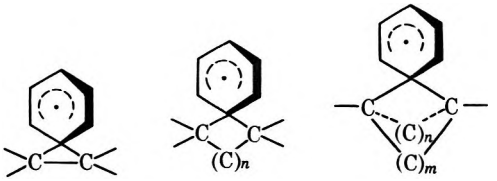
The radical rearrangement in solution of a phenyl group across a cyclohexane ring *via* bicyclo[2.2.1]heptyl and [2.2.2]octyl species has been achieved. This transannular rearrangement did not occur in analogs *via* smaller sized bicyclic species. In these cases the parent structures were retained or ring opening occurred.

The vicinal migration of a phenyl group *via* **1** (the neophyl rearrangement) is well known.[3] Less common, but still recorded,[4] are analogous further rearrangements *via* **2**. It was the intent of the present study to seek phenyl shifts *via* **3**, a process we term

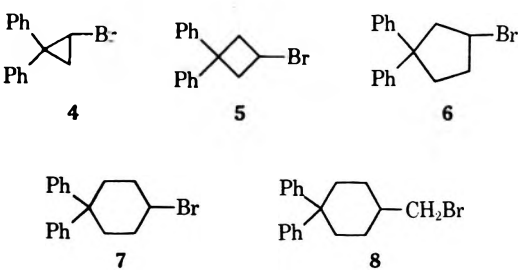


1 **2** **3**

the "transannular neophyl rearrangement."[5] Quite clearly, such rearrangements will be sensitive to the bicyclic ring size of the intermediate; so a series of these were investigated.

Any of several extant free radical processes that exhibited rearrangement *via* **1** or **2** could be chosen for application to **3**. However, in recent years the generation of carbon radicals from the reaction of halides with organotin hydrides has become widespread.[6] This method recommended itself for the present purpose for several reasons: the temperature of the reaction can be varied readily, as can the concentration of the tin hydride. Generally speaking, higher temperatures and lower concentrations of the hydride favor radical rearrangement processes.[7] Also, as one of its best features, the process produces the radical of interest directly and not *via* intervening species.

As precursors to the radicals under study, the series of bromides **4**–**8** was prepared and characterized. The



4 **5** **6**

7 **8**

rationale for using a *gem*-diphenyl function was twofold. First, one of the phenyls is always situated appropriately for migration. Second, the other phenyl group serves as a stabilizer for the radical center formed subsequent to rearrangement. Coincidentally, this second phenyl group serves also as a rearrangement marker through its influence on the nmr spectrum of the product. Secondary bromides sometimes present a problem in their synthesis because carbonium ion rearrangements can occasionally plague the customary routes to them.[8] For this reason, a noncarbonium ion process (eq 1) was chosen to prepare most

$$\underset{\mathbf{11,\ 17,\ 19}}{\mathrm{ROTs}} + \mathrm{LiBr} \xrightarrow[\text{or diglyme}]{\text{acetone}} \underset{\mathbf{5\text{–}7}}{\mathrm{RBr}} + \mathrm{LiOTs} \qquad (1)$$

of those needed for this study. The requisite tosylates were made as shown (eq 2–4). The sequences shown are straightforward and will not be discussed. Details may be found in the Experimental Section. Diagnosis by spectral and chromatographic methods indicated that reaction 1 proceeded without rearrangement in every instance. Bromides **4** and **8** were, however, prepared alternatively (eq 5, 6). In all cases the structures were supported by combustion analytical and spectral data.

One may notice that the transannular neophyl re-

(1) Taken from (a) the Dissertation of R. A. D., 1970; and (b) the M.S. Thesis of K. C. W., 1970.

(2) Presented at the Third Great Lakes Meeting of the American Chemical Society, Northern Illinois University, De Kalb, Ill., June 1969, Abstracts of Papers, paper 58.

(3) *Cf.* R. Kh. Freidlina in "Advances in Free-Radical Chemistry," Vol. 1, G. H. Williams, Ed., Academic Press, New York, N. Y., 1965, pp 249–260.

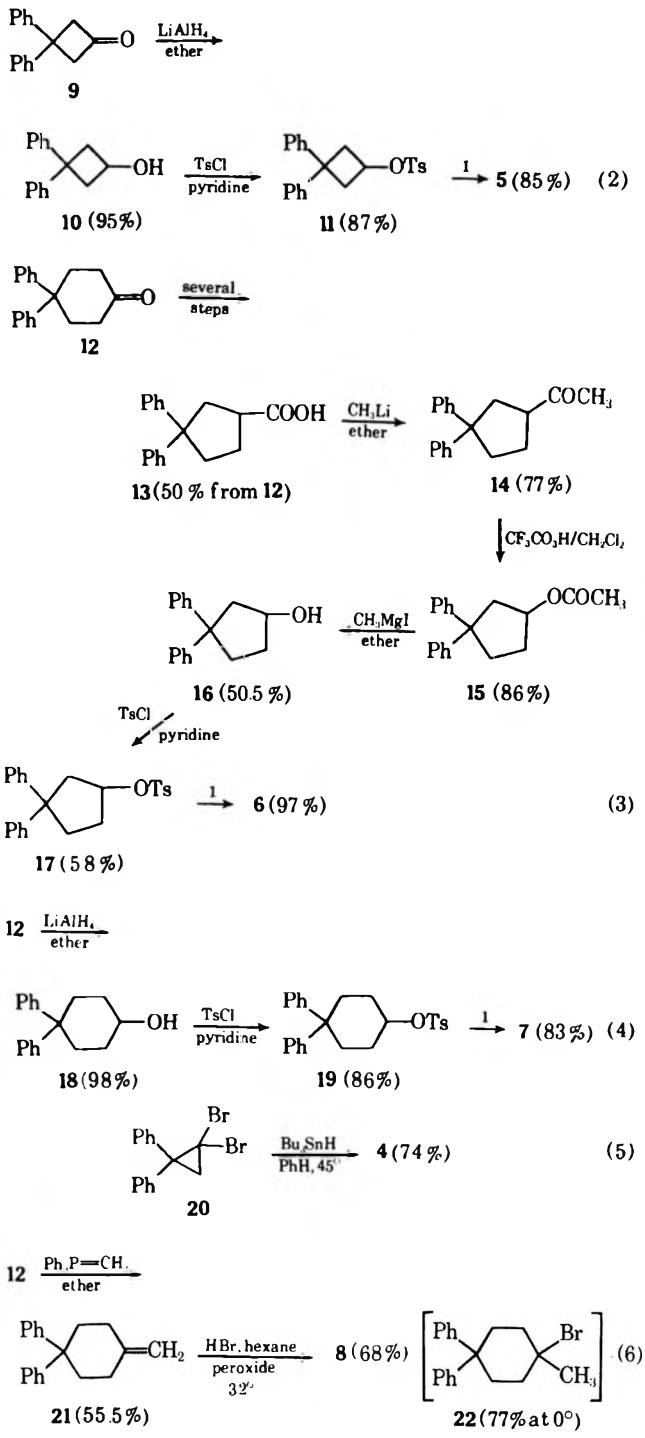
(4) S. Winstein, R. Heck, and S. Lapporte, *Experientia*, **12**, 138 (1956).

(5) Although perhaps properly applied only to the rearrangement of the β-phenylisobutyl ("neophyl") radical itself, the term "neophyl rearrangement" is used here for the radical migration of an aromatic group from a carbon atom origin to any other carbon atom terminus.

(6) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 229 (1968).

(7) L. Kaplan, *J. Amer. Chem. Soc.*, **88**, 4531 (1966).

(8) *Cf.* J. Cason and J. S. Correia, *J. Org. Chem.*, **26**, 3645 (1961).



arrangement in the systems represented by **4**–**8** would engender a particular bicyclic intermediate $Ar_1[x.y.z]$[9,11] as shown (eq 7). For reference, the strain energies, measured and/or calculated, for the bicycles of concern are collected in Table I. Although the

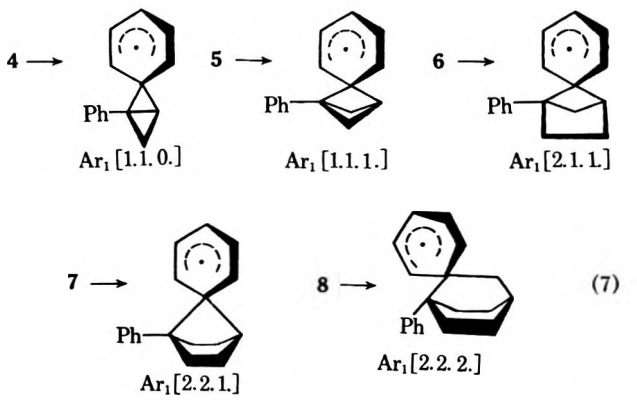


TABLE I

Bicyclo-	Strain energy, kcal mol^{-1}
[1.1.0]butane	66.5,[a] 64.7[b]
[1.1.1]pentane	92.23[c]
[2.1.1]hexane	44.64[c]
[2.2.1]heptane	17.55,[a] 17.95[c]
[2.2.2]octane	11.01,[a] 13.22[c]

[a] P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970). [b] K. B. Wiberg, *Rec. Chem. Progr., Kresge-Hooker Sci. Libr.*, **26**, 143 (1965). [c] N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, **93**, 1637 (1971).

$Ar_1[x.y.z]$ intermediates are perhaps not exactly comparable to these bicyclic species,[12] the trend in the values in Table I allows at least a qualitative comparison. So some simple deductions from these data may be mentioned. In both **7** and **8**, for example, transannular rearrangement obviously requires a boat conformation in the rearranging radical (eq 8, 9). Plausibly, the initially formed radicals **7**· and **8**· are predominantly chairlike more than boatlike[13] and energy must be expended to convert them to **7′**· and **8′**·. The energy required for the change **7**· → **7′**· is presumably not great, however, because boat and chair conformers of cyclohexanone (a passable model for a cyclohexyl radical) are easily interconvertible.[14] If this be so, then only a modest further energy expenditure would be necessary to accommodate the strain involved in the transannular phenyl shift. For the change **8**· → **8′**·, the energy required would be somewhat more, perhaps the *ca.* 10 kcal required of methylcyclohexane,[15] although the *gem*-diphenyl function could alter this somewhat. Nonetheless, the decreased strain present in the $Ar_1[2.2.2]$ intermediate relative to all the others (Table I) makes rearrangement appear possible here as well. Clearly, the situa-

(9) *A priori*, $Ar_1[x'.y'.z']$ intermediates are conceivable for the processes also. Indeed, Ar_1-6 intermediacy has been noted before in certain radical rearrangements.[4,10] Normally, however, such Ar_1-*m* intermediates lead to cyclized products *via* aromatization by hydrogen atom donation to some acceptor species. As no such products implicating this route were detected, we believe that Ar_1 involvement is more probable in the present examples.

(10) U. K. Pandit and I. P. Dirk, *Tetrahedron Lett.*, 891 (1963).

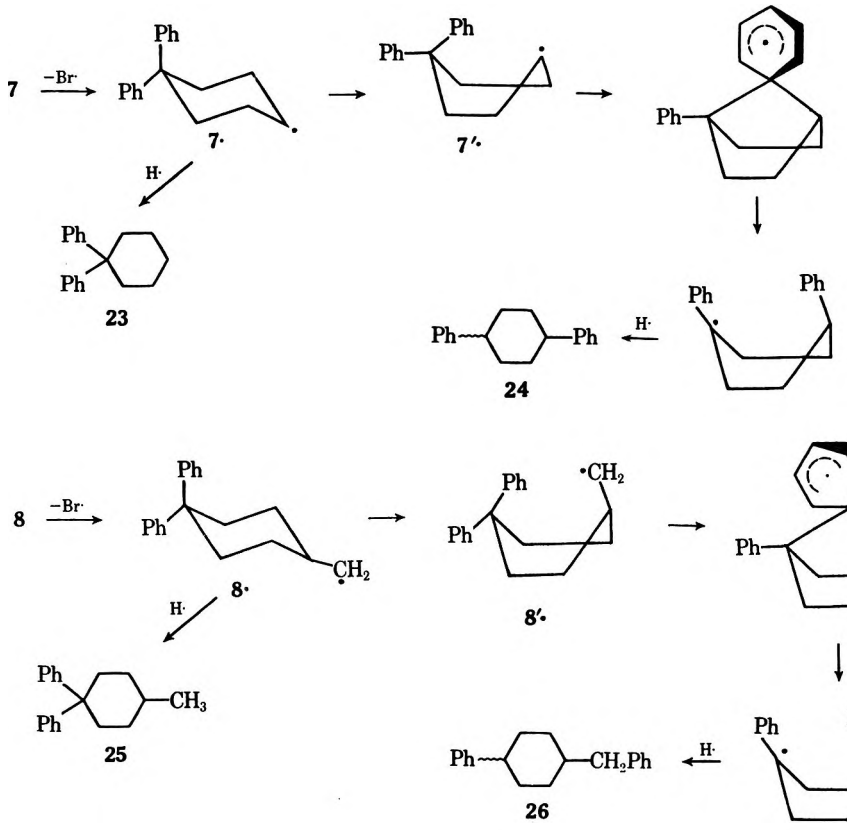
(11) The $Ar_1[2.2.1]$ intermediate has previously been invoked to explain transannular phenyl migration: (a) H. Pines, W. F. Fry, N. C. Sih, and C. T. Goetschel, *J. Org. Chem.*, **31**, 4094 (1966), obtained *p*-terphenyl from 1,1-diphenylcyclohexane over nonacidic chromia–alumina B at 390–497°, a process they suggested involved the same radical rearrangement sought here. Incidentally, no rearrangement attended passage of 1,1-diphenylcyclohexane over glass beads at these temperatures. (b) In an elimination reaction of **19** with sodium *tert*-butoxide, the 1,4 phenyl shift observed by A. R. Abdun-Nur and F. G. Bordwell, *J. Amer. Chem. Soc.*, **86**, 5695 (1964), was rationalized by an ionic analog of the [2.2.1] intermediate. In this brief communication, the radical possibility was termed "unlikely."

(12) *I.e.*, the influence of the additional phenyl and cyclohexadienyl moieties on these bicyclic strain energies is unknown. Moreover, the *transition states* may not be symmetrical with regard to bonding of the migrator between the origin and terminus sites, thus changing the geometry of the aliphatic portion of the bicycle to some degree, relative to these *intermediates*.

(13) As a model for radical **7** one might choose ketone **12**. This ketone possesses a chair cyclohexane ring flattened near the carbonyl group with the phenyl rings at C-4 nearly perpendicular to one another: J. B. Lambert, R. E. Carhart, and P. W. R. Corfield, *J. Amer. Chem. Soc.*, **91**, 3567 (1969).

(14) The energy barrier for the conformational change chair → boat is apparently unknown for cyclohexanone, although an upper limit of 6 kcal mol^{-1} has been suggested by E. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison in "Conformational Analysis," Interscience, New York, N. Y., 1965, p 186. Just what effect the 4,4-diphenyl function would have on this barrier is also unknown.

(15) Reference 14, p 185.



(8)

(9)

tion for such rearrangement grows bleaker in the smaller rings.

These naive expectations based upon such strain considerations were fulfilled. *Transannular neophyl rearrangement indeed occurred with* **7** *and* **8**, whereas none at all was found for **4**–**6**. Frankly, the fact that rearrangement occurred at all for **7** and **8** is surprising. In order to have rearrangement, energy-rich conformers of short-lived radicals are required and the competitive chain transfer reaction to produce unrearranged hydrocarbon is quite fast ($k_t = 10^6\ M^{-1}\ \text{sec}^{-1}$ at 25°[16]). Although the results obtained are inadequate for an accurate determination, the activation energy for the rearrangements in these systems is obviously low.[17] The results of the studies on **7** and **8** are shown in Table II. The rearranged product, in

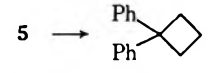
TABLE II

Bromide	M[a]	Temp, °C (bath)	% rearrangement[b]
7	0.318	145	1.0[c,d]
	0.306	155	2.6[d]
	0.102	150	3.2[d]
8	0.304	145	Trace[c,e]
	0.030	145	0.7[e]
	0.015	145	1.1[e]

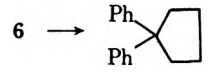
[a] In dry, thiophene-free benzene with 1.1 equiv of tri-*n*-butyltin hydride present. [b] Yields of hydrocarbon product were over 90%. Duplicate runs agreed within 5%. [c] No rearranged product at 78°. [d] Rearranged product isolated by column chromatography. [e] By gas–liquid partition chromatography.

one case hydrocarbon **24** and in the other **26**, was resolvable chromatographically from the related unrearranged product **23** or **25**. Comparison with an authentic sample established the structure for each.

The results with bromides **5** and **6** were unexciting. Each afforded the *gem*-diphenylcycloalkane, as indicated in eq 10 and 11.

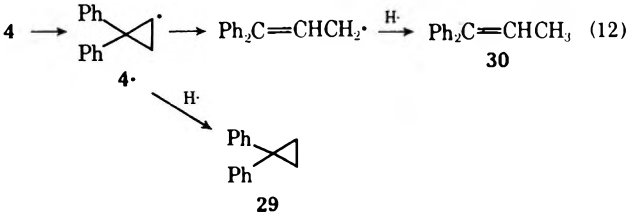


(10)



(11)

Bromide **4**, however, led to ring-opened product **30** along with the expected *gem*-diphenyl product **29** (eq 12).



(12)

Ring opening, an uncommon reaction of cyclopropyl radicals in spite of the *ca.* 30 kcal mol^{-1} release of strain energy,[18] became more pronounced with increased temperature and/or lowered tin hydride concentrations. The data is given in Table III. This ring opening of **4**· is undoubtedly assisted by the ability of the phenyl groups to stabilize the opened radical.[19,20]

(16) D. J. Carlsson and K. U. Ingold, *J. Amer. Chem. Soc.*, **90**, 7047 (1968).

(17) Approximate calculations yielded a value of about 15 kcal mol^{-1} for the activation energy associated with **7** → **24**.[1a]

(18) J. D. Roberts and D. Schuster, *J. Org. Chem.*, **27**, 51 (1962).

(19) Approximate calculations yielded a value of *ca.* 11 kcal mol^{-1} for the ring opening in **4**.[1a]

(20) For another instance of such phenyl assistance, *cf.* H. M. Walborsky and J.-C. Chen, *J. Amer. Chem. Soc.*, **92**, 7573 (1970).

TABLE III

4, M[a]	Bu_3SnH, M	Temp, °C	% 30[b]
0.320	0.330	78	13
0.105	0.110	78	38
0.320	0.330	150[c]	76
0.105	0.110	150[c]	91

[a] In benzene. Reaction time 24 hr. [b] *Via* glpc. [c] Bath temperature.

The neophyl rearrangement, with its surprising reach, thus appears to be one of the more adaptable radical rearrangements known. This study, together with an earlier one,[21] also illustrates the utility of the tin hydride reduction method for uncovering seemingly unpropitious rearrangements.

Experimental Section

Melting points were taken on a calibrated Fisher-Johns block. Boiling points are not corrected for stem exposure. Combustion analyses were by Micro-Tech Laboratories, Skokie, Ill., or by the analytical laboratories of G. D. Searle and Co., Skokie, Ill. Gas–liquid partition chromatography (glpc) was carried out on Varian Aerograph A-90P and Hewlett-Packard Model 5750 instruments with disc and electronic integration, respectively. Infrared, nmr, and mass spectra were determined on Beckman IR-5A, Varian A-60A, and Perkin-Elmer Model 270 instruments, respectively.

Preparation of Bromides. 2-Bromo-1,1-diphenylcyclopropane (4).—2,2-Dibromo-1,1-diphenylcyclopropane[22] [20, mp 149.5–151°, δ (CCl_4) 7.35 m (Ar H) and 1.03 s (CH_2) (lit.[22] mp 150–151°), 14.83 g, 0.042 mol] in benzene (100 ml) was stirred at 45° under nitrogen as tri-*n*-butyltin hydride[23] (12.13 g, 0.042 mol) in benzene (50 ml) was added dropwise over 20 min. The mixture was allowed to stir for an additional 90 min. Removal of solvent left an oil which was taken up in 95% ethanol (75 ml) and refrigerated. White needles of **4** were collected (8.44 g, 74%, mp 76–78°). Recrystallization from 95% ethanol gave an analytical sample: mp 81–82.5°; δ (CCl_4) 7.3 m (Ar H), 3.60 t (CHBr, J = 6 Hz), 1.78 d (CH_2). The deceptive A_2X system became ABX in benzene, δ 3.48 dd (CHBr, J = 5 and 8 Hz), 1.50 m (CH_2).

Anal. Calcd for $C_{15}H_{13}Br$: C, 65.96; H, 4.79. Found: C, 66.11; H, 4.50.

3-Bromo-1,1-diphenylcyclobutane (5).—3,3-Diphenylcyclobutanone (9) was reduced with lithium aluminum hydride and the alcohol 10 so obtained (95%) was converted to the tosylate 11 (87%, mp 116–117°).[24] A solution of tosylate 11 (0.5 g, 1.4 mmol) and lithium bromide (0.4 g, 46 mmol) in dry diglyme (20 ml) was heated at 120° for 20 hr. The orange solution was cooled, poured into ice water, and extracted with chloroform. The chloroform extracts were dried ($MgSO_4$) and carefully evaporated. The solid residue was chromatographed over silica gel with hexane as the eluting solvent to give bromide **5** (0.34 g, 85%). Recrystallization from hexane afforded an analytical sample: mp 93–94°; δ (CCl_4) 7.25 m (Ar H), 4.55 pentuplet with further splitting (CHBr), 3.35 m (CH_2).

Anal. Calcd for $C_{16}H_{15}Br$: C, 66.91; H, 5.26. Found: C, 66.84; H, 5.23.

3-Bromo-1,1-diphenylcyclopentane (6).—4,4-Diphenylcyclohexanone (12) was converted to 3,3-diphenylcyclopentanecarboxylic acid (13) as reported.[25] Acid **13** (4.0 g, 14 mmol) in ether was stirred at 25° while excess ethereal methyllithium was added dropwise over 5 min. Ten minutes after the addition was completed, the reaction was quenched at 0° with saturated ammonium chloride. The ether layer was separated, washed with 10% sodium carbonate solution, water, and brine, and then dried (Na_2SO_4). Distillation gave **methyl 3,3-diphenylcyclopentyl ketone** [14, 2.9 g, 77%, bp 190–197° (0.2 mm)]. About 5% (3,3-diphenylcyclopentyl)dimethylcarbinol was also present in this material. Ketone 14 was purified *via* regeneration from its semicarbazone as a colorless oil: bp 167–169° (0.1 mm); λ (neat) 5.90 (C=O), 7.40 (CH_3); δ (CCl_4) 7.25 m (Ar H), 3.20–2.65 m (CH), 2.62–1.50 m (CH_2), 2.00 s (CH_3).

Anal. Calcd for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.54; H, 7.38.

The orange **2,4-dinitrophenylhydrazone** was readily prepared, mp 152.5–153.5° dec from ethyl acetate.

Anal. Calcd for $C_{25}H_{24}O_4N_4$: N, 12.61. Found: N, 12.59.

In an ice bath, crude ketone **14** (2.63 g, 10 mmol) in methylene chloride (40 ml) containing suspended disodium hydrogen phosphate (9.2 g) was treated dropwise with trifluoroperacetic acid (from the reaction of trifluoroacetic anhydride, 7.3 g, 34 mmol, and hydrogen peroxide, 90%, 3 ml, in methylene chloride, 25 ml) over a 20-min period with efficient stirring. A slow rate of addition and the ice bath helped to control the exothermic reaction. After the addition the reaction material was stirred for an additional 1.75 hr. The salts present were filtered off and the methylene chloride solution was washed well with water, 10% sodium carbonate solution, water, and brine until neutral. Removal of solvent left crude **3,3-diphenylcyclopentyl acetate** (15, 2.42 g, 85%). A portion was chromatographed on alumina using 1:1 ether–hexane as the eluting solvent and then distilled in a micro-Hickman still. Ester **15** was a colorless oil with a floral odor: λ (neat) 5.82 (C=O), 7.31 (CH_3), 8.10 (acetate CO); δ (CCl_4) 7.00 m (Ar H), 4.90 m (CHOAc), 3.08 m (one H of the 2-CH_2, AB portion of ABX pattern), 2.60–2.00 m (all other ring H's), 1.90 s (-$OCOCH_3$).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.42; H, 7.31.

Ester **15** (crude product from the above preparation on a threefold larger scale) was added to methylmagnesium iodide (100 mmol) in ether. After 30 min the cooled solution was hydrolyzed with dilute sulfuric acid and the ether layer was separated and washed with 10% sodium bisulfite solution, water, and brine. Evaporation of the dried (Na_2SO_4) ether solution left an oily solid, **3,3-diphenylcyclopentanol** (16, 3.4 g, 50.5%). An analytical sample was obtained by three distillations in a micro-Hickman still as a colorless oil that slowly solidified: lit.[26] mp 55–57°; λ (neat) 2.95 (OH), 9.38 (CO); δ (CCl_4) 7.20 m (Ar H), 4.37 m (CHOH), 2.80 dd (one H of the 2-CH_2, J_{gem} = 15, J_{vic} = 7 Hz), 2.50–1.53 m (OH and all other ring H's).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.71; H, 7.81.

Conversion of alcohol **16** to its **tosylate 17** was achieved in 58% yield by the usual pyridine–tosyl chloride method.[27] An analytical sample of **17** was obtained from ether–petroleum ether (bp 30–60°), mp 80–81.5°.

Anal. Calcd for $C_{24}H_{24}O_3S$: C, 73.44; H, 6.16. Found: C, 73.51; H, 6.18.

A solution of tosylate **17** (1.0 g, 2.5 mmol) and lithium bromide (1.0 g, 11.5 mmol) in acetone (freshly distilled from potassium permanganate, 25 ml) was refluxed (drying tube attached) for 20 hr. The acetone was removed and the residue was treated with water to a volume of 50 ml. Ether extraction followed. The dried (Na_2SO_4) extracts were concentrated to produce bromide **6** (0.73 g, 97%). An analytical sample was obtained from hexane: mp 64–65.5°; δ (CCl_4) 7.2 s (Ar H), 4.30 m (CHBr), 3.15 dd, 2.65 dd (2-CH_2), AB portion of ABX pattern, J_{gem} = 14, J_{vic} = 7 and 9 Hz), 2.6–2.1 m (other ring H's).

Anal. Calcd for $C_{17}H_{17}Br$: C, 67.79; H, 5.69. Found: C, 67.76; H, 5.75.

4-Bromo-1,1-diphenylcyclohexane (7).—Reduction of ketone **12** with lithium aluminum hydride produced **4,4-diphenylcyclohexanol** (18, 98%, mp 139.5–140.5°) from benzene–petroleum ether).[11b] The alcohol was converted to the tosylate **19** in standard fashion[27] (86%, mp 123.5–125° from benzene–ether).

Anal. Calcd for $C_{25}H_{26}O_3S$: C, 74.04; H, 6.21. Found: C, 73.97; H, 6.46.

(21) J. W. Wilt, S. N. Massie, and R. A. Dabek, *J. Org. Chem.*, **35**, 2803 (1970).

(22) P. S. Skell and A. Y. Garner, *J. Amer. Chem. Soc.*, **78**, 5430 (1956).

(23) H. G. Kuivila and O. F. Beumel, Jr., *ibid.*, **83**, 1246 (1961).

(24) We are indebted to Dr. C. J. Michejda and Mr. R. Comnick, Department of Chemistry, University of Nebraska, for the details of their preparation of **9**, **10**, and **11** (March 12, 1969).

(25) F. G. Bordwell, R. R. Frame, R. G. Scamehorn, J. G. Strong, and S. Meyerson, *J. Amer. Chem. Soc.*, **89**, 6704 (1967).

(26) During the course of this work, A. Warshawsky and B. Fuchs, *Tetrahedron*, **25**, 2633 (1969), reported the preparation of alcohol **16** by another path. The nmr spectrum of **16** illustrated in their paper matched that of our sample.

(27) R. S. Tipson, *J. Org. Chem.*, **9**, 235 (1944).

In the manner described above for bromide **6**, tosylate **19** (2.58 g, 6.3 mmol) and lithium bromide (1.54 g, 17 mmol) in refluxing acetone (60 ml) for 115 hr[28] afforded bromide **7** (1.65 g, 83%, mp 95–99°). Colored acetone-derived aldol contaminants were easily removed with a cold petroleum ether wash. An analytical sample of **7** was obtained by chromatography on alumina with hexane as the eluting solvent: mp 100.5–102°; δ ($CDCl_3$) 7.20 m (Ar H), 4.34 m (CHBr), 2.85–1.95 m (CH_2's).

Anal. Calcd for $C_{18}H_{19}Br$: C, 68.58; H, 6.07. Found: C, 68.57; H, 6.16.

4-Bromomethyl-1,1-diphenylcyclohexane (**8**).—Under nitrogen, *n*-butyllithium in hexane (0.1 mol) mixed with dry ether (250 ml) was treated with methyltriphenylphosphonium bromide (28.5 g, 0.08 mol) suspended in more ether (250 ml). The orange solution of the ylide was stirred at 25° for 1 hr. Ketone **12** (20.0 g, 0.08 mol) in a slurry with ether (500 ml) was then added and the yellow mixture was refluxed for 80 min, after which time thin layer chromatography (tlc) indicated that the reaction was complete. The cooled solution was filtered and washed well with water. After being dried (Na_2SO_4), the solution was evaporated and the residual oil was taken up in benzene. After the material had been passed through a column of silica gel, it was distilled to afford **1-methylene-4,4-diphenylcyclohexane** (**21**): 12 g, 55.5%; bp 114–118° (0.04 mm); mp 48–49°; λ ($CHCl_3$) 3.28, 3.33, 6.06, 11.22 (C=CH_2); δ ($CDCl_3$) 7.26 m (Ar H), 4.62 s (C=CH_2), 2.32 sharp m (ring CH_2's).

Anal. Calcd for $C_{19}H_{20}$: C, 91.88; H, 8.12. Found: C, 92.05; H, 8.17.

With slight warming, benzoyl peroxide (0.29 g) was dissolved in mixed hexanes solvent (Skellysolve B, bp 56–71°, 120 ml) containing olefin **21** (2.98 g, 12 mmol). At 32° a slow stream of anhydrous hydrogen bromide was introduced over 2 hr, at which time tlc analysis showed complete reaction. The solution was washed with water, 10% ferrous sulfate solution, and water and then dried (Na_2SO_4). Removal of solvent left bromide **8** as an oil which solidified when triturated with a little ether. Further purification by low-temperature crystallization from ether gave pure **8** as a colorless solid: 2.37 g, 60%; mp 69–71°; δ ($CDCl_3$) 7.50–7.00 m (Ar H), 3.19 d (CH_2Br, J = 6 Hz), 3.00–0.99 m (other ring H's).

Ancl. Calcd for $C_{19}H_{21}Br$: C, 69.30; H, 6.47; Br, 24.24. Found: C, 69.64; H, 6.65; Br, 24.31.

Interestingly, the above reaction carried out at 0° gave a 77.4% yield of **4-bromo-4-methyl-1,1-diphenylcyclohexane** (**22**): mp 93–94° from ether; λ ($CHCl_3$) 7.23 (CH_3); δ ($CDCl_3$), 1.77 s (CH_3).

Anal. Calcd for $C_{19}H_{21}Br$: C, 69.30; H, 6.47; Br, 24.24. Found: C, 69.52; H, 6.44; Br, 23.95.

Presumably chain initiation at this temperature was inefficient relative to the competing ionic addition.

Preparation of Reference Hydrocarbons. 1,1-Diphenylcyclohexane (**23**).—Reduction of 2,2-diphenylcyclohexanone[29] by the Huang-Minlon method as described[30] gave **23** as colorless platelets: 30%; mp 42–44° from ethanol (lit.[30] mp 42–44°); δ (CCl_4) 7.23 s (Ar H), 2.25 m (2, 6-CH_2's), 1.50 m (other CH_2's).

***cis*- and *trans*-1,4-Diphenylcyclohexane** (**24**).—The hydrocarbon was prepared by catalytic hydrogenation (2.5 atm, Pd/C catalyst, 25°, 17 hr) of 1,4-diphenylcyclohexene in acetic acid, largely as described.[11a] The product formed white platelets: mp 158–168° from benzene–hexane (lit.[11a] mp 159–173°); δ ($CDCl_3$) 7.35 s (Ar H), 2.67 broad m (1, 4-CH), 2.16–1.38 m (remaining H's); mass spectrum[31] (70 eV) base peak 91 (tropylium ion), other peaks greater than 50% of the base peak, 236 (parent), 158, 117, 104 amu. The melting point range of this product was identical with that of the product from the reduction of **7** (*vide infra*). From this range, each product is undoubtedly a cis–trans mixture. No investigation of the composition of the mixture was made, however.

4-Methyl-1,1-diphenylcyclohexane (**25**).—Olefin **21** (590 mg) was reduced in absolute ethanol (4 ml) and benzene (2 ml) with hydrogen gas (52 psig) over a Pd/C catalyst (5%) for 2.5 hr. Removal of the catalyst and solvent left **25** as a colorless solid: 390 mg, 66.2%; mp 41–43°; λ ($CHCl_3$) 7.24 (CH_3); δ (CCl_4) 7.5–7.0 m (Ar H), 2.90–0.70 m (ring H's), 0.81 distorted d (CH_3, J = *ca.* 5 Hz).

Anal. Calcd for $C_{19}H_{22}$: C, 91.14; H, 8.86. Found: C, 91.27; H, 8.83.

***cis*- and *trans*-1-Benzyl-4-phenylcyclohexane** (**26**).—4-Phenylcyclohexanone[32] (7.31 g, 42 mmol) was treated with benzylmagnesium chloride (51 mmol) in ether under nitrogen at reflux for 90 min. The reaction material was poured into ice water containing hydrochloric acid (30 ml of acid). The separated ether layer, together with ether extracts of the aqueous phase, were washed with water until neutral, dried (Na_2SO_4), and evaporated. The resulting oil crystallized upon addition of Skellysolve B and subsequent chilling. **1-Benzyl-4-phenylcyclohexanol** formed white crystals: 5.55 g, 50%; mp 87–88°; λ ($CHCl_3$), 2.78 (OH), 8.76 (CO); δ ($CDCl_3$) 7.20 d (Ar H), 2.78 s (CH_2Ph), 1.90–1.40 m (ring H's), 1.20 s (OH, exchanges).

Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.33; O, 6.01. Found: C, 86.03; H, 8.35; O, 5.95.

This alcohol (3.15 g, 11.4 mmol), together with potassium bisulfate (1.57 g, 11.4 mmol), was refluxed in chlorobenzene (50 ml) for 50 min. After being washed with water until neutral, the chlorobenzene solution was dried (Na_2SO_4) and evaporated. The residual oil was distilled to give **1-benzyl-4-phenylcyclohexene**, 2.0 g, 71.8%, bp 136–137° (0.2 mm), containing about 17% **4-phenyl-1-benzylidenecyclohexane**: δ ($CDCl_3$) 7.23 s (Ar H), 6.30 m (=CHPh), 5.55 m (CH=C<), 3.30 m (-CH_2Ph), 3.0–1.3 m (other ring H's).

Anal. Calcd for $C_{19}H_{20}$: C, 91.88; H, 8.12. Found: C, 91.82; H, 8.17.

This mixture of olefins (500 mg) was hydrogenated for 3 hr over Pd/C (5%, 100 mg) in 1:1 benzene–ethanol (100 ml). After separation of the catalyst and evaporation of the solvent, hydrocarbon **26** was obtained as an oil: 500 mg, quantitative yield; δ ($CDCl_3$) 7.20 m (Ar H), 2.80 m (>CHPh), 2.62 broad d (-CH_2Ph of trans isomer, J = 7 Hz), 2.55 broad d (-CH_2Ph of cis isomer, J = 7 Hz), 2.1–1.0 m (other ring H's). Integration data indicated an approximate 1:1 ratio of cis and trans isomers. The mixture was not resolved on any of several glpc columns. It was essentially identical with the mixture obtained by the reduction of bromide **8** (*vide infra*).

Anal. Calcd for $C_{19}H_{22}$: C, 91.14; H, 8.86. Found: C, 91.40; H, 8.72.

1,1-Diphenylcyclobutane (**27**).—Reduction of tosylate **11** (0.6 g, 1.6 mmol) with lithium aluminum hydride (0.8 g, 23.5 mmol) in tetrahydrofuran (50 ml) was achieved under reflux for 16 hr. The cooled solution was hydrolyzed with water (100 ml) containing hydrochloric acid (6 *N*, 10 ml). The solution was extracted with ether. The ether extracts were washed with water and brine until neutral, dried (Na_2SO_4), and evaporated. The residual oil was chromatographed on alumina using hexane as the eluting solvent. Distillation of the purified oil in a micro-Hickman still gave **27** as a colorless oil: 150 mg, 45%; δ (CCl_4) 7.03 m (Ar H), 2.60 t (2, 4-CH_2, J = 7 Hz), 1.83 pentuplet with further splitting (3-CH_2).

Anal. Calcd for $C_{16}H_{16}$: C, 92.25; H, 7.75. Found: C, 91.96; H, 7.77.

1,1-Diphenylcyclopentane (**28**).—In similar fashion, tosylate **17** was reduced with lithium aluminum hydride in ether under reflux for 90 min. Hydrocarbon **28** was obtained as white needles from 95% ethanol: mp 72–72.5°; δ (CCl_4) 7.20 m (Ar H), 2.30 m (2, 5-CH_2), 1.73 m (3, 4-CH_2).

Anal. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.95; H, 8.29.

1,1-Diphenylcyclopropane (**29**).—Spectral identification of material isolated in these studies (*vide infra*) was made by comparison with that previously reported:[33] δ (CCl_4) 7.15 s (Ar H), 1.24 s (CH_2).

1,1-Diphenylpropene (**30**).—Preparation was achieved as reported:[34] 65%, mp 46–47° from 95% ethanol; δ (CCl_4) 7.20 m (Ar H), 6.12 q (>C=CH, J = 7 Hz), 1.74 d (CH_3, J = 7 Hz).

Reduction of Bromides with Tri-*n*-butyltin Hydride. Bromide

(28) The increased reaction time reflects the decreased S_N2 reactivity in this system compared to the cyclopentyl case.

(29) Prepared by the method of A. Burger and W. B. Bennett, *J. Amer. Chem. Soc.*, **72**, 5414 (1950).

(30) F. J. Bojer and H. W. Post, *J. Org. Chem.*, **27**, 1422 (1962).

(31) We deeply thank Dr. Henry F. Dabek, Jr., for the mass spectral determinations.

(32) We thank Dr L. Chinn of G. D. Searle and Co. for a generous supply of this ketone.

(33) C. Walling and L. Bollyky, *J. Org. Chem.*, **28**, 256 (1963).

(34) A. Klages, *Ber.*, **35**, 2646 (1902).

7.—Amounts of the bromide (1.1–4.84 g) were dissolved in thiophene-free, dry benzene to make solutions of molarities given in Table II. Freshly distilled tri-*n*-butyltin hydride (1.1 equiv relative to the amount of **7** used) was then added and the solutions were sealed in pressure bottles under nitrogen. The reaction mixtures were placed in sand baths for 42 hr at 145° and 24 hr at 155 and 150°. The vessels were cooled and opened and the contents were reduced in volume to about 5 ml by distillation of the benzene solvent. In each case the material was then chromatographed on alumina using hexane as the eluting solvent. Hydrocarbon **23** eluted first with the rearranged product **24** afterward. On occasion the elutions were speeded by use of 25–50% benzene–hexane mixtures as the eluting agent. Identification of products was by mixture melting point and spectral (ir, nmr, and mass) comparison with authentic material. Yields were calculated from the weights of isolated product.

Bromide **8**.—The procedure here was similar to the above, except that all reactions were conducted at 145° for 44 hr and all the benzene was removed after the heating period. The chromatographic eluting agents employed were Skellysolve B, followed by a 1:1 mixture of Skellysolve B with benzene. Gas–liquid partition chromatography (4 ft SE-30 column at 170°) was then used on this column-chromatographed material to separate products **25** (retention time 5.79 min) and **26** (retention time 9.27 min). Identification of products was by coinjection of and spectral comparison with knowns. Compositions were calculated by electronic integration of the glpc peaks and yields by weight of column chromatographed product.

Bromides **5** and **6**.—Approximately 0.1 *M* solutions of these bromides (0.4 g scale) in benzene were reduced with tri-*n*-butyltin hydride as described for **7** at 150° for 20–24 hr. Chromatography on alumina afforded only unrearranged product. Runs conducted at 78° (refluxing benzene) gave identical results.[35]

Bromide **4**.—Amounts of **4** (0.27–1.00 g) were dissolved in benzene to give the molarities shown in Table III. Reduction with tri-*n*-butyltin hydride was carried out in sealed ampoules under nitrogen and the reaction material was chromatographed on alumina as described above for **7**. Analysis by glpc (4 ft polypropylene glycol succinate column at 190°) gave the composition data. Yields were obtained from the weight of the column chromatographed product. Identification of **29** and **30** was by coninjection of and spectral comparison with known samples. No evidence was found for the known[36] rearrangement possibility, 1,2-diphenylcyclopropane.

Registry No.—**4**, 32812-52-5; **5**, 32812-53-6; **6**, 32812-54-7; **7**, 32812-55-8; **8**, 32812-56-9; **14**, 32812-57-0; **14** 2,4-DNP, 32812-58-1; **15**, 32812-59-2; **16**, 24771-20-8; **17**, 32812-61-6; **19**, 807-24-9; **21**, 32812-63-8; **22**, 32812-64-9; **25**, 32812-65-0; *cis*-**26**, 32819-58-2; *trans*-**26**, 32819-59-3; **27**, 32812-66-1; **28**, 32812-67-2; **30**, 778-66-5; 1-benzyl-4-phenylcyclohexanol, 32812-69-4; 1-benzyl-4-phenylcyclohexene, 32812-70-7; 4-phenyl-1-benzylidenecyclohexane, 32812-71-8.

(35) A referee has objected that rearrangement in these cases is not precluded because no comparison was made of these reduction products with the appropriate 1,3-diphenylcycloalkane. While no such comparison was made, detailed examination by spectral and chromatographic methods of the reduction products (the interested reader may see ref 1a) showed *only* unrearranged product. Within the certainty that such results possess we claim that no rearrangement occurred under the conditions studied.

(36) C. G. Overberger, R. E. Zangaro, and J.-P. Anselme, *J. Org. Chem.*, **31**, 2046 (1966), and references therein.

Mass Spectra of Trimethylsilyl Derivatives of Pyrimidine and Purine Bases

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Trimethylsilyl derivatives of pyrimidine and purine bases were prepared by reaction with *N,O*-bis(trimethylsilyl)acetamide or *N,O*-bis(trimethylsilyl)trifluoroacetamide, and their mass spectra studied in detail using high-resolution and deuterium-labeling techniques. The position of thiation or methylation (C-5 *vs.* C-6) in pyrimidines can be established from a major ion species composed of C-4,5 and their attached groups, which is derived from the abundant M − Me ion. A similar process is followed in the decomposition of O^2,N^4-bis(trimethylsilyl)-cytosine following migration of trimethylsilyl to N^4 to produce *m/e* 170. Bases containing methylated amino functions characteristically eliminate methylene imine in parallel to the behavior of free bases and nucleosides. Mass spectra of bases which bear more than one trimethylsilyl group often exhibit intense peaks associated with the doubly charged species $(M - 2Me)^{2+}$, which was found by deuterium labeling to have different mechanistic origins in different bases.

Basic electron impact induced fragmentation reactions of the common pyrimidine and purine bases from ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) have been studied in some detail[1] and are clearly useful for the characterization of such compounds.[2] However, since the isolation of small quantities of biologically modified bases as single components from RNA or DNA hydrolysates for mass spectrometry is often not feasible, we have examined the mass spectra of the more volatile trimethylsilyl derivatives, which are suitable for gas chromatography–mass spectrometry. Although these derivatives[3] have been used for a number of years in synthetic procedures, the work of Sasaki and Hashizume[4] first drew our attention to their gas chromatographic properties.[5]

The present report is based on a detailed study of the mass spectra of trimethylsilyl derivatives of 33 bases, with emphasis on those compounds which are derived from RNA and DNA.[6]

(1) (a) J. M. Rice, G. O. Dudek, and M. Barber, *J. Amer. Chem. Soc.*, **87**, 4569 (1965); (b) K. C. Smith and R. T. Aplin, *Biochemistry*, **5**, 2125 (1966); (c) J. M. Rice and G. O. Dudek, *J. Amer. Chem. Soc.*, **89**, 2719 (1967); (d) J. L. Occolowitz, *Chem. Commun.*, 1226 (1968); (e) J. Ulrich, R. Teoule, R. Massot, and A. Cornu, *Org. Mass Spectrom.*, **2**, 1183 (1969); (f) E. G. Brown and B. S. Mangat, *Biochim. Biophys. Acta*, **177**, 427 (1969); (g) S. M. Hecht, A. S. Gupta, and N. J. Leonard, *ibid.*, **182**, 444 (1969).

(2) For additional references to the mass spectrometry of modified pyrimidine and purine bases, see (a) J. A. McCloskey in "Basic Principles in Nucleic Acid Chemistry," P. O. P. Ts'o, Ed., Academic Press, New York, N. Y., in press; (b) J. Deutsch, Z. Neiman, and F. Bergmann, *Org. Mass Spectrom.*, **3**, 1219 (1970).

(3) For example, (a) E. Wittenburg, *Chem. Ber.*, **99**, 2380 (1966); (b) B. Shimizu, M. Asai, and T. Nishimura, *Chem. Pharm. Bull.*, **15**, 1847 (1967); (c) T. Nishimura and I. Iwai, *ibid.*, **12**, 352 (1964); (d) T. Nishimura, B. Shimizu, and I. Iwai, *ibid.*, **11**, 1470 (1963); (e) T. Nishimura and I. Iwai, *ibid.*, **12**, 357 (1964); (f) E. Wittenburg, *Collect. Czech. Chem. Commun.*, **36**, 246 (1970).

(4) Y. Sasaki and T. Hashizume, *Anal. Biochem.*, **16**, 1 (1966).

(5) (a) Y. Mizuno, N. Ikekawa, T. Itoh, and K. Saito, *J. Org. Chem.*, **30**, 4066 (1965); (b) C. W. Gehrke, D. L. Stalling, and C. D. Ruyle, *Biochem. Biophys. Res. Commun.*, **28**, 869 (1967); (c) T. Hashizume and Y. Sasaki, *Anal. Biochem.*, **24**, 232 (1968); (d) C. W. Gehrke and C. D. Ruyle, *J. Chromatogr.*, **38**, 473 (1968); (e) W. C. Butts, *J. Chromatogr. Sci.*, **8**, 474 (1970); (f) J. E. Mrochek, W. C. Butts, W. T. Rainey, Jr., and C. A. Burtis, *Clin. Chem.*, **17**, 72 (1971); (g) C. W. Gehrke and D. B. Lakings, *J. Chromatogr.*, **61**, 45 (1971).

(6) E. White, V, and J. A. McCloskey in "Archives of Mass Spectral Data," Vol. 2, E. Stenhagen, S. Abrahamsson, and F. W. McLafferty, Eds., Wiley-Interscience, New York, N. Y., 1971, pp 450–525.

TABLE I

SELECTED IONS FROM THE MASS SPECTRA OF TRIMETHYLSILYL DERIVATIVES OF PYRIMIDINE AND PURINE BASES

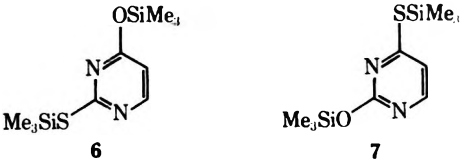
Parent base	No. of $SiMe_3$ groups	Mass (relative abundance) M	M − H	M − Me	c	o	m/e 147	m/e 84	m/e 73	Other characteristic ions
Purine (17)	1	192 (67)	191 (3.6)	177 (100)	119 (0.0)	81 (<1)	(0.0)	(8.6)	(21)	123 (29); m, 150 (7.3)
6-Methylpurine (11)	1	206 (73)	205 (3.5)	191 (100)	133 (0.0)	88 (1.5)	(0.0)	(9.0)	(23)	123 (16); m, 164 (5.6)
3-Methyladenine (9)	1	221 (52)	220 (4.1)	206 (100)	148 (0.7)	95.5 (11)	(0.0)	(14)	(21)	176 (8.2); m, 179 (17)
N^6-Methyladenine (15)	1	221 (100)	220 (19)	206 (53)	148 (6.5)	95.5 (0.6)	(0.0)	(10)	(53)	n, 192 (28); 193 (25)[a]
6-Chloropurine (18)[b]	1	226 (96)	225 (1.1)	211 (100)	153 (0.0)	98 (<1)	(0.0)	(6.4)	(45)	m, 184 (8.0); 191 (6.0)
6-Methylthiopurine (19)	1	238 (100)	237 (9.0)	223 (17)	165 (17)[a]	104 (0.0)	(0.0)	(6.9)	(83)	164 (4.4); 192 (8.9)
5-Methylcytosine	2	269 (37)	268 (2.8)	254 (100)	196 (2.4)	119.5 (17)	(12)	(3.7)[a]	(39)	1, 112 (13); 184 (6.0)
Hypoxanthine	2	280 (48)	279 (2.5)	265 (100)	207 (3.7)[a]	125 (5.5)	(3.9)	(4.2)	(47)	d, 206 (6.8); m, 238 (1.6)
1-Methyladenine[c]	2	293 (8.1)	292 (0.7)	278 (100)	220 (1.1)	131.5 (0.3)	(0.0)	(3.4)	(48)	206 (8.6); 221 (4.6)
2-Methyladenine	2	293 (32)	292 (2.4)	278 (100)	220 (3.0)	131.5 (1.5)	(0.0)	(5.6)	(40)	237 (1.7); 206 (10)
7-Methyladenine (12)	2	293 (37)	292 (24)	278 (100)	220 (2.9)	131.5 (2.4)	(0.0)	(26)	(57)	125 (17); 179 (16)
7-Methylguanine	2	309 (22)	308 (2.9)	294 (100)	236 (2.8)	139.5 (2.6)	(3.0)	(14)	(51)	k, 99 (10); f, 180 (17)
7-Methylxanthine	2	310 (50)	309 (11)	295 (100)	237 (1.9)	140 (6.6)	(18)	(8.8)	(42)	k, 100 (5.2); f, 180 (8.0)
5-Hydroxyuracil	3	344 (41)	343 (20)	329 (100)	271 (1)	157 (0.5)	(10)	(1.4)	(84)	255 (7.8); 270 (6.6)
6-Hydroxyuracil	3	344 (75)	343 (52)	329 (100)	271 (1)	157 (1.3)	(38)	(0.0)	(62)	241 (4.1); 270 (7.0)
5-Hydroxymethylcytosine (14)	3	357 (100)	356 (5.1)	342 (42)	284 (6.5)	163.5 (0.0)	(27)	(6.1)[a]	(92)	254 (11); 268 (5.2)
5-Hydroxymethyluracil (13)	3	358 (60)	357 (5.0)	343 (29)	285 (3.1)	164 (0.0)	(17)	(3.6)[a]	(100)	k, 100 (16); 255 (7.8)[a]
Xanthine	3	368 (72)	367 (3.7)	353 (100)	295 (8.5)[a]	169 (0.8)	(26)	(2.5)	(80)	f, 238 (2.5); 279 (12)
Orotic acid	3	372 (7.0)	371 (3.6)	357 (52)	299 (0.0)	171 (0.0)	(21)	(0.9)	(94)	254 (100); 329 (2.6)
Uric acid	4	456 (78)	455 (4.0)	441 (57)	383 (6.9)[a]	213 (0.5)	(18)	(1.6)	(100)	367 (5.1); 382 (16)

[a] Doublet; intensity uncorrected. [b] Masses and abundances of chlorine containing ions correspond to ^{35}Cl species. [c] Contaminated by an isomeric derivative; see Experimental Section.

Results and Discussion

As reported in a preliminary communication,[7] the mass spectra of trimethylsilylated bases exhibit far fewer fragment ions than the corresponding nucleosides because of the exceptional stabilization afforded by the aromatic nucleus. However, the certainty of identification and of structure correlations for fragment ions of low abundance is maintained largely through the use of gas chromatography–mass spectrometry, which precludes most ions otherwise present which could arise from artifacts and impurities. In addition, the complementary use of d_9-trimethylsilyl derivatives[8] [*e.g.*, $-Si(CD_3)_3$] and of high-resolution techniques constitutes a highly useful means for identification of minor ions.

General Fragmentation Reactions.—Mass spectra of trimethylsilyl derivatives of the five major bases from RNA and DNA (**1**–**5**) are shown in Figure 1. Molecular ion (M) abundances are generally high, reflecting their aromatic character. As shown in Table I, greatest molecular ion stability is shown by derivatives in which the charge can be localized on an exocyclic heteroatom not bearing a trimethylsilyl group, such as 6-methylthiopurine and N^6-methyladenine. Also of interest are the lower molecular ion stabilities exhibited by derivatives of 2- and 4-thiouracil (**6** and **7**) compared with that of uracil (**1**), in contrast to the opposite behavior usually shown by sulfur analogs.[9] Similar effects were found in the spectra of *O*,*S*-bis(trimethylsilyl) derivatives of 5- and 6-methyl-2-thiouracil, and 6-propyl-2-thiouracil, and are in all cases attributed to the enhanced stability of the M − CH_3 fragment ion, discussed below.



6 **7**

As indicated in Figure 1 and Table I, loss of hydrogen or methyl radicals from M constitute major fragmentation pathways. The spectra of a number of d_9-trimethylsilyl derivatives, including the representative examples shown in Table II, reveal that hydrogen lost

TABLE II

HYDROGEN RANDOMIZATION IN THE FORMATION OF M − HYDROGEN AND M − METHYL IONS IN THE MASS SPECTRA OF d_9-TRIMETHYLSILYL DERIVATIVES

Compd	(M − H)/(M − D)[a]	(M − CD_2H)/(M − CD_3)
O^2,O^4-Bis(d_9-trimethylsilyl)uracil	2.1	0.02
O^2,O^4-Bis(d_9-trimethylsilyl)-6-methyluracil	1.6	0.05
O^2,O^4-Bis(d_9-trimethylsilyl)-5,6-dihydrouracil	6.2	0.04
O^2,N^4-Bis(d_9-trimethylsilyl)-cytosine	1.8	0.05
d_9-Trimethylsilyl O^2,O^4-bis(d_9-trimethylsilyl)orotate	1.7	0.01
1,N^6-Bis(d_9-trimethylsilyl)-7-methyladenine	2.1	0.09
6-Methyl-9-(d_9-trimethylsilyl)-purine	2.0	0.22

[a] Corrected for naturally occurring heavy isotopes.

(7) J. A. McCloskey, A. M. Lawson, K. Tsuboyama, P. M. Krueger, and R. N. Stillwell, *J. Amer. Chem. Soc.*, **90**, 4182 (1968).

(8) J. A. McCloskey, R. N. Stillwell, and A. M. Lawson, *Anal. Chem.*, **40**, 233 (1968).

(9) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, Chapter 7.

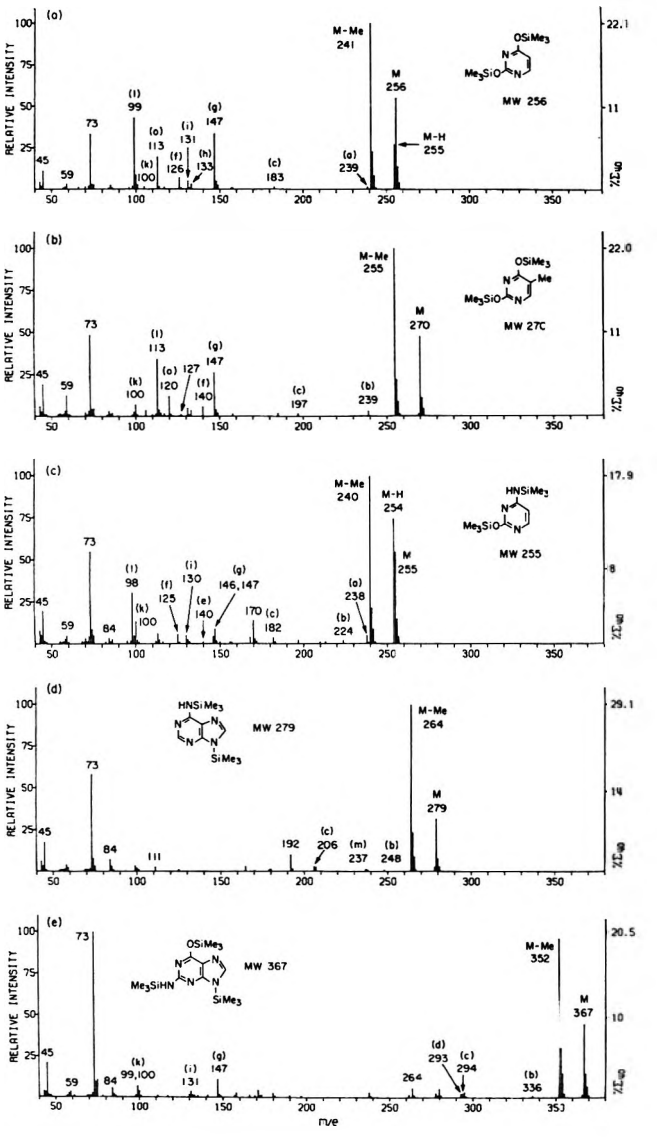


Figure 1.—Mass spectra of (a) O^2,O^4-bis(trimethylsilyl)uracil (1), (b) O^2,O^4-bis(trimethylsilyl)thymine (2), (c) O^2,N^4-bis(trimethylsilyl)cytosine (3), (d) N^6,9-bis(trimethylsilyl) adenine (4), (e) N^2,O^6, 9-tris(trimethylsilyl)guanine (5).

in the formation of M − H originates both from trimethylsilyl functions and the base. An intense M − H peak is also found in the spectrum of free 7-methyladenine,[2] where it is derived mainly by loss of hydrogen from N^6.[2a] Although scrambling of trimethylsilyl hydrogens with other hydrogens during fragmentation has been reported,[10] simple loss of a hydrogen radical from the trimethylsilyl group has not to our knowledge been previously observed. It is therefore worthwhile to examine the ubiquitous loss of a methyl radical from the molecular ion, in the spectra of d_9-trimethylsilyl derivatives as shown in Table II. The ratio (M − 14)/(M − 15) from spectra of unlabeled derivatives can be measured with an accuracy of ~0.01. With the exception of the dihydrouracil derivative, the values of (M − CD_2H)/(M − CD_3) show that hydrogen randomization before loss of a methyl radical occurs to a slight to moderate extent in the compounds examined. Since the effect was greatest in the case of 6-methyl-9-(d_9-trimethylsilyl)purine, the ratio of (M − CD_2H)/(M − CD_3) in that compound was examined as a function of ionizing electron energy. The results, shown in Figure 2, show that hydrogen interchange between methyl functions and the base increases substantially at low voltage values. This behavior is attributed to increased molecular ion lifetimes in the low-energy region,[11] and therefore increased opportunity for interchange. Comparison of data from both columns in Table II indicates that the higher values of (M − H)/(M − D) relative to (M − CD_2H)/(M − CD_3) cannot be attributed primarily to hydrogen scrambling in the molecular ion, although it is undoubtedly a contributing factor.

(10) G. H. Draffan, R. N. Stillwell, and J. A. McCloskey, *Org. Mass Spectrom.*, **1**, 669 (1968).

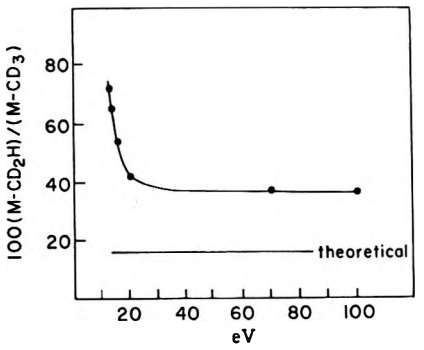
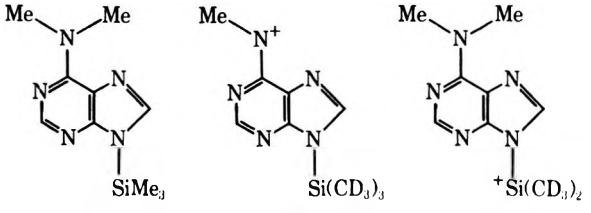


Figure 2.—Variation of the ratio (M − CD_2H)/(M − CD_3) as a function of ionizing electron energy in the mass spectrum of 6-methyl-9-(d_9-trimethylsilyl)purine.

Bases which contain methyl groups other than those in the trimethylsilyl moiety, as in N^6,N^6-dimethyl-9-(trimethylsilyl)adenine (**8**), can in principle lose methyl radicals from two sources. Several such examples have been examined as the d_9-trimethylsilyl derivatives in order to determine the extent to which nontrimethylsilyl methyls participate in the reaction. In the case of **8a**, approximately 77% of the methyl groups lost were

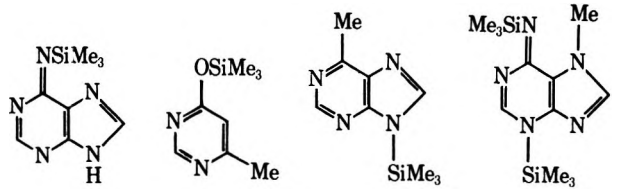


8 **8a**

found to be from N^6 (M − CH_3) as opposed to the remaining 23% (M − CD_3) from the trimethylsilyl group. Loss of methyl from N^6 is energetically favorable since the charge can be delocalized into the purine nucleus, as also shown by the analogous reaction which occurs with the free base.[12] Similarly, a substantial fraction (34%) of nontrimethylsilyl methyl is lost from the derivative of 3-methyladenine, **9**. However when the methyl group is bound to the aromatic nucleus its loss is suppressed in favor of fragmentation in the trimethylsilyl moiety, as shown by derivatives of 6-methyluracil (**10**) (loss <3%) and 6-methylpurine (**11**) (loss <2%). Of the labeled derivatives which were examined, the sole exception was the 7-methyladenine derivative **12**, in

(11) A. N. H. Yeo, R. G. Cooks, and D. H. Williams, *Chem. Commun.*, 1269 (1968).

(12) Y. Rahamim, J. Sharvit, A. Mandelbaum, and M. Sprecher, *J. Org. Chem.*, **32**, 3856 (1967).



9 10 11 12

which only 4% of total methyl groups lost were from N-7, in spite of the well-stabilized ion which would be formed From these limited data it is apparent that by use of deuterium-labeled silylating reagents, the presence of methyl groups can be recognized in some but not all cases, by examination of the M − methyl ion.

In numerous instances loss of either a hydrogen or a methyl radical from the molecular ion is followed by expulsion of methane involving methyl from the trimethylsilyl moiety (*e.g.*, ions a and b, in Figure 1). The origin of additional hydrogen lost in forming ion a as shown by the d_9-trimethylsilyl derivatives is difficult to determine because of minor isotopic impurities associated with the M − CD_3 peak, although net losses of both CD_3H_2 and CD_4H were found to occur. In the case of ion b the fourth hydrogen in methane was determined to originate both from trimethylsilyl functions and from the ring and its substituents.

Most mass spectra examined showed the formation of ions 72, 73, or 74 mass units below the molecular ion. The ion corresponding in mass to M − 72, which was observed most often in spectra of purines, was determined by measurement of exact mass to differ from the molecular ion by C_3H_8Si. Deuterium labeling in the trimethylsilyl moiety resulted in a shift to 81 mass units below M, in support of an elemental composition equivalent to M − $Si(CD_3)_3$ + H, but not M − $CD_2Si(CD_3)_2$. From this we conclude that, even though the samples are introduced by gas chromatograph and are generally homogeneous, some molecules which contain one fewer trimethylsilyl group than the principal species are present or are formed by exchange in the ion source, giving rise to a molecular ion 72 mass units below M. By contrast, the prominent peak at *m/e* 192 in the spectrum of the adenine derivative (Figure 1d) was determined to be derived by loss of Me_3SiCH_2 from *m/e* 264 (M − Me). Appropriate metastable peaks were observed in the mass spectra of **4** (139.6 calcd, 139.8 found) and its d_{18}-trimethylsilyl analog (141.9 calcd, 141.9 found), and was confirmed by metastable defocussing for **4**. The peak shifted seven mass units upon labeling in the trimethylsilyl moiety, clearly showing retention of a silyl hydrogen from the neutral species which is lost.

The characteristic peak frequently observed at M − 73 (ion c; see Table I) arises from loss of a trimethylsilyl radical from the molecular ion. The peak one mass unit lower found in many spectra (ion d) involves loss of Me_2SiO from M, which was verified both by measurements of exact mass and shifts of six mass units in the mass spectra of d_9-trimethylsilyl derivatives. In the case of the thiated uracil analogs **6** and **7** the loss of Me_2SiS (*m/e* 182) but not Me_2SiO (*m/e* 198) occurs as shown in Figure 3, indicating no apparent positional specificity. However, the analogous Me_2SiNH is not lost on electron impact from **3** or any of its derivatives. Formation of ion d requires migration and retention of

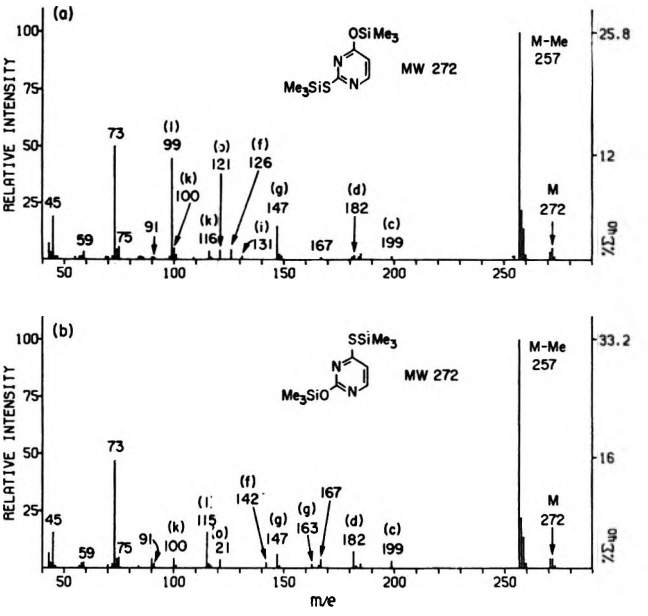
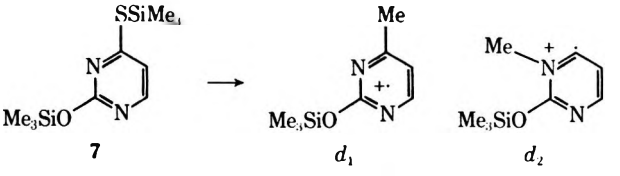


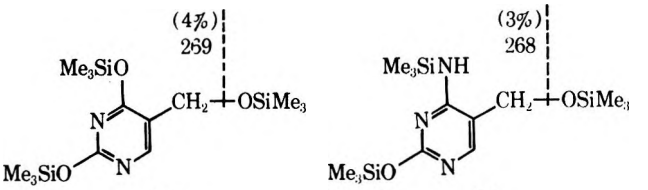
Figure 3.—Mass spectra of (a) S^2,O^4-bis(trimethylsilyl)-2-thiouracil (**6**), (b) O^2,S^4-bis(trimethylsilyl)-4-thiouracil (**7**).

a trimethylsilyl methyl group, *e.g.*, **7** → d_1 or d_2, and serves as a minor but diagnostic indicator of the presence of sulfur or oxygen in the base. Participation of nitrogen in the methyl migration either directly (d_2) or



7 d_1 d_2

indirectly seems probable since the analogous ion of mass 180 is absent from the mass spectrum of the bis(trimethylsilyl) ether of resorcinol. Similarly, loss of Me_3SiX was found to often produce a small peak at M − 89 (X = O), except in the case of **6** and **7** which preferentially gave M − 105 (X = S). This process was more favored in the 5-hydroxymethyl pyrimidine derivatives **13** and **14** due to stabilization afforded by the



13 14

adjacent aromatic ring, but their high-resolution spectra showed minor contributions at the same nominal mass from ions equivalent to M − CH_4 − Me_3Si.

Disruption of the aromatic ring with expulsion of MeSiOCN (ion e) was observed as a minor process in several pyrimidines, including **1** (*m/e* 141, 0.6% rel intensity), **3** (*m/e* 140, Figure 1c), and the trimethylsilyl ethers of 5-hydroxyuracil (*m/e* 229, 1.3%), 6-azauracil (*m/e* 142, 6.3%), and 6-azathymine (*m/e* 156, 2.0%). Analogous ions of the correct nominal mass, containing NH instead of O, were observed in the spectra of **4**, **9**, and **11** but failed tests of either exact mass measurement or required shifts of nine mass units in d_9-tri-

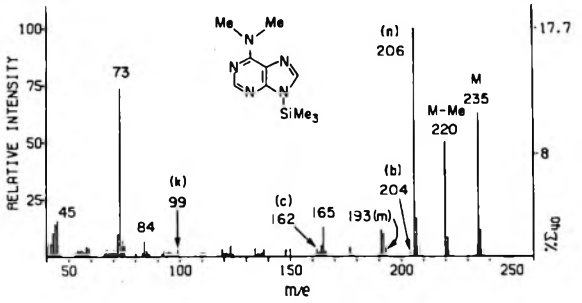


Figure 4.—Mass spectrum of N^6,N^6-dimethyl-9-(trimethylsilyl)adenine (8).

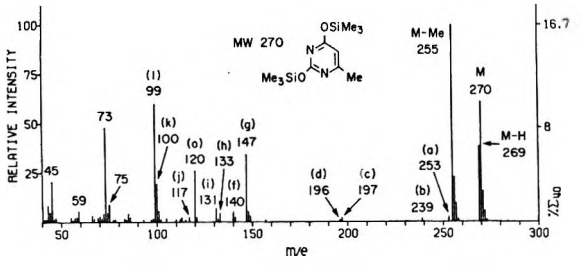
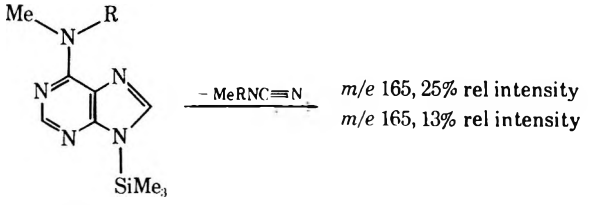


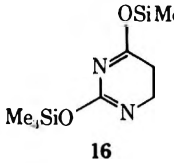
Figure 5.—Mass spectrum of O^2,O^4-bis(trimethylsilyl)-6-methyluracil (10).

methylsilyl derivatives. However, a similar process involving expulsion of a C–N fragment of the aromatic nucleus occurs in the spectra of N^6-methylated adenine derivatives **15** and **8** (Figure 4), in which N-1 and C-6 and its substituents are lost.



15, R = H
8, R = Me

If the elimination of Me_3SiXCN (X = O, S, NR) proceeds from M − Me rather than the molecular ion, an additional peak in the spectrum (ion f) appears 15 mass units lower than ion e. This ion is produced in the fragmentation of numerous compounds, including **1**, **10** (Figure 5), and O^2,O^4-bis(trimethylsilyl)-5,6-dihydrouracil (**16**) (Figure 6), as well as **8** and **15**. The



16

6-methylpurine derivative **11** shows the same behavior, CH_3CN being lost (*m/e* 150, 4.4% rel intensity). When its d_3-labeled counterpart was examined it was found that ion f (*m/e* 156) also contained contributions at *m/e* 155 and 154. These latter ions reflect hydrogen exchange between the trimethylsilyl function and the base as previously discussed, in support of the identity of M − Me as the precursor of ion f. Comparison of ion f from the thiated models (Figure 3) shows retention of the heteroatom at C-4 (*m/e* 126, 142). From this it can be inferred that expulsion of Me_3-

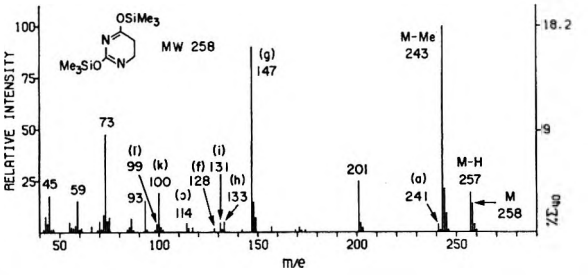
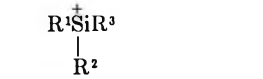


Figure 6.—Mass spectrum of O^2,O^4-bis(trimethylsilyl)-5,6-dihydrouracil (16).

SiXCN in forming the precursor (ion e) from pyrimidines occurs predominantly from C-2, with loss of either N-1 or N-3.

In the spectra of all compounds examined a substantial portion of the total ion current was carried by silicon-containing ions which include little or none of the base skeleton. The simplest of these are the rearranged species *m/e* 45 and 59,[13] and the ubiquitous trimethylsiliconium ion *m/e* 73. Deuterium labeling in the trimethylsilyl moiety shows that both rearranged hydrogens in *m/e* 45 originate to greater than 80% from trimethylsilyl groups, while, for *m/e* 59, 20% (**16**) to 60% (**1**) of the single rearranged hydrogen sta-



m/e 45, $R^1 = R^2 = H$; $R^3 = Me$
m/e 59, $R^1 = H$; $R^2 = R^3 = Me$
m/e 73, $R^1 = R^2 = R^3 = Me$
m/e 82, $R^1 = R^2 = R^3 = CD_3$

tistically comes from the same or another trimethylsilyl function. In the case of *m/e* 73, which one would assume to arise by simple cleavage, over 90% of the original hydrogens were generally retained. Exceptions were the derivatives of 6-methylpurine and 7-methyladenine, which showed the incorporation of about 16 and 22%, respectively, of hydrogen from the base skeleton in *m/e* 73. These data are in qualitative agreement with the $(M - CD_2H)/(M - CD_3)$ ratios shown in Table II, which indicate the relatively greater tendency for hydrogen scrambling in those compounds. The ubiquitous fragment $MeSi^+$ (*m/e* 43)[13] is also formed as a common fragment in the low-mass region of all spectra.

The oxygen-containing fragment *m/e* 75 is a common product of trimethylsilyl ether fragmentation[14] which normally serves no diagnostic purpose. However, all five thiouracils examined (see Figure 3) showed contributions at *m/e* 91 from the sulfur analog of *m/e* 75, while the analogous nitrogen ion (*m/e* 74) was

essentially absent in the high-resolution spectra of *N*-silyl model compounds. By contrast, the sulfur analog *m/e* 163[10] of the well known *m/e* 147[8,15] (ion g)

(13) J. H. Beynon, R. A. Saunders, and A. E. Williams, "The Mass Spectra of Organic Molecules," Elsevier, New York, N. Y., 1968, p 424.

(14) H. Budzikiewicz, D. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 471.

(15) J. Diekman, J. B. Thomson, and C. Djerassi, *J. Org. Chem.*, **33**, 2271 (1968), and references cited therein.

was generally not found in the spectra of the thiated bases (*e.g.*, Figure 3), while the corresponding amino

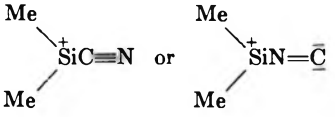
$Me_3SiX\overset{+}{S}iMe_2$
g
X = O, *m/e* 147
X = S, *m/e* 163
X = NH, *m/e* 146

species *m/e* 146 was observed in the spectra of all three cytosine derivatives, **3**, **14**, and O^2,N^4-bis(trimethylsilyl)-5-methylcytosine. Several additional interesting but diagnostically unimportant ions which are structurally though not necessarily mechanistically related to ion g were present in most spectra. These may be represented as ion h in the case of ethers. Companion

$Me_2HSiO\overset{+}{S}iMe_2$
h, *m/e* 133

ions 16 mass units lower than g and h were also usually present (ions i and j). Measurement of exact mass showed that their compositions differ by CH_4, but no metastable ion evidence was found to indicate the formation of i or j by expulsion of methane from ions g or h.

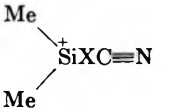
An ion of composition C_3H_6NSi (*m/e* 84) was observed in every mass spectrum except that of the trimethylsilyl derivative of barbituric acid. In some instances, such as compound **2**, contributions from other ions of different compositions were apparent. Mass 84 was found to be most abundant in spectra of purine derivatives, with a maximum value of 26% in **12**. Deuterium labeling revealed the presence of two trimethylsilyl methyl groups, which leads to the possible isomeric structures shown below. The greater



m/e 84

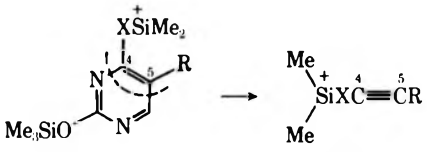
prominence of this ion in the spectra of purines (Table I) suggests the inclusion of N-9; however, the spectrum of 8-^{14}C-**4** indicates that C-8 is not involved. Although its formation from many of the pyrimidines requires extensive rearrangement, the structures shown are well stabilized, and there is ample precedent for rearrangement of partial or intact trimethylsilyl groups.[16]

A structurally similar ion containing a heteroatom was observed in the spectra of nearly all bases. Deuterium labeling and measurement of exact mass leads to the structure as ion k. Its presence in the spectra of five 2-thiouracil derivatives at both *m/e* 100 and *m/e* 116 (*e.g.*, Figure 3a) indicates no positional preference for the origin of the heteroatom. Carbon-14 labeling showed the absence of C-8 in ion k from **4** (Figure 1d), even though structural rearrangement would not be required.



k
X = O, *m/e* 100
X = S, *m/e* 116
X = NH, *m/e* 99

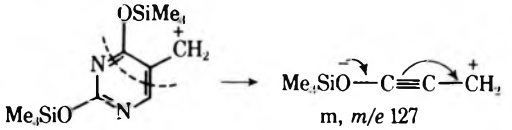
Ions Characteristic of Either Pyrimidines or Purines. —The most structurally diagnostic ion in the spectra of pyrimidine derivatives arises from opening of the aromatic nucleus after formation of M − Me. Measurement of exact mass and deuterium labeling leads to the formulation shown as ion l. Spectra of the isomeric thiouracils shown in Figure 3 indicate that the heteroatom attached to C-4 is exclusively involved, thus also requiring the presence of C-5 and its substituents.



X = O, S, NH ion l

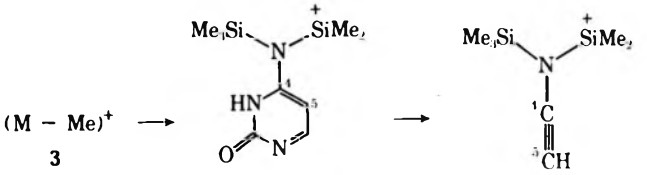
	m/e		
R	O	S	NH
H	99	115	98
Me	113	129	112

As shown by comparison of Figures 1a, 1b, and 6, ion l can be used as a prominent indicator of the position of C-methylation in pyrimidines, in addition to the determination of the position of thiation. A similar cleavage across the aromatic ring in fragment ions of several 5-substituted pyrimidines (*e.g.*, **2**, **13**, **14**) also produces a minor but characteristic fragment, such as *m/e* 127 in Figure 1b.



m/e 269 (**2**)

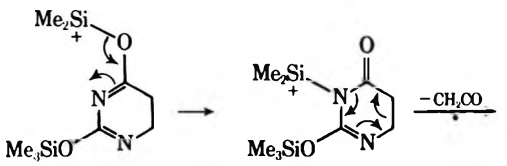
In the spectrum of the cytosine derivative **3**, rupture of the aromatic ring in M − 15 is preceded by migration of a trimethylsilyl function to N^4. The resulting prominent peak (*m/e* 170, Figure 1c) shifts to *m/e* 184 in the spectrum of the 5-methyl derivative (5% rel intensity), confirming the inclusion of C-4 and CH5, and providing a means of distinguishing methylation at C-5 *vs.* C-6.



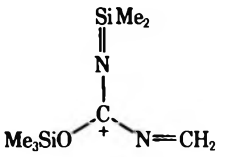
m/e 170

The presence of a saturated 5,6 moiety in the pyrimidine nucleus was observed to lead to several significant changes in fragmentation behavior. As shown in Figure 6, formation of ion l (*m/e* 99) is suppressed, but the prominent ion *m/e* 201 occurs, which has no counterpart in the mass spectrum of **1**. Metastable ion evidence for the transition *m/e* 243 → 201 supported by measurement of exact mass points to a mechanism involving expulsion of ketene from C-4,5.

(13) For leading references, see E. White, V, and J. A. McCloskey, *J. Org. Chem.*, **35**, 4241 (1970).

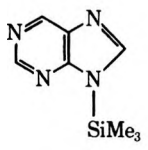


m/e 243 (16)

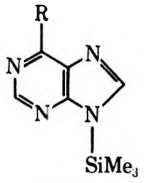


m/e 201

The most common fragmentation reactions of free (underivatized) purines involve sequential expulsion of HCN.[1c,17,18] In the present case the presence of the trimethylsilyl moiety changes the course of fragmentation such that direct elimination of HCN from M is a minor process, occuring in few cases (*e.g.*, **9**, **11**, **12**, **17**, and **18**). Loss of HCN from the even-electron M − Me ion was found to be somewhat more common (ion m, Table I) and was most abundant in the purine derivatives **11**, **17**, and **18**. The spectrum of 8-^{14}C-**4**



17



18, R = Cl
19. R = SMe

showed that about half of the carbon lost as HCN to form ion m originated from C-8, in contrast to the expulsion of HCN from the molecular ion of adenine, which does not involve C-8.[1d]

As demonstrated by the above discussion, disruption of the aromatic purine nucleus appears to be most extensive in compounds which have the least opportunity for charge delocalization outside of the ring system. Another example of this effect is represented by a relatively common fragment ion of mass 123, $C_5H_7N_2Si$. Deuterium labeling shows the presence of two silyl methyl groups, and 8-^{14}C-**4** indicates retention of C-8, so that the ion apparently represents the imidazole portion of the base. Its abundance is greatest in the spectra of **11** and **17** (Table I), and is zero in spectra of polyfunctional molecules such as trimethylsilyl derivatives of guanine (**5**) and uric acid.

Opening of the ring is also demonstrated by the models **18** and **19**, in which external heteroatoms (Cl, S) are spatially removed from the trimethylsilyl function at N-9. In both cases a series of ions is produced by direct interaction of the two groups presumably after ring opening, although the possibility of silyl migration from N-9 to N-7 across the intact ring cannot be excluded. The isotopic pair *m/e* 93, 95 (Me_2SiCl^+)

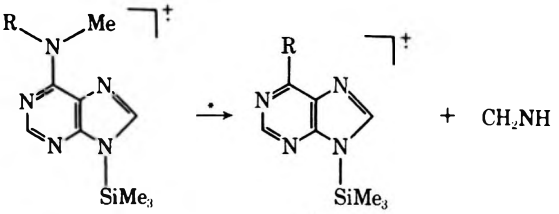
		% rel intensity	
		^{35}Cl	MeS
18, 19 →	Me_2SiR^+	48	3.1
	$MeHSiR^+$	4.3	1.2
	SiR^+	8.4	<1

(17) S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **92**, 2510 (1970).

(18) J. S. Shannon and D. S. Letham, *New Zealand J. Sci.*, **9**, 833 (1966).

is undoubtedly a general ion in the spectra of molecules containing both chlorine and a trimethylsilyl function, and is therefore not restricted to purines, since its presence in the spectra of long-chain halo ethers and halo esters has been established.[16]

Methylation of amino groups, as in compounds **8** and **15**, is readily characterized by ions (ion n) resulting from expulsion of methylene imine, which has been visualized as proceeding by migration of methyl or hydrogen to either N-1[12] or C-6.[17] As shown in Figure 4 (**8**) and Table I (**15**) the production of ion n rep-



n

8, R = CH_3 *m/e* 206
15, R = H *m/e* 192
20, R = $SiMe_3$

resents a major and therefore highly diagnostic process. The corresponding reactions have been documented for free bases[12,18] and nucleosides.[17,19] There is presently no reason to believe the reaction would not occur in the case of pyrimidines, such as N^4-methylcytosine or its trimethylsilyl derivative, but relevant data have not been reported. Ion n in the spectrum of **15** is accompanied by a peak of nearly equal intensity one mass unit higher, confirmed by measurement of exact mass to represent the loss of CH_2N from the molecular ion. If the derivatization reaction is carried out at higher temperatures, the disilyl compound **20** is produced in significant amount, but the characteristic ion n is essentially absent.

The presence of certain functional groups, such as propyl or methylthio, was observed to lead to a number of characteristic fragmentation paths, in addition to those discussed above. Although the details of these reactions are not included in the present communication, they can in general be ascertained by consideration of deuterium labeling and metastable ion data,[20] and by examination of the literature pertinent to each specific functional group.[21]

Multiply Charged Ions.—The presence of abundant doubly charged ions in a mass spectrum often provides a useful means of characterization, if the structural features[22] that are responsible can be identified. In the present study the most abundant doubly charged ions are associated primarily with loss of two methyl radicals from different silyl functions, a process which has been observed in other systems.[10,23] The resulting ions (o) occur at *m/e* (M − 30)/2 and can be recognized by their occurence at half-mass values (odd molecular mass), or by their half-mass first isotope

(19) S. H. Eggers, S. I. Biedron, and A. O. Hawtrey, *Tetrahedron Lett.*, 3271 (1966).

(20) E. White, V, and J. A. McCloskey, unpublished results.

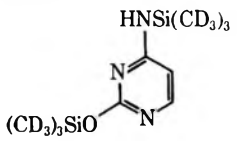
(21) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

(22) For example, (a) P. Vouros and K. Biemann, *Org. Mass Spectrom.*, **2**, 375 (1969); (b) G. G. Smith and C. Djerassi, *ibid.*, **5**, 505 (1971).

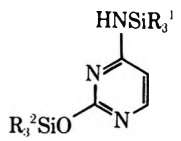
(23) (a) J. L. Smith, J. L. Beck, and W. J. A. VandenHeuvel, *ibid.*, **5**, 473 (1971), and references cited therein to these authors' previous work; (b) V. Y. Orlov, N. S. Nametkin, L. E. Gusel'nikov, and T. H. Islamov, *ibid.*, **4**, 195 (1970).

peaks (even molecular mass). In Figure 1c–e the intensity values for ion o (not shown) follow: **3**, *m/e* 112.5, 27%; **4**, *m/e* 124.5, 4%; **5**, *m/e* 168.5, 1%. The relatively high abundance of ion o, particularly in the spectra of pyrimidine derivatives, provides a potentially useful means of identifying bases and confirming the value of M in multicomponent mixtures such as nucleic acid hydrolysates.

In order to determine to what extent silyl methyls are lost from different functions, a mixture of trimethylsilyl derivatives of cytosine (**3**, **3a**, or the isomers **3b**) was prepared using a mixture of labeled and unlabeled reagents.[8] The three possible values of ion o from **3a** [(M − 30)/2, (M − 33)/2, (M − 36)/2] were separated in mass from those of **3b**, and showed that at least 95% of the methyl groups lost are from different silyl moieties. In the spectra of d_9-trimethylsilyl derivatives of methylated bases, a variety of combinations



3a

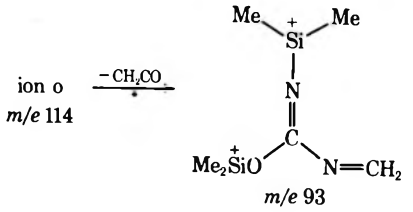


3b, $R^1 = CH_3$; $R^2 = CD_3$
or
$R^1 = CD_3$; $R^2 = CH_3$

was observed. Derivatives of 6-methylpurine (**11**) and 7-methyladenine (**12**) showed a maximum of 11% of ion o to involve the native methyl function [(M − 33)/2], while the *N*,*N*-dimethyl derivative **8** produced 59% (M − 33)/2, 15% (M − 30)/2, and 26% (M − 36)/2 in accordance with the mixed nature of ion a (M − CH_3) previously discussed. Surprisingly, the 3-methyladine derivative **9**, which produced the most abundant ion o of any purine derivative examined (11% rel intensity), showed essentially quantitative (>99%) loss of two methyls from a single silyl group. This behavior indicates that the formation of ion o is mechanistically diverse and in some cases requires rearrangement or opening of the ring.

Other less prominent doubly charged ions are also formed, apparently by fragmentation of ion o. In the pyrimidines the principal species corresponds to elimination of methane to produce *m/e* (M − 2Me − CH_4)/2 (**1**, *m/e* 105, 2%; **2**, *m/e* 112, 1%; **3**, *m/e* 104.5, 3%). By contrast, most purines characteristically undergo further expulsion of HCN to provide *m/e* (M − 2Me − HCN)/2, which corresponds to *m/e* 111 in Figure 1d, and is absent (incorrect exact mass) in the spectrum of **5**.

Also worthy of note is the prominent doubly charged ion of *m/e* 93 in the mass spectrum of the dihydrouracil derivative **16** (Figure 6). High-resolution data indicate the composition $C_6H_{14}N_2OSi_2$, while labeling in the trimethylsilyl moiety shows the presence of four methyl groups (shift of six mass units, or 12/2). A metastable peak at *m/e* 75.9 confirms the formation



of *m/e* 93 from the doubly charged ion o (*m/e* 114). Its mechanism of formation therefore involves elimination of the elements of ketene from C-4,5, in parallel to production of singly charged *m/e* 201 as discussed previously.

The triply charged species $(M - 3Me)^{3+}$ was observed in approximately one-third of the spectra which were studied, with a maximum intensity of 0.6% in the spectrum of the tris(trimethylsilyl) derivative of 6-hydroxyuracil.

Experimental Section

Low-resolution mass spectra were recorded using an LKB 9000 instrument, with sample introduction through the gas chromatographic inlet system (3, 6, and 9 ft, 1% SE-30 and 1% OV-17). Ion source and carrier gas separator temperatures were 250–270°, ionizing energy was 70 eV. Particular care was taken to record the spectra on the apex of the eluting peak in order to avoid bias due to changing sample concentration during the scan.

High-resolution mass spectra of **1–5**, **8**, **10**, **11**, **13–16**, **18**, **19**, and the trimethylsilyl derivatives of 5-methylcytosine, 6-methyl-

TABLE III
PREPARATION AND GAS CHROMATOGRAPHY OF TRIMETHYLSILYL DERIVATIVES

Compd	Methods of preparation	Column temp, °C	Column
Uracil-$(SiMe_3)_2$ (**1**)	A, B	80	A
Thymine-$(SiMe_3)_2$ (**2**)	A, B	89	B
Cytosine-$(SiMe_3)_2$ (**3**)	B	140	D
Adenine-$(SiMe_3)_2$ (**4**)	B	180[a]	D
Guanine-$(SiMe_3)_3$ (**5**)	B[b]	208[a]	D
2-Thiouracil-$(SiMe_3)_2$ (**6**)	A, B	110	A
4-Thiouracil-$(SiMe_3)_2$ (**7**)	A, B	97	F
N^6,N^6-Dimethyladenine-$(SiMe_3)$ (**8**)	A, B	133	C
3-Methyladenine-$(SiMe_3)$ (**9**)	C	177	D
6-Methyluracil-$(SiMe_3)_2$ (**10**)	B	123	D
6-Methylpurine-$(SiMe_3)$ (**11**)	B	160	D
7-Methyladenine-$(SiMe_3)_2$ (**12**)	C	174	D
5-Hydroxymethyluracil-$(SiMe_3)_3$ (**13**)	B	155[a]	D
5-Hydroxymethylcytosine-$(SiMe_3)_3$ (**14**)	B	136	A
N^6-Methyladenine-$(SiMe_3)$ (**15**)	B	150	A
5,6-Dihydrouracil-$(SiMe_3)_2$[d] (**16**)	C	120	A
Purine-$(SiMe_3)$ (**17**)	A, B	119	D
6-Chloropurine-$(SiMe_3)$ (**18**)	A, B	139	D
6-Methylthiopurine-$(SiMe_3)$ (**19**)	B	200	D
5-Methylcytosine-$(SiMe_3)_2$	B	150	D
Hypoxanthine-$(SiMe_3)_2$	B	150	A
1-Methyladenine-$(SiMe_3)_2$	C	160	A
2-Methyladenine-$(SiMe_3)_2$	A	148	A
7-Methylguanine-$(SiMe_3)_2$	C	185	D
7-Methylxanthine-$(SiMe_3)_2$	B[c]	145	A
5-Hydroxyuracil-$(SiMe_3)_3$	B	123	A
6-Hydroxyuracil-$(SiMe_3)_3$	B	128	E
Xanthine-$(SiMe_3)_3$	B	170	A
Orotic acid-$(SiMe_3)_3$	A, B	119	C
Uric acid-$(SiMe_3)_4$	B[c]	163	A
5-Methyl-2-thiouracil-$(SiMe_3)_2$	A, B	107	F
6-Methyl-2-thiouracil-$(SiMe_3)_2$	A, B	112	A
6-Propyl-2-thiouracil-$(SiMe_3)_2$	A, B	123	A

[a] Starting temperature; temperature programmed at 2 or 3°/min. [b] Heated for 3 hr. [c] Heated for 12 hr. [d] Methods of preparation which require heating resulted in partial conversion to **1**.

2-thiouracil, 6-propyl-2-thiouracil, hypoxanthine, 2-methyladenine, xanthine, and orotic acid were photographically recorded on a CEC 21-110B instrument using a gas chromatographic inlet system[24] (6 ft, 1% OV-17). Ion source and carrier gas separator temperatures were 250°; ionizing energy was 70 eV. Exact masses were measured of all ions having relative abundances greater than ~0.5%.

All pyrimidine and purine bases were purchased commercially with the exception of 4-thiouracil (7), which was obtained from the Cancer Chemotherapy National Service Center of the National Institutes of Health. 8-^{14}C-4 containing 67 mol % ^{14}C (equivalent to 40 mCi/mmol) was purchased from International Chemical and Nuclear Corp. Compounds were checked for purity by gas chromatography and mass spectrometry of their trimethylsilyl derivatives.

Formation of Trimethylsilyl Derivatives.—Derivatives were prepared from 0.5–1.5 mg of base at concentrations of 4–10 μg/μl, by one of the three following methods. (A) The base was heated at 100° for 1–2 hr with bis(trimethylsilyl)trifluoroacetamide (BSTFA) (Peninsular ChemResearch, Inc.) and 1% added trimethylchlorosilane in a screw-capped vial. (B) The same procedure as A was followed using bis(trimethylsilyl)acetamide (BSA) (Pierce Chemical Co., distilled before use) in place of BSTFA. (C) The base was allowed to stand at room temperature for 1 hr with occasional shaking in a mixture of BSA and acetonitrile (1:3) with trimethylchlorosilane (1%). d_9-Trimethylsilyl derivatives were prepared by method C, using bis(d_9-trimethylsilyl)acetamide and d_9-trimethylsilylchlorosilane (Merck Sharp and Dohme of Canada, Ltd.).

The method of preparation and column temperature for the LKB gas chromatograph are shown for each compound in Table III. The columns used at a flow rate of 30–40 cc He/min were (A) 9 ft, 1% SE-30; (B) 3 ft, 1% SE-30; (C) 3 ft, 1% OV-17; (D) 6 ft, 1% OV-17; (E) 9 ft, 1% OV-17; (F) 6 ft, 1% SE-30.

The successful gas chromatography of 9-(trimethylsilyl)purine (17) was found to depend strongly on the age and condition of the column. The chromatogram of N^6,9-bis(trimethylsilyl)-1-methyladenine showed a broad, low peak followed closely by a normal peak. Mass spectra of the two peaks showed the same fragment ions but differing relative abundances. Data given in Table I relate to the sharp chromatographic peak, but include some contamination from the second component.

Mass spectra of all compounds were free of peaks above that of the molecular ion, and at improbable mass values below that of the molecular ion. The number of trimethylsilyl groups exchanged during the derivatization reaction was determined from the mass spectra. In some instances, derivatives of purine bases can have structures isomeric with those shown in the text. In most cases silylation is assumed to occur at enolizable carbonyl groups, on amino groups external to the ring, and at N-9, based on infrared[3c,4] and nmr data,[4] and by known reactions of these derivatives in synthetic procedures.[3b,d] In particular, other structures cannot be completely excluded for derivatives of 3-methyladenine (9), 7-methyladenine (12), purine (17), 6-chloropurine (18), and 1-methyladenine (discussed above).

(24) P. M. Krueger and J. A. McCloskey, *Anal. Chem.*, **41**, 1930 (1969).

Registry No.—**1**, 10457-14-4; **2**, 7288-28-0; **3**, 18037-10-0; **4**, 17995-04-9; **5**, 18602-85-2; **6**, 32865-74-0; **7**, 32865-75-1; **8**, 32865-76-2; **9**, 32865-77-3; **10**, 32865-78-4; **11**, 32865-79-5; **12**, 32865-80-8; **13**, 31517-04-1; **14**, 32865-82-0; **15**, 32865-83-11; **16**, 32865-84-2; **17**, 32865-85-3; **18**, 32865-86-4; **19**, 32865-87-5; 5-methylcytosine-$(SiMe_3)_2$, 32865-88-6; hypoxanthine-$(SiMe_3)_2$, 17962-89-9; 1-methyladenine-$(SiMe_3)_2$, 32958-85-3; 2-methyladenine-$(SiMe_3)_2$, 32865-90-0; 7-methylguanine-$(SiMe_3)_2$, 32958-86-4; 7-methylxanthine-$(SiMe_3)_2$, 32865-91-1; 5-hydroxyuracil-$(SiMe_3)_3$, 32865-92-2; 6-hydroxyuracil-$(SiMe_3)_3$, 31111-39-4; xanthine-$(SiMe_3)_3$, 18551-03-6; orotic acid-$(SiMe_3)_3$, 32865-94-4; uric acid-$(SiMe_3)_4$, 18547-59-6; 5-methyl-2-thiouracil-$(SiMe_3)_2$, 32865-96-6; 6-methyl-2-thiouracil-$(SiMe_3)_2$, 32865-97-7; 6-propyl-2-thiouracil-$(SiMe_3)_2$, 32958-88-6.

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Photochemical Oxidations. V. Concerted *vs.* Radical Stepwise Addition of Oxygen to the Carbon–Hydrogen Bond of Hydrocarbons

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The stereochemistry of the initial stage of the photooxidation of hydrocarbons was studied. During this stage, the reaction products originate directly from the excitation of a contact charge transfer complex between oxygen and the hydrocarbons. The liquid-phase oxidation of (+)-3-methylhexane produces a racemic tertiary alcohol, and the *cis*- and *trans*-decalins give mixtures of cis and trans tertiary decalols. Thus, a radical, stepwise mechanism for the formation of the intermediate alkyl hydroperoxides is postulated rather than a concerted oxygen insertion into the carbon–hydrogen bond.

The primary process occurring during the photooxidation of saturated hydrocarbons has now been shown to be the excitation of a contact charge transfer complex between oxygen and hydrocarbons.[1-4] Product accumulation studies on the photooxidation of hydrocarbons have demonstrated that alkylhydroperoxides are the primary products and the secondary products are alcohols and ketones.[1] Relative reactivity studies of primary, secondary, and tertiary C–H bonds of several hydrocarbons proved that the C–H bond rather than the C–C bond was the donor site in the contact charge transfer complex.[5]

Equations 1–3 summarize the initial steps in the

(1) N. Kulevsky, P. V. Sneeringer, and V. I. Stenberg, *Photochem. Photobiol.*, **12**, 395 (1970).

(2) V. I. Stenberg, L. D. Grina, and P. V. Sneeringer, Abstracts, 2nd Great Lakes Regional Meeting of the American Chemical Society, Milwaukee, Wis., June 1968, p 19.

(3) P. V. Sneeringer, and V. I. Stenberg, Abstracts, 4th Great Lakes Regional Meeting of the American Chemical Society, Fargo, N. D., June 1970, p 14.

(4) L. D. Grina, B.S. Thesis, University of North Dakota, Grand Forks, N. D., 1965.

(5) V. I. Stenberg, P. V. Sneeringer, C. H. Niu, and N. Kulevsky, unpublished results.

$$R{-}H + O_2 \rightleftharpoons R{-}H\cdots O_2 \overset{h\nu}{\rightleftharpoons} R{\cdot}H^+\cdots O_2^- \quad (1)$$

$$R{\cdot}H^+\cdots O_2^- \longrightarrow R\cdot + HO_2\cdot \quad (2)$$

$$R\cdot + HO_2\cdot \longrightarrow RO_2H \quad (3)$$

recently formulated photooxidation mechanism for saturated hydrocarbons.[1] Alternately, a concerted insertion of the O_2 into the C–H bond could be envisioned, *i.e.*, according with or similar to eq 4 and 5.

$$R{-}H\cdots O_2 \overset{h\nu}{\longrightarrow} [R{-}H\cdots O_2]^* \quad (4)$$

$$[R{-}H\cdots O_2]^* \longrightarrow RO_2H \quad (5)$$

The results of studies designed to determine which set of reactions is actually involved are discussed here. Two separate experiments were performed for this purpose: the photooxidation of (+)-3-methylhexane and the corresponding reaction of the *cis*- and *trans*-decalins.

Results and Discussion

It has been well documented that, when free alkyl radicals are formed at the single asymmetric center of an optically active compound, racemic products are produced.[6,7] This lack of stereospecificity is interpreted in terms of a planar arrangement of the atoms attached to the radical center or a set of nonplanar radicals in rapid equilibrium with each other. Presumably a concerted insertion of oxygen into the C–H bond would lead to retention of stereochemistry. These concepts form the basis for evaluating the results of the experiments described here. Using this idea, Wiberg and Foster[8] interpreted the chromic acid oxidation of (+)-3-methylheptane to (+)-3-methyl-3-heptanol in terms of a stereospecific mechanism.

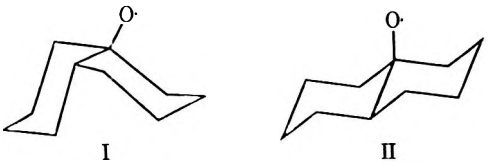
There are two stages in the photoxidation of hydrocarbons: the first where the reactions occurring in solution result directly from excitation of the charge transfer complex, and the second more rapid stage where the excitation process is augmented by a radical chain process. Since it is only the steps directly resulting from the excitation process that we are interested in, it is necessary to restrict the oxidation to the first stage, which means working with low conversions, *ca.* <0.01%, and a concomitant difficult isolation problem.

The saturated hydrocarbon, (+)-3-methylhexane, which could be synthesized by known methods,[9,10] was selected as the optically active starting material. Although a number of products could be expected from the photooxidation of this compound, the tertiary C–H bond is the most reactive,[5] and, as a consequence, a sufficiently high yield for isolation of its corresponding tertiary alcohol was expected. The tertiary alcohol, 3-methyl-3-hexanol, was isolated by glpc. The alcohol exhibited no detectable optical activity when either the sodium D lines (589.0 and 589.6 nm) or the Hg line (546.1 nm) was used. The difficulty with the analysis of this result is that the specific rotation of the pure, optically active alcohol is unknown. However, if the alcohol has a specific rotation greater than 3.0°, the optical activity would have been observed at the concentration used. It is safe to assume that the optical rotation of the alcohol is larger than 3.0°. The basis for this is that the chromophore of the alcohol is nearer the monitoring wavelengths than that of the hydrocarbons, which has a specific rotation of 9.43°. As a consequence of the lack of rotation of the tertiary alcohol, the stepwise mechanism for the initial steps of the photooxidation is favored. However, because of the assumption made concerning the optical rotation of the alcohol, supplementary evidence on this conclusion was sought *via* the photooxidation of *cis*- and *trans*-decalin.

The stereochemistry of 9-decalyl free radicals has been studied by Bartlett, *et al.*[11] The radicals were generated by the thermal decomposition of *cis*- and *trans*-9-carbo-*tert*-butylperoxydecalins in cyclohexane. In the presence of 1 atm of oxygen, the radicals react to form hydroperoxides at the 9 position of decalin. These hydroperoxides were reduced to alcohols and the compositions were determined. Starting from the *cis*-9-carbo-*tert*-butylperoxydecalin, the alcohols formed were 89% trans and 11% cis. The data was interpreted in terms of the reaction having an intermediate 9-decalyl free radical. On the other hand, Hamilton, *et al.*,[12] demonstrated a large amount of retention of stereochemistry during the ozonation of *cis*- and *trans*-decalins. *trans*-Decalin gave 80% *trans*- and 20% *cis*-decalols while *cis*-decalin gave 85% *cis*- and 15% *trans*-9-decalols.

In the photooxidation described here, *trans*-decalin produced a mixture of 81% *trans*- and 19% *cis*-9-decalols after lithium aluminum hydride reduction. Under identical conditions, *cis*-decalin produced a mixture of 66% *trans*- and 34% *cis*-9-decalols. Clearly, considerable isomerization had taken place; however, it was incomplete. This implies the presence of a cage effect or a more rapid spin interconversion relative to interconversion of *cis*-9-decalyl radical to trans (or to a planar radical) for the photooxidation reaction, which allows only partial isomerization of the reacting carbon of the intermediates.

Tertiary alkoxy radicals are known to partially decompose by cleavage of an adjoining C–C bond. In other words, the tertiary decalols are some of the products coming from the proposed intermediates I and II. In this study of the *cis*- and *trans*-decalins,



I II

the assumption is made that I and II decompose with C–C bond cleavage at similar rates and, therefore, would not interfere with the percentage of alcohols formed at the tertiary C–H centers.

The two sets of results, that of the photooxidation of (+)-3-methylhexane and the decalins, prove that considerable stereochemical equilibration at the C–H site takes place during the photooxidation of hydrocarbons. Thus the concerted insertion of O_2 into a

(6) H. C. Brown, M. S. Kharasch, and T. H. Chao, *J. Amer. Chem. Soc.*, **62**, 3435 (1940).
(7) H. J. Dauben, Jr., and L. L. McCoy, *ibid.*, **81**, 5404 (1959).
(8) K. B. Wiberg and G. Foster, *ibid.*, **83**, 423 (1961).
(9) D. H. Brauns, *J. Res. Nat. Bur. Stand.*, **18**, 315 (1937).
(10) U. von Weber, *Z. Physik. Chem.*, **179A**, 295 (1937).
(11) P. D. Bartlett, R. E. Pincock, J. H. Rolston, W. G. Schindel, and L. A. Singer, *J. Amer. Chem. Soc.*, **87**, 2590 (1965).
(12) G. A. Hamilton, B. S. Ribner, and T. M. Hellman, *Advan. Chem. Ser.*, **77**, 15 (1968).

C–H bond can be ruled out, and the dissociative, stepwise mechanism in a solvent cage can be invoked to explain the existing data.

In retrospect the radical, stepwise mechanism is the most logical. Molecular oxygen is a ground-state triplet, and its two highest occupied degenerate antibonding π^* orbitals contain one electron each. In the charge-transfer process an electron from the donor hydrocarbon C–H is transferred to one of the occupied orbitals of molecular oxygen and is paired with the electron already present in the orbital. The remaining two electrons, one on the hydrocarbon and the other in the still untouched degenerate π^* orbital of oxygen, must then be unpaired. Before the hydroperoxide can be formed, the hydrogen ion must be transferred to the now negatively charged oxygen, and the remaining two electrons must become paired in order to form the covalent C–O bond in the hydroperoxide (step b of reaction 6). The unpaired spins of the species re-

$$R\cdot H^+\cdots O_2^- \xrightarrow{a} R\cdot\uparrow + \uparrow\cdot O_2H \xrightarrow{b} R\cdot\uparrow + \downarrow\cdot O_2H \xrightarrow{c} RO_2H \quad (6)$$

sulting from step a of reaction 6 allows time for equilibration to occur.

Experimental Section

Apparatus.—The light source for the irradiations was a 550-W Hanovia lamp (673A36) placed inside a quartz immersion well. A Beckman GC-5 gas chromatograph equipped with a flame ionization detector and a 20% Carbowax 20M–Chromosorb W column was used. Optical rotations were determined on a Rudolph Model 80 polarimeter.

Preparation and Purification of Materials.—The criterion of purity used for the hydrocarbons was that the sample, when flushed with nitrogen and placed in a 1-cm quartz spectrophotometric cell, be virtually transparent to 200 nm. Aldrich 97% pure *trans*- and 99% pure *cis*-decalins were insufficiently pure for the purposes of these experiments. The *trans*-decalin was stirred overnight with fuming sulfuric acid at 50°, extracted with cold, concentrated sulfuric acid until both layers were clear, extracted with water, dried, and distilled at reduced pressure. It was found that *cis*-decalin reacted with fuming sulfuric acid. However, the cis compound, that survived treatment with fuming sulfuric acid, was passed over a column of activated alumina which made it sufficiently pure for use.

Eastman (−)-2-methyl-1-butanol (328 g) was treated with 542 g of phosphorus tribromide to form 381 g of (+)-2-methyl-1-bromobutane.[9] The nmr spectrum of the bromide was characteristic of its structure showing a downfield doublet at τ 6.9, while the infrared spectrum agreed with that in the literature.[13] The specific rotation of the bromide, $[\alpha]^{25}D$, was +3.18° (lit.[9] $[\alpha]^{25}D$ +4.04°. The crude bromide (213 g) was coupled with 461 g of ethyl bromide and 100 g of sodium.[10] The crude reaction mixture was fractionally distilled to give 48 g of (+)-3-methylhexane, bp 92–93°. The crude hydrocarbon (48 g) was then refluxed for 1 hr with sodium and absolute ethanol, in order to destroy any bromine compounds still present. The reaction mixture was then distilled, extracted with cold, concentrated sulfuric acid several times, washed with water, dried, and redistilled. Preparative glpc gave 17 g of (+)-3-methylhexane, bp 92–93° (lit.[10] 91°). The specific rotation of the hydrocarbon, $[\alpha]^{25}D$, was +7.50° (lit.[14] $[\alpha]^{19.5}D$ +9.43°). The nmr spectrum of the compound was characteristic of a saturated hydrocarbon, showing only upfield absorption in the alkyl region. The glpc retention time of the compound was slightly longer than that of 3-methylpentane. The mass spectrum of the compound showed an intense peak at *m/e* 100. Standard samples for the 9-decalols were prepared from independently synthesized materials.[15,16]

Irradiation Procedures.—The immersion well containing the lamp was placed in a water bath kept at 10° (±0.1°). The water in the bath was monitored to ensure that it was still transparent to uv light. The hydrocarbons were placed in a 1-cm quartz absorption cell and a fine stream of oxygen was introduced *via* a finely-drawn capillary connected to a microvalve.

Identification of Products.—The product of interest from the irradiation of (+)-3-methylhexane was 3-methyl-3-hexanol. This was identified in the reaction mixtures after reduction by triphenylphosphine[1] by a comparison of the retention times and spiking procedures with those of an authentic sample of 3-methyl-3-hexanol (Aldrich). It was then isolated from the reaction mixtures by preparative glpc. The isolated product was then diluted to 1.5 ml with carbon tetrachloride and its concentration (3.3 mg/ml) was determined by a glpc comparison with a standard solution of the alcohol. The solution had no optical rotation using sodium light (589.0 and 589.6 nm) or mercury light (546.1 nm). In order to ensure that racemization had not taken place during the preparative glpc isolation of the alcohol, a sample of (−)-2-methyl-1-butanol was injected and collected from the gas chromatograph. No loss of optical activity occurred during this procedure.

Two samples of *cis*- and two of the *trans*-decalin were irradiated separately for 20 min. The irradiated samples were then diluted with ether treated with triphenylphosphine and refluxed with lithium aluminum hydride for 1 hr. After cooling the solutions, a small amount of a saturated solution of sodium sulfate was added, the resulting suspension was filtered, and the ether was distilled until 1–2 ml remained. This treatment prevented ketonic products from interfering with the gas chromatographic analysis. For this analysis three different columns were employed, namely 20% Carbowax 20M, 20% 1,2,3-tris(2-cyanoethoxy)propane, and 20% tetracyanoethylated pentaerythritol on Chromosorb W. The 9-decalols were identified by retention time comparison with known samples on all three columns. Since Carbowax offered the best resolution, it was used to determine the percentage of *cis*- and *trans*-9-decalols in in the reaction mixtures. The percentages reported are the averages for two runs, each for *cis*- and *trans*-decalin. The agreement for each set of two runs was within 3%.

Registry No.—*trans*-Decalin, 493-02-7; *cis*-decalin, 493-01-6; (+)-3-methylhexane, 6131-24-4.

Acknowledgment.—We gratefully acknowledge the National Aeronautics and Space Administration for a traineeship (P. V. S.), and the University of North Dakota for a Summer Research Professorship (N. K.) and a Public Health Service Career Development Award (No. IK 04 GM 09888-01-V. I. S.).

(13) G. Y. Brokaw and W. R. Brode, *J. Org. Chem.*, **13**, 196 (1948).

(14) B. C. Easton and M. K. Hargreaves, *J. Chem. Soc.*, 1413 (1959).

(15) J. R. Durland and H. Adkins, *J. Amer. Chem. Soc.*, **61**, 429 (1939).

(16) M. C. Whiting, A. J. N. Bolt, and J. H. Parish, *Advan. Chem. Ser.*, **77**, 4 (1968).

Mechanism of Oxidative Polymerization of 2,6-Disubstituted Phenols. Structure of Polymers from Mixed Dimers of 2,6-Dimethylphenol and 2,6-Diphenylphenol

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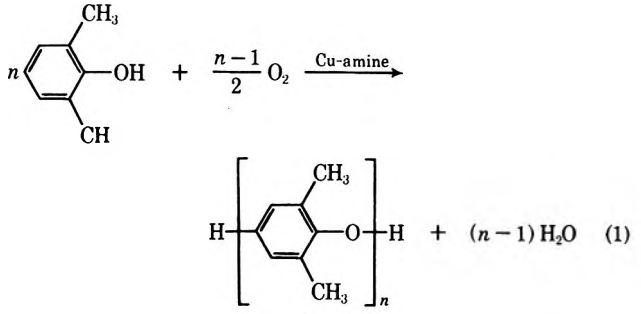
Mixed dimers of 2,6-dimethylphenol and 2,6-diphenylphenol have been prepared and polymerized by oxidative coupling to poly(arylene oxides). Both 2,6-diphenyl-4-(2,6-dimethylphenoxy)phenol (IV) and 2,6-dimethyl-4-(2,6-diphenylphenoxy)phenol (V) reacted with oxygen at 25° in the presence of a cuprous chloride–pyridine catalyst to produce polymers with a random arrangement of methyl- and phenyl-substituted rings, identical with the polymer obtained by oxidation of a mixture of the two monomers. The nmr spectra show four methyl proton signals with chemical shifts corresponding to those calculated for each of the four possible three-ring sequences, including sequences of three or more similar units, which can arise only as a result of redistribution. Oxidation of V at −25° in pyridine yielded low-molecular-weight polymer (DP ≃25) in which the strongest proton nmr signals were those corresponding to sequences of similar units, showing that even under conditions favoring coupling by rearrangement of an intermediate quinone ketal the redistribution process determines the polymer structure.

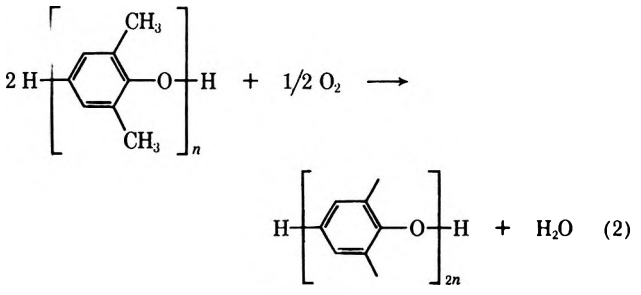
The oxidative coupling of 2,6-disubstituted phenols to produce poly(1,4-arylene oxides), first reported by Hay in 1959,[1] differs in many ways from the usual addition or condensation polymerization reaction and has been the subject of extensive investigation, summarized in several recent review articles.[2-5] The reaction is a



(1)

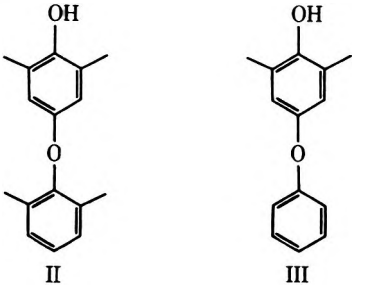
I

free-radical chain process, with aryloxy radicals as the intermediates, but has the characteristics of a polycondensation; that is, growth occurs by the coupling of polymer molecules.



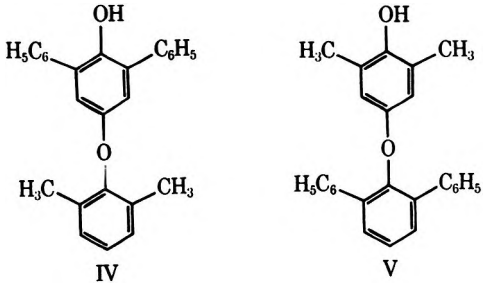
(2)

The details of this polymer–polymer coupling reaction have been difficult to resolve; three different explanations have been advanced for the coupling of polymeric aryloxy radicals to poly(1,4-aryleneoxy)-phenols. Much of the evidence for these mechanisms rests on the identification of the initial products of oxidation of "dimers", such as II and III, which may be regarded as the simplest representatives of structure I, with $n = 2$.



II III

The dimers previously examined either have the same substitution pattern in both rings, as in II, so that the rings cannot be distinguished in the product, or have an open ortho position in one or both rings, as in III, which prevents the formation of linear high polymers. We here report the preparation and oxidative polymerization of two "mixed dimers," IV and V. In these compounds both rings correspond to phenols capable of being oxidized to linear high polymers, allowing the mechanism of coupling to be inferred from the structure of the polymeric product.



IV V

Proposed Coupling Mechanisms.—Three mechanism by which coupling of two polymeric aryloxy radicals may lead to a polymeric phenol were first outlined by Finkbeiner[6] and each has since received some experi-

(1) A. S. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, *J. Amer. Chem. Soc.*, **81**, 6335 (1959).

(2) A. S. Hay, *Advan. Polym. Sci.*, **4**, 496 (1967).

(3) G. D. Cooper, *Ann. N. Y. Acad. Sci.*, **159**, 278 (1969).

(4) G. D. Cooper and A. Katchman, *Advan. Chem. Ser.*, No. 91, 660 (1969).

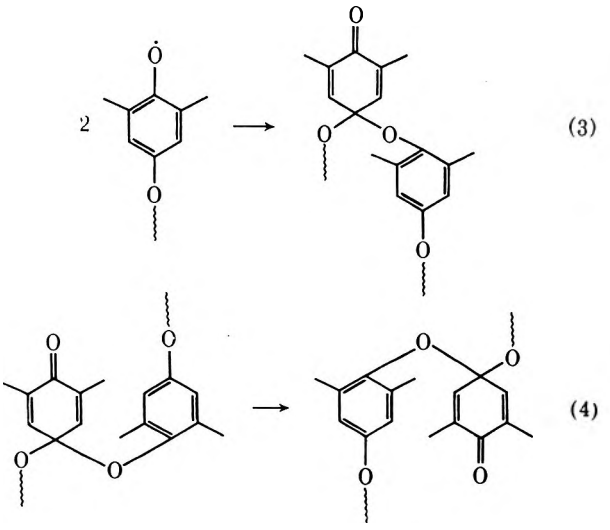
(5) H. L. Finkbeiner and A. S. Hay, "Newer Polymerization Reactions," J. Heller, Ed., Interscience, New York, N. Y., in press.

(6) H. L. Finkbeiner, G. F. Endres, H. S. Blanchard, and J. W. Eustance, *Trans. Soc. Plastics Eng.*, **2**, 112 (1962).

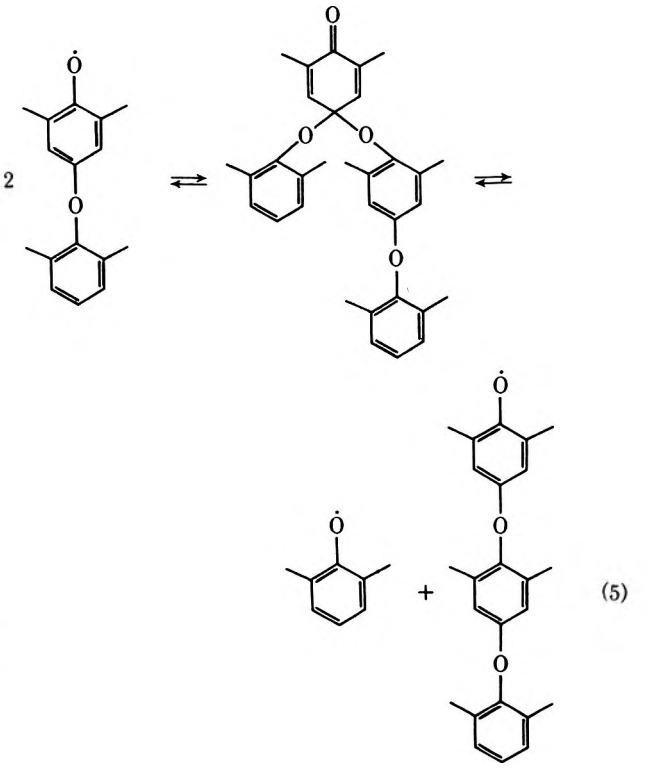
mental support.[7-11] These mechanisms and their structural consequences are outlined below.

A. End Linking.—The polymeric aryloxy radicals couple head to tail, with the oxygen of the first attacking the para position of the terminal ring of the second. This process, applied to a dimer AB, yields a perfectly alternating copolymer (ABABABAB...). The phenolic ring in every polymer molecule must be an A unit, that is, the same as the phenolic ring of the dimer.

B. Quinone Ketal Rearrangement.—Coupling of the two radicals yields a quinone ketal; that is, the oxygen of one radical attacks the para position of the phenolic ring of the second. Rearrangement of the dienone yields a new ketal, in which the second ring has become the "head", or dienone ring. When by successive rearrangements of this type one of the terminal rings becomes the dienone ring, tautomerization yields the coupled phenol. This process can lead to many different sequences of rings in the polymer from dimer AB, but cannot yield any species having more than two similar rings in succession; the sequences ABA, AAB, BBA, etc., are possible, but not BBB or AAA.[12] The phenolic ring of every polymer molecule must be a B ring.



C. Quinone Ketal Redistribution.—This mechanism also postulates that the initial product of reaction of aryloxy radicals is the quinone ketal, but assumes that the ketal rapidly dissociates either to regenerate the radicals from which it was formed or to produce two new radicals, one containing one more and the other one fewer aryloxy units than the original. The coupling of polymer radicals to polymeric phenols is the result of rapid redistribution of polymeric phenols to produce monomer, which couples with another phenolic species. The combination of redistribution and coupling reactions allows the formation of polymer molecules having any sequence of rings, with either ring of the dimer appearing as the phenolic ring of the polymer.[13]



Experimental Section

Nmr spectra were taken in $CDCl_3$ solution with a Varian HA-100 spectrometer, using tetramethylsilane as an internal standard. Melting points were determined with a Perkin-Elmer DSC IB differential scanning calorimeter. Gas chromatographic analyses of reaction mixtures were carried out after conversion of the phenols to trimethylsilyl ethers by reaction with bis(trimethylsilyl)acetamide in pyridine. Near-infrared spectra were measured in carbon disulfide solution with a Beckman DK 2A spectrophotometer.

2,6-Diphenyl-4-bromoanisole.—The dry sodium salt of 2,6-diphenyl-4-bromophenol (86 g, 0.25 mol) was dissolved in 100 ml of a 2 *M* solution of sodium methoxide in methanol, 30 g of dimethyl sulfate was added, and the solution was stirred for 16 hr. The precipitate was filtered off, washed with water, dried, and recrystallized from 95% ethanol, yielding 62 g (73%) of 2,6-diphenyl-4-bromoanisole, mp 91.5–92°.

Anal. Calcd for $C_{19}H_{15}OBr$: C, 59.4; H, 4.2; Br, 30.3. Found: C, 59.5; H, 4.4; Br, 30.7.

2,6-Diphenyl-4-(2,6-dimethylphenoxy)anisole.—A solution of 23 g of potassium *tert*-butoxide in 40 ml of dimethylformamide was added to a three-neck round-bottom flask equipped with a stirrer, a nitrogen by-pass, and a Dean–Stark trap. A solution of 25 g (0.205 mol) of 2,6-xylenol in 36 g of hexamethylphosphoramide was added and the mixture was refluxed under nitrogen with vigorous stirring for 3 hr, during which time 20 ml of distillate was withdrawn from the Dean–Stark trap. The mixture was allowed to cool and 4.0 g of cuprous bromide was added, followed by 100 ml of dimethylformamide and 60 g (0.177 mol) of 2,6-diphenyl-4-bromoanisole. The mixture was again refluxed and the first 30 ml of distillate was removed from the

(7) W. A. Butte, Jr., and C. C. Price, *J. Amer. Chem. Soc.*, **84**, 3567 (1962).

(8) G. D. Cooper, H. S. Blanchard, G. F. Endres, and H. L. Finkbeiner, *ibid.*, **87**, 3996 (1965).

(9) E. McNelis, *J. Org. Chem.*, **31**, 1255 (1966).

(10) D. M. White, *Poly. Prepr., Amer. Chem. Soc., Div. Polym. Chem.*, **9**, 663 (1968).

(11) These mechanisms are critically discussed in the review articles of ref 2–5, which include experimental results not published elsewhere.

(12) When two polymeric radicals couple in this fashion one of the terminal rings becomes the phenolic ring of the product. The sequence of rings is obtained by counting backwards from the tail to the head of one radical, then from head to tail of the other (ref 2. 5). Thus trimers ABC and DEF can form two hexamers, CBADEF and FEDABC. The sequences possible from the coupling of dimer AB to high polymer may be established by following the reaction for a few steps. Coupling of dimer produces tetramer BAAB, reaction of tetramer with dimer forms hexamers BABAAB and BAABAB, coupling of hexamers with dimer can yield three octamers (BABABAAB, BAABABAB, BABAABAB); coupling of tetramer yields BAABBAAB. None of the oligomers has two similar units in sequence either at the head or tail of the chain and no further coupling of these species with each other or with dimer can form any three-ring sequence not present in the octamers.

(13) The only restriction on polymer structure in this case is that every polymer molecule must have as its terminal ring a unit which was a terminal ring of the dimer. This restriction is common to all three mechanisms.

Dean–Stark trap. Refluxing and stirring was continued for 3 hr. After cooling, 125 ml of methanol was added, followed by 50 ml of concentrated hydrochloric acid, and the mixture was poured over cracked ice. The red, tarry mixture was extracted with benzene and the extract was washed thoroughly with water, then twice with 15% sodium hydroxide solution, and finally with water. The solution was dried over sodium sulfate and the benzene was removed on a rotary evaporator. The residue, after recrystallization from ethanol, yielded 25 g (37%) of 2,6-diphenyl-4-(2,6-dimethylphenoxy)anisole as a light tan powder, mp 134–135°.

Anal. Calcd for $C_{27}H_{24}O_2$: C, 85.2; H, 6.3. Found: C, 84.9; H, 6.3.

2,6-Diphenyl-4-(2,6-dimethylphenoxy)phenol (IV).—2,6-Diphenyl-4-(2,6-dimethylphenoxy)anisole (20 g, 0.053 mol) was refluxed for 16 hr, under nitrogen, with 50 ml of glacial acetic acid and 20 ml of 57% hydriodic acid. The mixture was poured over crushed ice and extracted with benzene. The extract was washed thoroughly with water, dried over sodium sulfate, and evaporated to dryness. Gas chromatographic analysis of the residue showed that uncleaved ether was still present; so the hydriodic acid treatment was repeated and the product was isolated as before. Recrystallization from *n*-hexane yielded 9.2 g (48%) of 2,6-diphenyl-4-(2,6-dimethylphenoxy)phenol, mp 140–141.5°.

Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.3; H, 6.0. Found: C, 84.7; H, 6.1.

2,6-Dimethyl-4-(2,6-diphenylphenoxy)anisole.—A solution of 123 g (0.5 mol) of 2,6-diphenylphenol, 56 g (0.57 mol) of potassium *tert*-butoxide, 90 g of hexamethylphosphoramide, and 100 ml of dimethylformamide was refluxed for 3 hr, under nitrogen, as in the preparation of the methyl ether of IV described previously. At the end of this time 60 ml of distillate was collected and discarded. After cooling the solution, 10 g of cuprous bromide, 110 g (0.49 mol) of 2,6-dimethyl-4-bromoanisole, and 175 ml of dimethylformamide were added. The mixture was refluxed for 3 hr and methanol and hydrochloric acid were added as in the previous case. The mixture was poured over ice and extracted with benzene, and the extract was washed with water. Extraction with 15% sodium hydroxide solution produced a large amount of gelatinous precipitate which was removed by filtration through glass wool. The dark blue extract was then washed repeatedly with water until the blue color disappeared. The solution was dried over sodium sulfate and concentrated on a rotary evaporator. Some diphenylphenol separated at this point; this was filtered off and washed with *n*-hexane; and the filtrate and washings were combined. Gas chromatographic analysis showed that in addition to the desired product the solution contained large amounts of unreacted diphenylphenol and 2,6-dimethyl-4-bromoanisole. Attempts to remove the diphenylphenol by extraction with Claisen's potash were unsuccessful and the solvent was again removed. Addition of *n*-hexane to the residue caused the separation of 2.2 g of light tan plates melting at 87–89°. The filtrate was again stripped and the residue was distilled under vacuum. One fraction of 16 g, boiling at 210–245° (2.5 mm), crystallized on seeding with the crystals previously isolated. The total yield of crude product was 28.2 g (15%). Recrystallization from hexane yielded pure 2,6-dimethyl-4-(2,6-diphenylphenoxy)anisole as colorless plates, mp 92–93°.

Anal. Calcd for $C_{27}H_{24}O_2$: C, 85.2; H, 6.3. Found: C, 85.2; H, 6.4.

2,6-Dimethyl-4-(2,6-diphenylphenoxy)phenol (V).—2,6-Dimethyl-4-(2,6-diphenylphenoxy)anisole (25 g, 0.066 mol) was refluxed for 16 hr, under nitrogen, with 75 ml of glacial acetic acid and 25 ml of 57% hydriodic acid. The mixture was poured over ice and extracted with benzene. The extract was washed with water, then with 1% ammonium carbonate solution, and again with water. The solution was dried over sodium sulfate and the benzene was stripped off under vacuum, leaving a colorless and extremely viscous glass. Gas chromatographic analysis of this product indicated that it contained, in addition to the major component, a small amount of uncleaved ether, a large amount, possibly one-third the total, of diphenylphenol, and at least one higher boiling compound. Some of these products arose from decomposition in the injection port, as the apparent concentration of diphenylphenol was substantially reduced upon conversion to the trimethylsilyl ethers by reaction with bis(trimethylsilyl)acetamide in pyridine. Solution chromatography on an alumina column did not yield any fraction which could be induced to crystallize or was significantly purer than the starting material. The fractions were therefore combined, dissolved in pyridine, and refluxed with 10 ml of bis(trimethylsilyl)acetamide. After evaporation of the solvent the residue was distilled under vacuum. A fraction of 9.5 g, boiling at 210–220° (0.33 mm), was shown to be essentially pure by gas chromatographic analysis. It was dissolved in 25 ml of methanol, one drop of concentrated hydrochloric acid was added, and the solution was allowed to stand for 1 hr at room temperature. The methanol was stripped off under vacuum, leaving 7.8 g (37%) of colorless solid, which appeared to melt at 45–50° when heated in a capillary tube in the usual manner, but was shown by differential scanning calorimetry to be amorphous. Gas chromatographic analysis showed this material to be more than 95% pure, with the principal impurities being diphenylphenol and the methyl ether of V. Repeated efforts to crystallize this material were unsuccessful, and it was used without further purification.

Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.3; H, 6.0. Found: C, 85.3; H, 6.1.

Redistribution of Dimers.—Catalytic redistribution of the dimers was carried out by refluxing a solution of 0.5 g of the dimer and 0.015 g of tetramethyldiphenoquinone in 10 ml of benzene.[14] After 2 hr, 2 ml of pyridine and 0.5 ml of bis(trimethylsilyl)acetamide were added. Refluxing was continued for 10 min and the mixture was analyzed by gas chromatography. Thermal redistributions were carried out by refluxing a solution of 0.25 g of dimer in 3 ml of chlorobenzene for 1 hr, followed by trimethylsilylation and gas chromatographic analysis.

Polymerization.—In most cases oxidation of the dimers was carried out at 25° in a 50 ml flask stirred by a Vibro-Mixer stirrer and connected to a gas buret filled with oxygen. In a typical example 5 mg of cuprous chloride was stirred in the reaction flask under oxygen for 10 min in 8 ml of benzene and 2 ml of pyridine. A solution of 0.732 g (0.002 mol) of dimer V in 3 ml of benzene was added and oxygen absorption was measured at intervals of approximately 1 min. Absorption ceased after approximately 30 min, at which time 19.4 ml (87% of theory) had been absorbed. After 2 hr, the mixture was washed several times with 10% hydrochloric acid, and the benzene layer was separated, dried over sodium sulfate, and evaporated to dryness. The residue was dissolved in 2 ml of chloroform and filtered, and the polymer was precipitated with methanol, yield 0.605 g (83%).

Low-temperature polymerizations were carried out following the procedures described for low-temperature oxidation of the dimer of 2,6-xylenol.[10] A solution of 1.0 g of "methanol green," copper complex having the empirical formula $[py\ CuCl(OCH_3)]_z$,[15] in 10 ml of pyridine was cooled to −25° and 366 mg of V was added. The solution was stirred for 2 hr at −25°, after which the temperature was lowered to −50° and the reaction was terminated by the addition of 5 ml of 36% hydrochloric acid. The solution was allowed to warm to room temperature and 75 ml of water and 50 ml of benzene were added. The organic layer was separated, washed repeatedly with 5% hydrochloric acid and with water, and concentrated to a volume of 2–3 ml. Addition of methanol yielded 288 mg (78%) of colorless polymer; the molecular weight (determined by vapor osmometry) was 4250 and the composition (by comparison of intensity of methyl and aromatic protons in the nmr spectrum) 45 mol % diphenyl and 55% dimethyl units. Gas chromatographic analysis of the methanol filtrate showed the presence of diphenylphenol, a little unreacted V, and a high-boiling material, probably a trimer.

Results

Synthesis of Dimers.—Both dimers were prepared by the Ullmann coupling of a potassium phenoxide with a 4-bromoanisole, followed by hydriodic acid cleavage of the methyl ether. The general procedure has been previously described,[16] but was modified in this case by the use of a mixture of dimethylformamide and hexamethylphosphoramide as the solvent, and cuprous

(14) G. D. Cooper, A. R. Gilbert and H. Finkbeiner, *Polym. Prepr., Amer. Chem. Soc., Div. Polym. Chem.*, **7**, 166 (1966).

(15) H. S. Blanchard, H. L. Finkbeiner, and G. A. Russell, *J. Polym. Sci.*, **58**, 469 (1962).

(16) G. F. Endres and J. Kwiatek, *ibid.*, **58**, 593 (1962).

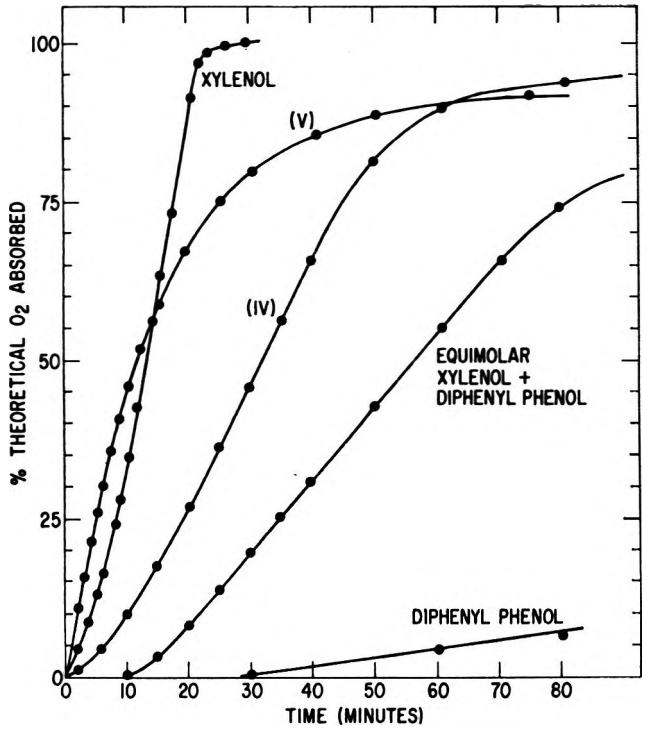
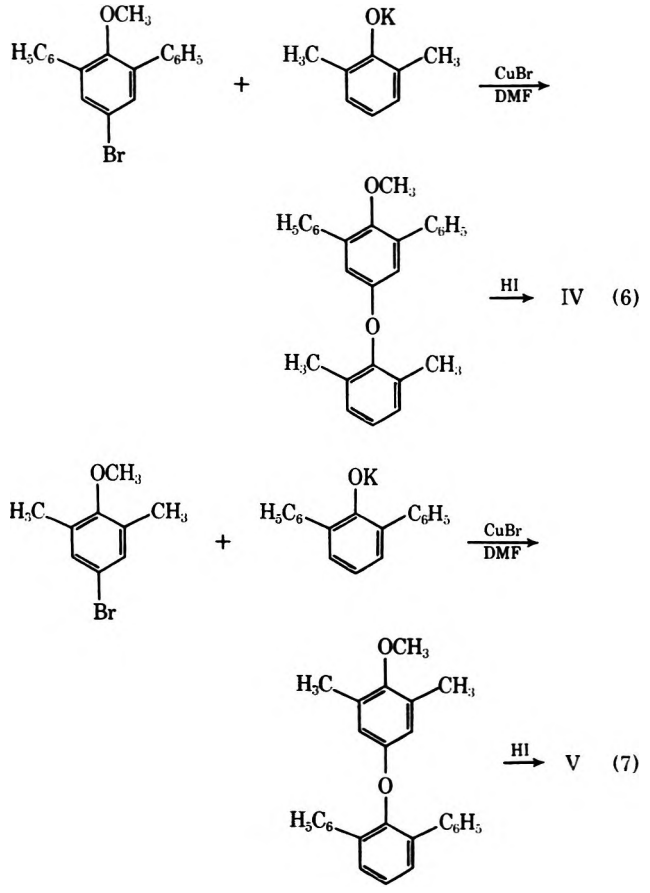


Figure 1.—Rate of oxygen absorption of phenols in benzene at 25°; CuCl–pyridine catalyst.

bromide rather than copper powder as the coupling agent.[17]



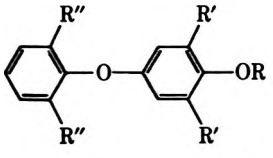
Preparation of IV in this way presented no difficulties and it was obtained in 16% overall yield. The yield in the Ullmann coupling reaction leading to V was much lower and the methyl ether could not easily be separated from the large amount of unreacted diphenylphenol. The final product V, furthermore, could not be induced to crystallize and could not be distilled because of thermal redistribution to diphenylphenol, trimers, tetramers, etc. It was obtained in a satisfactorily pure state (>95%) by conversion to the trimethylsilyl ether, distillation, and cleavage with dilute hydrochloric acid in methanol, but the overall yield was only 5%.

Oxidation of Dimers.—Both IV and V were readily oxidized to poly(arylene oxides) by means of a pyridine–cuprous chloride catalyst at 25°. Dimer V, with the methyl substituents in the phenolic ring, absorbed oxygen at approximately twice the rate of IV, which has phenyl substituents in the phenolic ring; the difference is in the direction expected on the basis of the reactivity of the corresponding monomers, xylenol being oxidized much more rapidly than diphenylphenol. It is somewhat surprising that IV oxidizes as fast as it does, as the oxidation of diphenylphenol is extremely slow under these conditions.[18] An equimolar mixture of dimethylphenol and diphenylphenol, however, can be oxidized quite readily (Figure 1), both monomers being consumed completely. Methanol-insoluble copolymers were obtained in 80–90% yield from IV, V, and from the mixture of dimethylphenol and diphenylphenol.

Determination of Polymer Structure.—Distinguishing among the proposed coupling mechanisms requires the identification of specific sequences of units in the copolymers, a problem which was attacked by analysis of the methyl region of the proton nmr spectra. If only the effects of the nearest neighboring unit are considered, there are four possible magnetic environments for the methyl protons of a dimethylphenoxy unit. The dimethylphenoxy unit may be situated between two other methyl substituted units (M*M*M), between two phenyl-substituted units (P*M*P), or between one of each type; in this case there are two different arrangements, depending on whether the phenyl substituted ring is directed toward the head of the chain (M*M*P) or toward the tail (P*M*M).

In Table I are listed the chemical shifts of the methyl protons in the phenolic dimers II, IV, V, and their

TABLE I
CHEMICAL SHIFTS OF METHYL PROTONS IN DIMERS



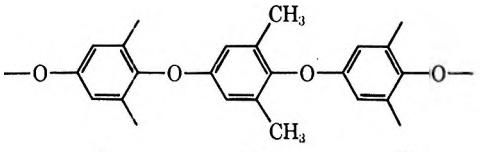
R	R'	R''	δ, ppm "Head" ring	δ, ppm Terminal ring
H	CH_3	CH_3	2.12	2.10
H	C_6H_5	CH_3		2.19
H	CH_3	C_6H_5	1.89	
CH_3	CH_3	CH_3	2.20	2.12
CH_3	C_6H_5	CH_3		2.19
CH_3	CH_3	C_6H_5	1.95	

(17) H. L. Finkbeiner and D. M. White, private communication.

(18) The production of high-molecular-weight homopolymer from 2,6-diphenylphenol requires a high temperature and a very active polymerization catalyst, such as tetramethylethylenediamine–cuprous bromide: A. S. Hay, *Macromolecules* **2**, 107 (1969).

methyl ethers. Substitution of phenyl groups for methyl in the head (phenolic) ring of II resulted in a downfield shift of 0.09 ppm for the methyl protons of the terminal ring, while replacement of methyl by phenyl in the terminal ring caused an upfield shift of 0.23 ppm for the methyl protons of the head ring; the same pattern is observed for the methyl ethers. Apparently the orientation of the methyl groups to the plane of the pendant phenyl groups in structures of this type depends on whether the adjacent unit is directed toward the head or the tail of the chain, a fortunate circumstance which makes it possible to distinguish between the M*M*P and P*M*M sequences.

Consider a three-ring segment (VI) of a polymer chain with the rings labeled as shown below.



VI

The methyl groups of poly(2,6-dimethyl-1-4-phenylene oxide) absorb at 2.08 ppm, establishing the position of the M*M*M sequence. Substitution of phenyl groups into ring A should shift the methyl protons of B upfield by 0.23 ppm from this value; substitution in ring C should produce a downfield shift of 0.09 ppm. If additivity is assumed, then introduction of phenyl groups in both A and C should result in an upfield shift of 0.14 ppm.

Polymer Nmr Spectra.—The nmr spectra of the polymers prepared from IV, V, and from an equimolar mixture of 2,6-dimethylphenol and 2,6-diphenylphenol are shown in Figure 2. All have four peaks in the methyl region, with chemical shifts corresponding closely to the values predicted above for the four sequences possible in a random copolymer of dimethylphenol and diphenylphenol (Table II). Further evidence of the random

TABLE II
CHEMICAL SHIFTS OF METHYL PROTONS IN POLYMERS

	δ, ppm			
Polymer source	P*M*M	P*M*P	M*M*M	M*M*P
Calculated[a]	1.85	1.94	2.08	2.17
IV	1.87	1.94	2.08	2.14
V	1.84	1.93	2.08	2.14
Mixture of monomers	1.86	1.93	2.08	2.13

[a] Calculated from chemical shifts in phenolic dimers.

nature of the polymers is shown in the region of the aromatic backbone hydrogens. Each polymer shows at least six of these peaks,[19] two of which, at 6.25 and 6.46 ppm, correspond to the homopolymers of diphenylphenol and dimethylphenol, respectively, and thus are presumably due to P*P*P and M*M*M sequences.[20]

(19) The type of analysis applied to the methyl protons was not attempted because of the complexity of this region of the spectrum. Assuming only nearest neighbor interactions there are eight possible types of backbone protons (four from each type of unit). Some of these probably do not differ enough in their chemical shifts to be resolved; others may be obscured by interference from the protons of the pendant phenyl rings.

(20) J. G. Bennett, Jr. and G. D. Cooper, *Macromolecules*, **3**, 101 (1970).

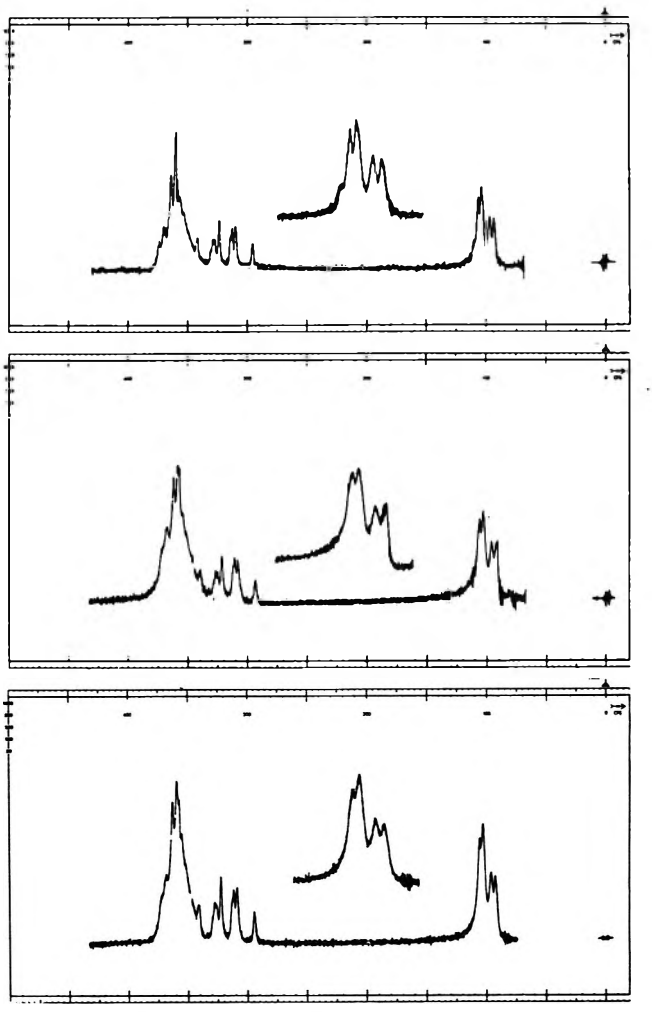


Figure 2.—Nmr spectra of poly(arylene oxides) produced at 25°: top, polymer from IV; center, polymer from V; bottom, polymer from equimolar mixture of 2,6-dimethylphenol and 2,6-diphenylphenol.

End Groups.—The stretching frequency of the diphenylphenol hydroxyl in IV is 3540 cm^{-1}; that of the dimethylphenol group in V is 3610 cm^{-1}. The near-infrared spectra of the three copolymers shows a single peak at 3545 cm^{-1}, Clearly all, or nearly all, of the polymer molecules have a diphenylphenol unit at the head of the chain. The absorption coefficient of the hydroxyl in IV is approximately three times that of V, but it is estimated that, if as much as 5% of the total hydroxyl in these low molecular weight copolymers were of the dimethylphenol type, its presence would be easily detectable.

Discussion

Although there are minor differences in the relative intensities of some of the signals, the nmr spectra of copolymers from IV and V are essentially the same as that of the copolymer obtained by oxidation of the mixture of monomers. They show all of the four possible methyl group signals, including that due to the M*M*M sequence, and the same group of peaks due to aromatic backbone protons. Of the three coupling mechanisms discussed above, only C, in which growth takes place by redistribution to form monomer and removal of monomer by coupling, is consistent with the observed structure. Neither mechanism A nor B allows

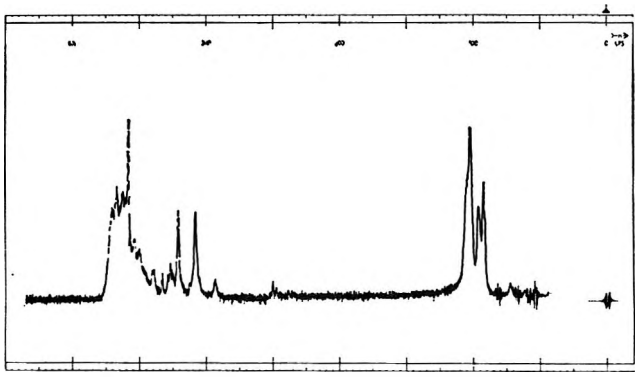
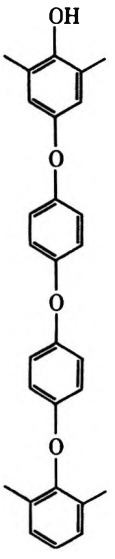


Figure 3.—Nmr spectrum of polymer obtained by oxidation of V at −25° in pyridine.



VII

the formation of M*M*M or P*P*P sequences from the dimers; these groups can occur only as the result of the redistribution reaction. Furthermore, the formation of polymer molecules with diphenylphenol head groups from V is not consistent with mechanism A, nor is their formation from IV permitted by mechanism B. The preponderance of this type of phenolic group is to be expected from the redistribution mechanism. Molecules with a diphenylphenol group at the head of the chain are less readily oxidized than those with the dimethylphenol group and consequently accumulate in the polymer as the more reactive molecules are removed.

The fact that redistribution occurs does not rule out polymerization by other processes, as long as it is accompanied by redistribution, although the largely randomized structure of the polymer[21] shows that the redistribution is extensive and mechanism C is sufficient alone to explain the coupling reaction.

Low-Temperature Polymerization.—The products of oxidation of dimers at low temperature are, in many cases, different from those obtained at higher temperatures. The initial products of oxidation at 25° of II are a mixture of monomer, dimer, trimer, etc., that is, redistribution products.[8] At −25° with a limited amount of a preformed copper complex, [py CuCl(OCH$_3$)]$_z$, as the oxidizing agent only compounds with an even number of rings are obtained,[10] principally tetramer, with smaller amounts of hexamer and higher products. Similarly, III, the mixed dimer of phenol and xylenol, forms redistribution products at 25°,[3,22] but at −25° yields tetramer VII, which has the structure expected of coupling by formation and rearrangement of the ketal, mechanism B.[23] Other lightly substituted dimers behave in the same way.[22]

These observations suggest that the activation energy for rearrangement of the intermediate ketal, eq 4, is lower than for dissociation according to eq 5, so that at a sufficiently low temperature redistribution becomes unimportant and polymer coupling occurs by mechanism B,[8] but this could not be tested by examination of polymer structure; dimer III, which has distinguishable rings, could not be oxidized past the tetramer stage, even with a large excess of the oxidizing agent.

Oxidation of IV at −25° in pyridine with an excess of the copper complex, conditions favoring coupling by rearrangement, yielded no isolable polymer. The only products detected, other than the unreacted started material, of which more than 90% was recovered, were small amounts of compounds having gas chromatographic retention times identical with those obtained by thermal or catalytic redistribution of IV.

Oxidation of V under the same conditions yielded 78% of methanol-insoluble polymer having a molecular weight of 4250 and a composition of 55 mol % M and 45% P units; the average molecule thus consists of 13 M and 11 P units. More than 98% of the hydroxyl groups were of the diphenylphenol type. The nmr spectrum of this polymer is shown in Figure 3. Methyl proton signals appear at δ 1.87, 1.93, and 2.07 ppm, with a shoulder at 2.12 ppm possibly representing the M*M*P sequence. The strongest signal in the methyl region is that for the M*M*M sequence, while in the aromatic backbone region the strong signals are those corresponding to M*M*M and P*P*P groups. The presence of the "forbidden" M*M*M and P*P*P sequences and the loss of approximately 15% of the P units provide conclusive evidence of redistribution.

Redistribution and rearrangement involve the same intermediate and are complementary reactions. Dissociation of the ketal into aryloxy radicals may occur at any stage of the progress of the dienone from the head to the tail of the chain, so that redistribution may proceed by transfer of more than one unit from one molecule to another. It has been suggested that the polymer coupling reaction involves both processes, with their relative importance determined by reaction conditions. The results with V show that, even under conditions favoring coupling by rearrangement, redistribution occurs with sufficient frequency to determine the polymer structure.[24]

(21) None of the copolymers are completely random. All possible arrangements appear to be present, but sequences of similar units occur somewhat more often than is statistically to be expected.

(22) W. J. Mijs, O. E. Von Lohuisen, J. Bussink, and L. Vollbracht, *Tetrahedron*, **23**, 2253 (1967).

(23) D. M. White, private communication.

(24) Each step in the rearrangement sequence is reversible. If all units are alike, rearrangement has an equal probability in either direction. The average number of individual rearrangement steps required for producing a polymer molecule by coupling and rearrangment of polymeric radicals is extremely large, so that there is a high probability that dissociation and redistribution will occur at some stage of the process.

Registry No.—IV, 32979-47-8; IV polymer, 33029-40-2; V, 32979-49-0; V polymer, 33029-41-3; 2,6-diphenyl-4-bromoanisole, 20104-39-6; 2,6-diphenyl-4-(2,6-dimethylphenoxy)anisole, 32979-46-7; 2,6-dimethyl-4-(2,6-diphenylphenoxy)anisole, 32979-48-9; copolymer of 2,6-dimethylphenol and 2,6-diphenylphenol, 26006-43-9.

Acknowledgment.—The authors are indebted to R. A. Kluge for assistance in the interpretation of the dsc and nmr results.

Nonstereospecific Oxidative Addition of Benzenethiol to Indene[1]

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The oxidative addition of benzenethiol to indene produces a mixture of three isomeric 2-phenylsulfinylindanols that contains 14–18% of the *cis*-hydroxy sulfoxide contrary to previous claims that this reaction leads stereospecifically only to trans addition products. The fourth isomeric 2-phenylsulfinylindanol (cis-syn) was prepared by the oxidation of the sulfide precursor. The examination of the concentration dependence of hydrogen bonding, of the nmr spectra, and of the relative yields permits the assignment of the configurations at the sulfur atom in all four isomers.

Results and Discussion

The four isomeric 2-phenylsulfinylindanols (trans-anti, trans-syn, cis-anti, and cis-syn)[4] have been described in the literature, but unfortunately the reports are inconsistent and incomplete. Thus, Ford and coworkers[5] claimed that direct cooxidation of indene and thiophenol produces only traces (0.25% maximum) of the cis products and described two trans isomers of mp 149.5–150.5 and 99°, respectively. The cis isomers were prepared in a roundabout fashion *via* 2-bromoindanone and were described as solids of mp 158 and 122–123°, respectively. Later Oswald[6] repeated the cooxidation reaction and reported the isolation of *three* isomeric hydroxy sulfoxides of this series of melting points 158–159, 148–150, and 132–135°, respectively. More recently, however, the same investigator[7] stated that only *trans*-2-phenylsulfinylindanols are produced, and the stereospecificity of this reaction has been assumed[8] in the consideration of the bridged nature of the intermediate olefin–thiyl radical adduct.[9] In view of this confusion, and also since "the relationship between the four isomers with respect to the orientation about the sulphur atom is not known,"[5] the cooxidation of indene and thiophenol was reinvestigated with care. The preparation of the cis isomers from 2-bromoindanone was also repeated.

Extensive application of thin layer chromatography (tlc) to the products of the cooxidation of indene and thiophenol showed that the reaction produced three isomers, namely two trans isomers of mp 158 and 101°, respectively, and a high-melting cis isomer (mp 158°). The relative yields of these three isomers were determined by careful column chromatography and by characterization of each fraction by tlc. Regardless of whether the cooxidation was carried out in benzene or hexane, the cis isomer of mp 158° was obtained in 14–18% yield[10] while the yields of the high- and low-melting trans isomers were 24–29 and 56–60%, respectively. In order to obtain information on the relative rates of formation of the three hydroxy sulfoxides during the cooxidation reaction, samples of the reaction mixture were subjected to tlc, and it was found that the cis isomer and the low-melting trans isomer were formed in approximately equal amounts during the early stage of the reaction, while the high-melting trans isomer did not begin to accumulate until later.

The missing cis hydroxy sulfoxide was synthesized in the manner previously described except that sodium borohydride, rather than lithium aluminum hydride, was used in the reduction of 2-phenylmercaptoindanone. It is of interest to note that while the latter reducing agent gave a ratio of hydroxy sulfides 4.6:1 in favor of the trans isomer, the use of the borohydride produced a 15:1 ratio in favor of the cis isomer. The difference in these results is due, in part, to the alkaline conditions of the sodium borohydride reduction, which are known[5] to bring about the decomposition of the *trans*-2-phenylmercaptoindanol. Thus, while the lithium aluminum hydride results are based on essentially quantitative yields of hydroxy sulfides, the total yield of hydroxy sulfides using sodium borohydride was only 33%. However, even if we assume that the loss of the missing hydroxy sulfide is due to the decomposition of the trans hydroxy sulfide, the ratio of trans:cis reduction products is only 2.2:1 in the case of the sodium borohydride. The fate of the *trans*-2-phenylmercaptoindanol during the alkaline decomposition was not ascertained by Ford and coworkers.[5] We have isolated essentially all of the missing phenylmercapto portion of the initial 2-

(1) Presented in part at the 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964.

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(3) The Puerto Rico Nuclear Center is operated by the University of Puerto Rico for the U. S. Atomic Energy Commission under Contract AT-(40-1)-1833.

(4) The names, in accord with the nomenclature employed by Ghersetti and coworkers, *J. Chem. Soc.*, 3718 (1963), refer, in the first place, to the relative orientation of the hydroxyl and sulfoxide functions, and, secondly, to the orientation of the oxygen of the sulfoxide relative to the benzene ring of indan when the conformation of the sulfoxide group is such that its phenyl group points away from the indan ring.

(5) J. J. Ford, R. C. Pitkethly, and V. O. Young, *Tetrahedron*, **4**, 3251 (1958).

(6) A. Oswald, *J. Org. Chem.*, **26**, 842 (1961).

(7) A. A. Oswald and T. J. Wallace in "Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Myers, Ed., Pergamon Press, Elmsford, N. Y., 1966, p 224.

(8) P. D. Readio and P. S. Skell, *J. Org. Chem.*, **31**, 759 (1966).

(9) P. S. Skell in "Organic Reaction Mechanism," Special Publication No. 19, The Chemical Society, London, 1965, p 143.

(10) H. H. Szmant and J. J. Rigau, *Tetrahedron Lett.*, 3337 (1967).

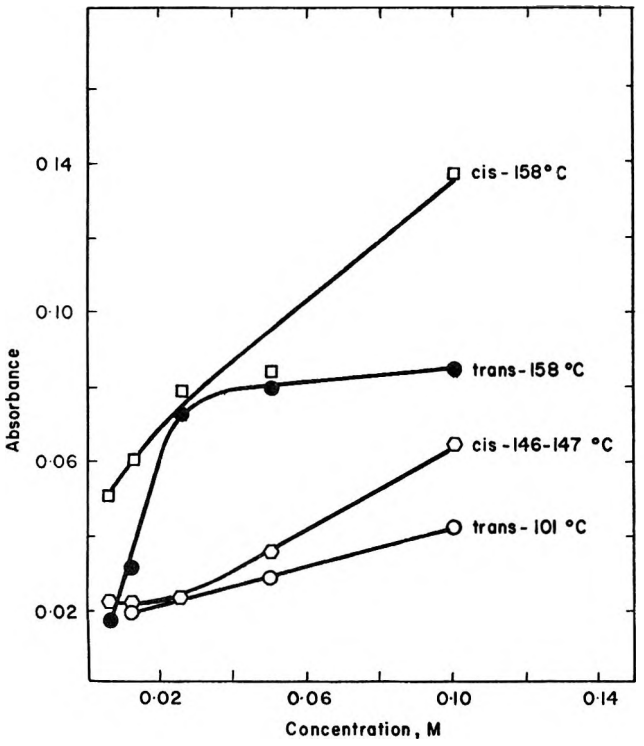

Figure 1.—Absorbance of "bound" O–H as a function of dilution.

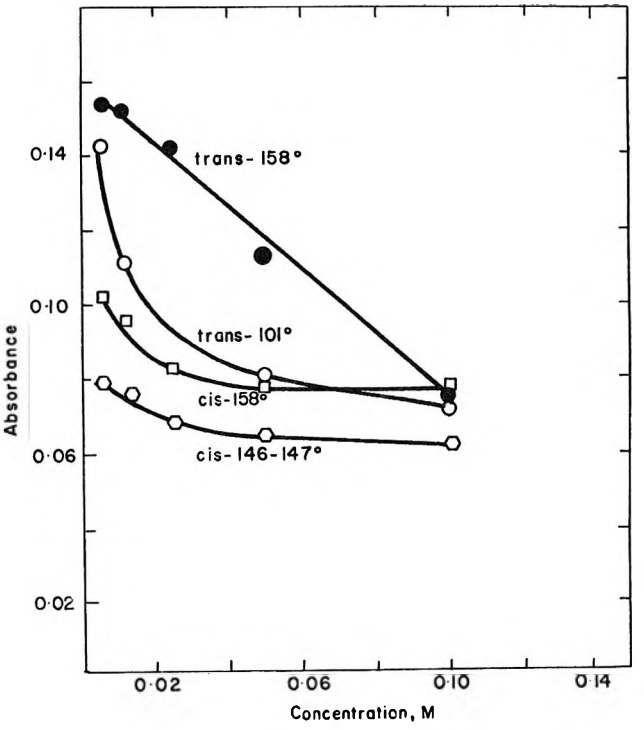

Figure 2.—Absorbance of "free" O–H as a function of dilution.

phenylmercaptoindanone as phenyl disulfide and the diphenyl thioacetal of 1-indanone.

The isomeric *cis*- and *trans*-2-phenylmercaptoindanols were also prepared by the Oswald modification of the oxidative addition of thiols to olefins in the presence of tertiary amines.[11]

The oxidation of *cis*-2-phenylmercaptoindanol with 30% hydrogen peroxide or *m*-chloroperbenzoic acid gave a mixture of two sulfoxides and the latter were separated by column chromatography (rather than by fractional crystallization employed by previous investigators) to give the missing isomer of mp 146° (and not 122–123°),[5] as well the isomer of mp 158° obtained in the cooxidation reaction. Similarly, *trans*-2-phenylmercaptoindanol was oxidized by *m*-chloroperbenzoic acid to the two sulfoxides of mp 158 and 101° also isolated from the cooxidation reaction, and as in the case of the latter, the low-melting isomer again predominated.

The cis or trans structure of each isomeric hydroxy sulfoxide was checked by conversion to the known[5] hydroxy sulfones. The identity of the *cis*- and *trans*-2-phenylsulfonylindanols was confirmed by means of their infrared spectra and the pronounced intramolecular hydrogen bonding[12] in the case of the first-mentioned isomer.

The assignment of the stereochemistry about the sulfur atom in each pair of isomeric hydroxy sulfoxides is based mainly on the concentration dependence of hydrogen bonding followed by infrared spectroscopy, and differences in the nmr spectra.

Hydrogen bond formation as a function of solute concentration was followed while the total number of solute molecules was maintained constant throughout a set of determinations. The concentration dependence of the absorption intensities of the "free" and "bound" hydroxyl bands is shown in Figures 1 and 2. The "free" hydroxyl band refers to the stretching frequency of the hydroxyl group when it is solvated by carbon tetrachloride or when it is subject to the weak interaction with the π system of indene.[11] The "bound" hydroxyl absorption refers, on the other hand, to the hydroxyl group that interacts rather strongly with the sulfoxide function and produces a large displacement (200–280 cm^{-1}) in the H–O stretching frequency. Examination of Figure 1 shows that the cis isomer of mp 158° is the only isomer that retains a relatively high absorbance with dilution, and, on this basis alone, we can assign to it the cis-anti structure that is conducive to intramolecular hydrogen bonding. This configurational assignment agrees with the fact that this is the only cis isomer obtained in the cooxidation reactions. It is known[13] that the hydroperoxide–sulfide is the intermediate in this reaction, and it stands to reason that its intramolecular disproportionation should give exclusively the cis-anti hydroxy sulfoxide. The configuration of the cis hydroxy sulfoxide of mp 158° finds additional support in the observation that the *m*-chloroperbenzoic acid oxidation of the cis hydroxy sulfide gives 80% of the high-melting sulfoxide and only 20% of the cis hydroxy sulfoxide of mp 146°. The stereoselectivity in the oxidation of sulfide to sulfoxide by peracids induced by the presence of a vicinal hydroxyl group was observed in the oxidation of thioxanthen-9-ol,[14] and is reminiscent of the induced stereoselectivity in epoxidation.[15]

Since in the course of the infrared examinations the number of solute molecules in the light path remains constant while their concentration is being changed, a horizontal plot in Figures 1 and 2 signifies that the given hydroxyl group absorption is unperturbed by changes in the opportunities for solute molecules to

(11) A. A. Oswald, F. Noel, and G. Fisk, *J. Org. Chem.*, **26**, 3974 (1961).
(12) H. H. Szmant and J. J. Rigau, *ibid.*, **31**, 2288 (1966).
(13) A. A. Oswald, *ibid.*, **24**, 443 (1959).
(14) A. L. Ternay, Jr., D. W. Chasar, and M. Sax, *ibid.*, **32**, 2465 (1967).
(15) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 115.

associate. The positive slope of the "bound" hydroxyl absorption plots given by three isomers (Figure 1) indicates that the increasing concentration induces the formation of hydrogen-bonded aggregates. The rise in the effective absorption is expected in view of the recognized[16] greater absorption intensity of intermolecular hydrogen bonds as compared to that of intramolecular hydrogen bonds, and especially that of the "free" hydroxyl band. The steep initial slope followed by the nearly horizontal plot given by the trans isomer of mp 158° reveals that this substance is prone to give polymeric, hydrogen-bonded aggregates, and that even at the low concentration of 0.02 *M* the association has progressed very far. Such a behavior can be expected of the trans-syn isomer, since this structure is most favorable for the formation of chainlike aggregates. The "free" hydroxyl plots shown in Figure 2 are consistent with the above conclusions. The leveling of the decrease in the "free" hydroxyl absorption reflects a relative reluctance to association in all the isomers except the last mentioned high-melting trans compound. The latter seems to form chainlike aggregates in a constant fashion over the range of concentrations investigated here. However, while the "free" hydroxyl absorption disappears regularly, the increase in the "bound" hydroxyl absorption cannot quite keep up and this discrepancy can be explained by the weakening of the absorptivity of hydrogen bonds in the larger chain aggregates.

The greater tendency of the higher-melting trans isomer to associate, and hence the likelihood of its trans-syn structure, is clearly demonstrated by the larger apparent molecular weight as compared to that of the lower-melting trans isomer under equivalent conditions (see Experimental Section), and also its lower solubility in solvents that are poor acceptors in hydrogen bonding.

The nmr spectra of the four isomers provide further evidence in favor of the structural assignments discussed so far. The chemical shifts (δ TMS) in deuteriochloroform are given together with the assigned preferred conformations in Figure 3.

As expected, the cis isomer of *mp* 158° exhibits an exceptional chemical shift for the hydroxylic proton in accord with the intramolecularly hydrogen bonded cis-anti structure. This hydrogen bond forces the sulfoxide phenyl group into the proximity of the methylene group of the indan ring with the consequent large shielding of one of its protons. In the low-melting cis-syn isomer, on the other hand, one of the methylenic protons is deshielded by the sulfoxide oxygen while the hydroxylic proton is shielded by the nonbonding sulfur electrons.

The low-melting trans isomer, in accord with the assigned anti configuration, shows a deshielded proton at C-1 indicative of the proximity of the sulfoxide oxygen. The equivalence of the methylenic protons indicates that the preferred conformation of the sulfoxide group allows the phenyl group to rotate freely while pointing away from the indane ring. In the high-melting trans-syn isomer, on the other hand, the sulfoxide oxygen deshields one of the methylenic protons, and the fact that the proton C-1 is not affected by the sulfoxide phenyl group indicates that the preferred conformation again allows the phenyl group to rotate freely while pointing away from the indan ring.

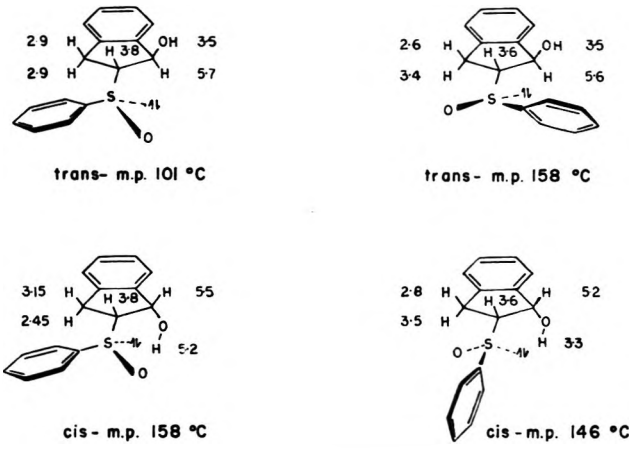

Figure 3.—Proposed structures and nmr assignments of isomeric 2-phenylsulfinyl-1-indanols (δ from TMS in $CDCl_3$).

The isolation of *ca.* 14% of cis product in the cooxidation of thiophenol and indene reveals that, while not stereospecific, the reaction is still stereoselective. The relevance of this observation to the question of classical *vs.* bridged sulfur-containing radicals has been touched upon elsewhere[10] and will be dealt with in greater detail in future publications.

Experimental Section[17]

Cooxidation of Indene and Thiophenol.—Freshly distilled (under oxygen-free atmosphere) indene, 5.32 ml, and thiophenol, 4.53 ml, were dissolved in 150 ml of hexane and the solution was stirred in a constant-temperature bath maintained at 25°. The flask was connected to a gas burette that could be conveniently refilled from an oxygen reservoir. A rapid rate of oxygen absorption over the first 10 min was followed by a slower absorption over the next 80 min. The reaction mixture was stirred under oxygen for 24 hr to ensure the absorption of the calculated 1100 ml of oxygen, and then was allowed to stand for 6 days. A precipitate first appeared at the end of the initial 10-min period and accumulated gradually as the reaction mixture rested. Filtration yielded 9.647 g of white solid and evaporation of the filtrate produced 2.465 g of viscous oil.

An essentially quantitative separation of the constituents present in the solid cooxidation product was achieved by using a 3.25 ft × 1 in. column containing 290 g of Baker's chromatographic grade silica gel per 1.000 g of product. The eluent was anhydrous ethyl acetate and there were separated 33 fractions ranging in volume from 30 to 300 cc in accordance with information procured by simultaneous tlc of each fraction as it was eluted from the column.

The tlc technique employed 8 × 8 in. plates covered with silica gel (grade G supplied by E. Merck, Darmstadt), and activated overnight at 125°. The plates were eluted[18] with anhydrous ethyl ether (45 min) and developed in an iodine atmosphere.[19]

The results of the separation using a 1.000-g portion of the solid reaction product are shown in Table I.

The analogous cooxidation experiment in 150 ml of benzene gave a nearly complete absorption of oxygen in 90 min at a rapid and essentially uniform rate. The reaction mixture was allowed to rest for 6 days, but filtration yielded only 2.60 g of solid. Evaporation of the filtrate gave an additional 9.51 g of product. The products were combined by dissolving in chloroform, and an aliquot representing 1.50 g of the combined products was sub-

(16) G. C. Pimentel and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman, San Francisco, Calif., 1960, pp 95, 101, 170, 197.

(17) Microanalyses by Dr. Alfred Bernhardt, Mülheim, Ruhr, Germany. Melting points were determined in a Mel-Temp apparatus and are otherwise uncorrected.

(18) M. Brenner, A. Niedermieser, G. Pataki, and A. R. Fahmy, *Experientia*, **18**, 101 (1962).

(19) G. C. Barrett, *Nature (London)*, **194**, 1171 (1962).

TABLE I

Fraction	Solid, g[a]	Isomer (mp, °C)	R_f	Analysis found[b] C	H	S
10–13	0.267	trans (158)	0.26	69.88	5.46	12.31
14–23	0.511	trans (101)	0.17	69.92	5.53	12.27
28–32	0.130	cis (158)	0.08	69.84	5.52	12.49

[a] The remaining 0.092 g was subjected to infrared examination and found to exhibit absorption bands typical of ketones, sulfides, and sulfoxides. [b] Calcd: C, 69.77; H, 5.46; S, 12.40.

jected to chromatographic separation, as described above. A total of 1.012 g of solids was isolated consisting of 0.244 g of the trans isomer, mp 158° (fractions 11–14), 0.610 g of the trans isomer, mp 101° (fractions 15–20), and 0.158 g of the cis isomer, mp 158° (fraction 24).

The cooxidation was also repeated using only 50 ml of benzene as solvent. The relative yields of the products as a function of the solvent and solvent concentration are tabulated in Table II.

TABLE II

2-Phenylsulfinylindanol (mp, °C)	Yields (in g)[a] of chromatographically pure fractions as function of solvent in cooxidation experiments: Hexane, 150 ml	Benzene 150 ml	Benzene 50 ml
Trans (158)	0.213	0.163	0.190
Trans (101)	0.407	0.407	0.408
Cis (158)	0.103	0.105	0.134
Total	0.723	0.675	0.732

[a] On the basis of 1.000 g of crude solid reaction product.

While all three cooxidation conditions also gave rise to the formation of some *trans*-2-phenylmercapto-1-indanol, the last-mentioned experiment produced a remarkably high yield of the hydroxy sulfide, namely 0.211 g per 1.000 g of crude reaction product. This material was identical with the sample prepared by the reduction of the corresponding ketone (see below).

An additional cooxidation experiment was carried out using 300 ml of benzene as solvent in order to prevent precipitation of solid products and to decrease the rate of reaction. Small samples of the reaction mixture were subjected to tlc at intervals of 3–5 min. After a reaction time of 15 min, spots corresponding to the trans isomer of mp 101° and to the cis isomer of mp 158° began to appear, and the intensity of these spots seemed to increase at about the same rate. The spot that corresponds to the trans isomer of mp 158° did not appear until approximately 90 min from the start of the reaction.

Reduction of 2-Phenylmercaptoindanone.—A solution of 2.5 g of sodium borohydride in water containing 0.2% of sodium hydroxide (44% borohydride concentration) was added in small portions to a solution of 34 g of 2-phenylmercaptoindanone[5] in 100 ml of isopropyl alcohol while the temperature was maintained at 35–45°. The reaction mixture was stirred for 2 days in an inert atmosphere and then was extracted with benzene to give 27.4 g of solid product. The insoluble residue was decomposed with 5 *N* hydrochloric acid and extraction with benzene yielded an additional 2.65 g of product. The combined solid products were separated by chromatography using a silica gel column and the eluents ligroin, benzene, and chloroform, in that order. There were isolated 8.55 g of diphenyl disulfide (identified by melting point and microanalysis), 7.70 g of solid, mp 76–77°, identified tentatively as the diphenyl thioacetal of 1-indanone on the basis of its infrared spectrum and analysis (Calcd: C, 75.40; H, 5.42; S, 19.17. Found: C, 74.74; H, 5.47; S, 19.73), 0.8 g of unidentified oil, 1.30 g of impure cis hydroxy sulfide, 9.23 g of analytically pure cis hydroxy sulfide, mp 71–75°, and 0.73 g of analytically pure trans hydroxy sulfide, mp 101°.

Cooxidation of Indene and Thiophenol in the Presence of Triethylamine.—A solution of 37.46 g (0.34 mol) of thiophenol, 12.78 g (0.11 mol) of indene, and 0.01 mol of triethylamine (previously dried over phosphorus pentoxide for 2 min) was oxygenated for 6 hr at room temperature. The reaction mixture was extracted three times with 100-ml portions of 5% potassium hydroxide, washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 32.30 g of product. Tlc on silica and using chloroform showed the presence of three components. A 10.200-g portion of the product was chromatographed on silica and 100-ml fractions of eluent were collected. The first ten fractions (benzene) and the following three fractions (chloroform) gave 5.228 g of pure diphenyl disulfide. Fractions 14–16 (chloroform) gave 0.311 g of *cis*-2-phenylmercaptoindanol. Fractions 17–24 (chloroform) gave 3.703 g of a mixture of trans and cis isomers, while fractions 25–28 (chloroform) gave 0.616 g of pure trans-2-phenylmercaptoindanol for a recovery of 9.858 g (96.6%) of sample subjected to column chromatography. The mixture of trans and cis isomers, 2.874 g, was subjected to a new chromatographic separation to give 0.153 and 1.001 g of pure cis and *trans* isomers, respectively, while 1.470 g was still recovered as a mixture.

Preparation of the Isomeric *cis*-2-Phenylsulfinylindanols.—The oxidation of *cis*-2-phenylmercaptoindanol was repeated as described in the literature[4] except that the products were separated by chromatography as described for the separation of the products of cooxidation. The two isomers were obtained in approximately equal amounts, and the higher-melting compound, mp 158°, was identical with the corresponding product isolated from the cooxidation reaction. The lower melting isomer, mp 146–147°, gave a R_f value of 0.17 (conditions described above), and gave correct analytical results (*Anal.* Calcd: C, 69.74; H, 5.46; S, 12.39. Found: C, 69.80; H, 5.34; S, 12.28). Both isomers were converted quantitatively to the identical sulfone,[4] mp 130–131°.

Oxidation of 2-Phenylmercaptoindanols with *m*-Chloroperbenzoic Acid.—A solution of 0.155 g (0.9 mmol) of *m*-chloroperbenzoic acid in 15 ml of methylene chloride was added dropwise to a stirred solution of 0.242 g (1 mmol) of the trans hydroxy sulfide in 10 ml of methylene chloride at 0°. After 12 hr the reaction mixture was filtered and the filtrate was washed with three 25-ml portions of aqueous sodium bicarbonate, dried over magnesium sulfate, and evaporated to give 0.192 g of product. The product was chromatographed (silica, ethyl acetate) to give 74.5 mg of unreacted hydroxy sulfide, and 35 and 67 mg of the *trans*-2-phenylsulfinylindanols of mp 158 and 101°, respectively.

An analogous experiment using 38 mg of *m*-chloroperbenzoic acid and 60 mg of cis hydroxy sulfide gave 23 mg of unreacted sulfide, and 2.4 and 9.6 mg of *cis*-2-phenylsulfinylindanols, mp 146 and 158°, respectively.

Determination of Infrared Spectra.—The spectra were determined by means of a Perkin-Elmer Model 237 spectrophotometer operating in a constant-temperature room. For the determination of the absorbance–concentration dependence, a variable thickness liquid absorption cell was employed, and special care was exercised to minimize changes in temperature during a given set of determinations. Limited solubility of the compounds required the use of dichloromethane (spectroquality) as the solvent, and did not permit the preparation of solutions of higher than 0.10 molar concentration (except in the case of the low-melting trans isomer where a 0.2 molar concentration could be attained). Starting with a 0.10 *M* solution and a 0.200 mm cell path, the dilution of the solutions and increase in the cell paths was carried out gradually until a solution of 0.00625 *M* was examined in the cell of 3.2 mm path length. The absorbances of the "free" and "bound" O–H stretching frequencies were determined at 3600 and 3350 cm^{-1}, respectively, and no significant changes in the positions of these bands were noticed as the concentration was varied. The results are shown in Figures 1 and 2 in which the absorbance of the "free" and "bound" O–H stretching frequencies is plotted as a function of concentration.

Nuclear Magnetic Resonance Spectra.—The nmr spectra were determined by the Spectroscopy Application Laboratories of Varian Associates at 60 Mcps using deuteriochloroform as a solvent. The assignments of some of the bands were checked by using a 100-Mcps spectrometer and pyridine as the solvent. The chemical shifts are shown in Figure 3.

Apparent Molecular Weight Determination.—The determination of apparent molecular weights by cryoscopy in benzene failed due to the limited solubility of the 2-phenylsulfinylindanols. Ebulliometric measurements were carried out in the case of the two trans isomers using benzene and a modified Cottrell apparatus. The trans isomer of mp 158° gave an apparent molecular weight of 363 at a molality of 0.0604, while the lower melting

trans isomer showed an apparent molecular weight of only 269–311 at the higher molality of 0.0691–0.1159.

Registry No.—Benzenethiol, 108-98-5; indene, 95-13-6; trans,[20] mp 101°, 32819-87-7; trans,[20] mp 158°, 32819-88-8; cis,[20] mp 158°, 32819-85-5; cis,[20] mp 146°, 32785-03-8; diphenyl thioacetal of 1-indanone, 32819-86-6.

(20) See Figure 3.

α Anions of Carboxylic Acids. II. The Formation and Alkylation of α-Metalated Aliphatic Acids

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The degree to which α anions of straight chain and α-branched chain carboxylic acids are formed by reaction with lithium diisopropylamide in solutions of tetrahydrofuran (THF) and tetrahydrofuran containing hexamethylphosphoramide (HMPA) was established by deuteration and carbonation. The determinations indicate the extent of the metalations of straight and α-branched chain acids to be unaffected by HMPA. Straight chain acids are converted to α anions to the extent of 95% in either solvent system. HMPA assists the carbanion reactions by solubilizing insoluble dianions of straight chain acids and by accelerating their rate of alkylation in producing nearly quantitative yields of the α-branched acids. α-Branched chain acids are α metalated in both solvent media to the extent of 30–45% at −5 to 25° and to about 93% at 50°. The dianions of α-branched acids are soluble in THF without HMPA but the presence of HMPA is deleterious for these alkylations by inducing the elimination reaction between alkyl halide and the bases (unreacted amide and dianion). A steric effect in branched dianions increases olefin formation with increasing size of the alkyl substituents at the expense of alkylation. High conversions of α-branched acids to dianions are obtained in THF at 50°. The dianions alkylate to trialkylacetic acids in yields exceeding 90%. α lithiation of sodium and potassium alkanoates is less satisfactory, but alkylation of the dianions proceeds to high yields of α-branched acids. Carbonation and deuteration of α-lithiocarboxylates are recommended as a preparative synthesis of α-alkylmalonic acids and α-deuterioalkanoic acids, respectively. Monoolefinic acids containing isolated double bonds (oleic and undecylenic acids) α alkylate normally, but the more reactive double bonds in linoleic acid are altered by the strong base to produce a complex mixture of alkylated acids.

The direct introduction of a substituent into the α-carbon position in fatty acids has been limited to a few reactions, namely ionic halogenation,[2] sulfonation,[2] and free-radical substitution reactions.[3,4] An extensive series of classical, indirect reactions generally use the displacement of a facile leaving group at the 2 position, but these reactions require the initial introduction of the displaceable substituent at the designated site. Carbanions are highly reactive species that should provide the countervailing method for accomplishing α substitutions of fatty acids directly and propitiously. The unique opportunities α carbanions offer to derivatizations of fatty acids has not been exploited owing to the lack of adequate methods for generating this species.

Several groups of investigators have formerly undertaken the preparation of dianions of small chain carboxylic acids with limited success. In 1938, Morton, Fallwell, and Palmer[5] first demonstrated the intermediate formation of the α anion of sodium phenylacetate and sodium hexanoate using phenylsodium as the base for the abstraction of α-methylene protons. The presence of α anions as the reactive intermediates was demonstrated by carbonation that yielded phenylmalonic acid (60%) and butylmalonic acid (17%), respectively. Subsequently, other investigators have α metalated sodium phenylacetate with sodium (potassium) amide in liquid ammonia[6] and sodium acetate with sodamide at 200°.[7] The latter reaction was unsuitable in its application to propionic, *n*-butyric, and isobutyric acids.[7] Some of the preparative difficulties in these metalations were finally surmounted by Creger[8] who prepared α anions of isobutyric and 2-methylbutyric acids by means of lithium diisopropylamide in tetrahydrofuran (THF)–hexane (heptane) solution (eq 1). A single-step, high-yield synthesis

$$\mathrm{CH_3CHCOOH} + 2\mathrm{LiN[CH(CH_3)_2]_2} \longrightarrow \underset{\mathrm{R}}{\mathrm{CH_3\bar{C}C\bar{O}O}} + 2\mathrm{HN[CH(CH_3)_2]_2} \quad (1)$$

$$\underset{\mathrm{R}}{\mathrm{CH_3\bar{C}C\bar{O}O}} \xrightarrow[2.\ \mathrm{H^+}]{1.\ \mathrm{R'Br}} \underset{\mathrm{R}}{\overset{\mathrm{R'}}{\mathrm{CH_3CCOOH}}} \quad (2)$$

R = Me, Et

of trialkylacetic acids by α alkylation of the dianions (eq 2) provided Creger with an elegant demonstration of the utility of his method.

In our preliminary publication[9] we reported the limitations of Creger's method in its application to straight chain and α-branched chain carboxylic acids from which low yields (30–60%) of dialkyl and trialkyl acetic acids, respectively, were obtained. The metalated straight-chain acids were insoluble in THF, but readily dissolved by the addition of the highly dipolar

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(8) P. L. Creger, *ibid.*, **89**, 2500 (1967).

(9) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **35**, 262 (1970).

solvent, hexamethylphosphoramide (HMPA). This modification resulted in the preparation of dialkylacetic acids in excess of 90% yields. In contrast to dianions of straight chain acids, the dianions of α-branched carboxylic acids were soluble in THF, but in the presence of HMPA they alkylated to trialkyl acetic acids in yields that rapidly diminished with increasing size of the α branch chain. For example, yields as low as 9% alkylated product were observed in the case of 2-butylnonanoic acid. Shortly following this publication, Creger[10] reported an extension of his method to straight-chain acids whereby the dianions were prepared in the form of mixed lithium–sodium salts that alkylated to dialkylacetic acids in good yields.

The extreme difference in behavior of HMPA in alkylations of straight and α-branched acids indicated the need to clarify the role of the dipolar solvent and to find conditions for the quantitative formation of α anions of long-chain α-branched acids. Two sets of reactions for the straight and α-branched acids clearly required inquiry. One set of reactions is concerned with determining the extent of the metalations in the presence and absence of HMPA in THF solutions by the use of deuterium oxide (eq 3) and carbon dioxide (eq 4) as quenching agents. The second is a study of

$$RR'\bar{C}C\bar{O}O \xrightarrow{D_2O} RR'CDCOO^- \xrightarrow{H_3O^+} RR'CDCOOH \quad (3)$$

$$RR'\bar{C}C\bar{O}O \xrightarrow[2.\ H_3O^+]{1.\ CO_2} RR'C(COOH)_2 \quad (4)$$

R = Alkyl; R′ = H, Alkyl

the subsequent alkylations of the metalated species in the two-solvent systems. The present paper reports these results and includes in the study an extension of these reactions to a few examples of olefinic acids.

Results

Straight-Chain Acids.—The conversions of straight-chain acids to α anions were determined by deuterium oxide and carbon dioxide quenchings. The results of these analyses are recorded in Table I for measurements obtained on three examples of straight-chain acids. The results produced by the two techniques on the two long-chain carboxylic acids are in good agreement and provide an average value of 94% α anion formation in the solvent systems THF and THF–HMPA. The α metalations are completed within 30 min.

The results for α alkylations of straight-chain acids in THF in the presence and absence of HMPA are assembled in Table II. Conversions of the carboxylic acids to α-alkylated products are nearly quantitative in solutions of HMPA (1 mol per mol of carboxylic acid). Compared to the low conversions observed in THF alone, the conversions of hexanoic acid, chosen as representative of homologous straight-chain series, are optimum at mole equivalents of HMPA and carboxylic acid (Figure 1). The alkylations were completed in 90 min, as determined by periodic sampling of the reaction containing equimolar concentrations of HMPA and acid. Higher mole ratios afford no advantage aside from solubilizing less soluble carboxylate salts and dianions as shown by the examples of acetic and stearic acids (Table II).

(10) P. L. Creger, *J. Amer. Chem. Soc.*, **92**, 1397 (1970).

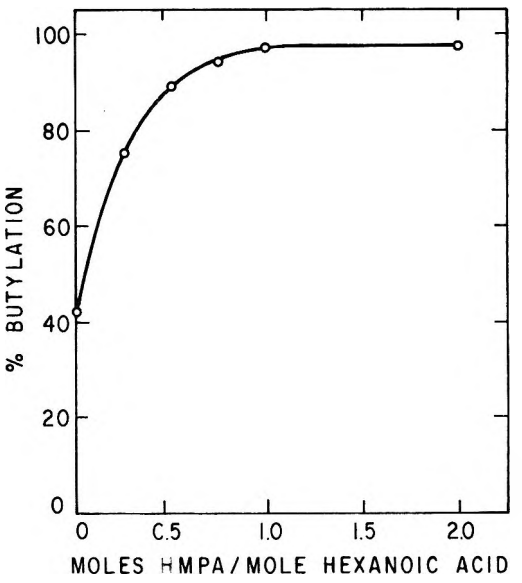


Figure 1.—α Butylation of hexanoic acid as a function of HMPA concentration. Dianion of hexanoic acid (0.247 *M*) and butyl bromide (0.370 *M*) in THF at 25°; time of reaction, 90 min.

TABLE I

DETERMINATION OF α-ANION CONTENT. REACTION OF METALATED STRAIGHT-CHAIN CARBOXYLIC ACIDS WITH D_2O AND CO_2[a]

Dianion	α-D Acid, %[b-d] THF	α-D Acid, %[b-d] THF–HMPA	Dioic Acid, %[d,e] THF	Dioic Acid, %[d,e] THF–HMPA
(Acetate)				
$LiCH_2CO_2Li$			41	65[f]
(Hexanoate)				
$CH_3(CH_2)_3CHLiCO_2Li$	93	94	95[g]	
(Nonanoate)				
$CH_3(CH_2)_6CHLiCO_2Li$	92	92	95[h,i]	95[h,i]

[a] Anion solutions were quenched after stirring for 30 min at 25°. [b] Determined by mass spectral and nmr analyses of the corresponding methyl esters. [c] Accuracy ±2%. [d] Dianion preparations with 1 mol of HMPA, except for acetate. [e] Determination by glpc analysis of the corresponding methyl esters except for acetate. [f] Dianion preparation with 3 mol of HMPA; analysis by nmr. [g] *n*-Butylmalonic acid, mp 102–103° (lit. mp 103–104): P. E. Verkade and J. Coops, Jr., *Recl. Trav. Chim. Pays-Bas*, 49, 568 (1930). [h] *n*-Heptylmalonic acid, mp 96–97° (lit. mp 83–95°): I. C. Promé and C. Asselineau, *Bull. Soc. Chim. Fr.*, 1964, (1964). [i] The same value was obtained after heating for 5 hr at 50° followed by carbonation.

α-Branched Acids.—The results for the α metalations of α-branched acids, with and without HMPA, as determined by deuteration and carbonation quenchings are recorded in Table III. The values derived by the two techniques give good agreement for the individual acids in both solvent systems.

The data for α alkylations of a homologous series of α-branched hexanoic acids are assembled in Table IV and graphed in Figure 2 for comparison with the corresponding data obtained for α alkylations in HMPA solutions.

Olefinic Acids.—The monounsaturated acids, 10-undecenoic and *cis*-9-octadecenoic acids, were converted to their α anions and the acids then were regenerated by aqueous quenching. The recovered acids

TABLE II

PREPARATIONS OF α-ALKYL CARBOXYLIC ACIDS

Reactants: Acid	Reactants: Alkyl bromide	Product acid[a]	Yield, %[b]: THF	Yield, %[b]: THF–HMPA	Bp, °C (mm), or mp, °C
CH_3CO_2H	$CH_3(CH_2)_3Br$	*n*-Hexanoic		34,[c] 58,[d] 82[e]	
$CH_3CH_2CO_2H$	$CH_3(CH_2)_3Br$	2-Methylhexanoic	53[f]	78	64[g]
$CH_3(CH_2)_4CO_2H$	CH_3CH_2Br	2-Ethylhexanoic		98[h]	70 (0.1)[i]
$CH_3(CH_2)_4CO_2H$	$CH_3(CH_2)_2Br$	2-Propylhexanoic		98[h]	92 (0.3)[j]
$CH_3(CH_2)_4CO_2H$	$CH_3(CH_2)_3Br$	2-Butylhexanoic	42[h]	90, 97[h]	89 (0.1)[k]
$CH_3(CH_2)_5CO_2H$	$CH_3(CH_2)_3Br$	2-Butylheptanoic	43	93	70–73 (30)[l]
$CH_3(CH_2)_7CO_2H$	CH_3CH_2Br	2-Ethylnonanoic			108–110 (0.2)[m]
$CH_3(CH_2)_7CO_2H$	$CH_3(CH_2)_2Br$	2-Propylnonanoic			124 (0.2)[n]
$CH_3(CH_2)_7CO_2H$	$CH_3(CH_2)_3Br$	2-Butylnonanoic	34	91	128–130 (0.2)[o]
$CH_3(CH_2)_7CO_2H$	$CH_3(CH_2)_7Br$	2-Heptyldecanoic		92	167–168 (0.5)[p]
$CH_3(CH_2)_{12}CO_2H$	$CH_3(CH_2)_3Br$	2-Butyltetradecanoic	29	87	172–173 (0.5)[q]
$CH_3(CH_2)_{16}CO_2H$	$CH_3(CH_2)_3Br$	2-Butyloctadecanoic	44	87[r]	45–46
$CH_2{=}CH(CH_2)_8CO_2H$	$CH_3(CH_2)_3Br$	2-Butyl-10-undecenoic		90	145–147 (0.5)
cis $CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2H$	$CH_3(CH_2)_3Br$	2-Butyl-*cis*-9-octadecenoic	25	90	199–200 (0.05)

[a] All compounds gave acceptable C and H analyses (±0.4). The data were made available to the referees and to the Editor. [b] Alkylations of dianions conducted at 25° for 90 min. Yields are based on distilled, recrystallized or chromatographed product except where indicated. [c] Using 1 mol of HMPA per mol of acid; obtained 17% 2-butylhexanoic acid as by-product. [d] Using 3 mol of HMPA per mol of acid; obtained 7% 2-butylhexanoic acid as by-product. [e] Using 3 mol of HMPA per mol of acid; dianion prepared at 50° (2 hr) prior to alkylation; obtained 8% 2-butylhexanoic acid as by-product. [f] This yield was reported in ref 10 for the alkylation of the mixed Li–Na metalated acid. [g] Lit. bp 105° (5 mm): P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **98**, 5 (1932). [h] Conversions determined by glpc. [i] Lit. bp 88–89° (1 mm): K. Shishido, K. Sei, and H. Nozaki, *J. Org. Chem.*, **27**, 2681 (1962). [j] Lit. bp 97° (1 mm): J. Wotiz, *J. Amer. Chem. Soc.*, **73**, 693 (1951). [k] Lit. bp 137–138° (12 mm): R. Friedling, S. N. Aminov, and A. Terent'ev, *Dokl. Akad. Nauk SSSR*, **156** (5), 1133 (1964). [l] Lit. bp 170–173° (28 mm): M. Sy, N. Buu-Hoi, and N. Dat-Xuong, *C. R. Acad. Sci.*, **239**, 1224 (1954). [m] Lit. bp 117–118° (5–6 mm): E. Bowden and H. Adkins, *J. Amer. Chem. Soc.*, **56**, 689 (1934). [n] Lit. bp 160–162° (10 mm): J. Braun, H. Kräper, and H. Weinhaus, *Chem. Ber.*, **62B**, 2880 (1929). [o] Lit. bp 148–149° (3 mm): B. F. Armendt and R. Adams, *J. Amer. Chem. Soc.*, **52**, 1289 (1930). [p] Lit. bp 184–187° (2–3 mm): C. M. Creer and R. Adams, *ibid.*, **52**, 2541 (1930). [q] Lit. bp 180–184° (4 mm): W. M. Stanley, M. S. Jay, and R. Adams, *ibid.*, **51**, 1261 (1929). [r] Insolubility of the dianion was overcome by using 2 mol of HMPA per mol of acid.

TABLE III

DETERMINATION OF α-ANION CONTENT.[a] REACTION OF METALATED α-BRANCHED CHAIN NONANOIC ACIDS WITH D_2O AND CO_2

Dianion	α-D Acid, %[b,c]: THF	α-D Acid, %[b,c]: THF–HMPA	Dioic acid: Product	Dioic acid: Conversion, %[d]	Dioic acid: Mp, °C
2-Methylhexanoic[e]			Methylbutyl malonic	78	97–98[f]
2-Ethylnonanoic	42		Ethylheptyl malonic	43, 72[g]	105–106
2-Propylnonanoic	41	40	Propylheptyl malonic	43, 67,[g] 15[h]	110.0–111.5[i]
2-Butylnonanoic	34, 92[h]	36	Butylheptyl malonic	38, 86,[j] 94[h]	117.5–118[l]
2-Octylnonanoic (2-Heptyldecanoic)		28	Octylheptyl malonic	31, 93[k]	*m*

[a] 30 min allotted for metalations before termination. [b] Analysis by mass spectrometry. [c] Accuracy ±2%. [d] Determined on the methyl esters by glpc; same results obtained for carbonation of the α anion in the presence and absence of HMPA. [e] Used in place of 2-methylnonanoic acid. [f] Lit. mp 98–99°: A. Norris and T. W. J. Tucker, *J. Amer. Chem. Soc.*, **55**, 4700 (1933). [g] Carbonation carried out on dianion following removal of volatile reaction products. [h] Dianion prepared with 6 mol of lithium diisopropylamide per mol of acid. [i] Lit. mp 110–111°: J. Braun, H. Kräper, and H. Wienhaus, *Chem. Ber.*, **62B**, 2880 (1929). [j] Six hours allotted for metalation before carbonation. [k] Metalation conducted at 50° for 2 hr; same result obtained in presence or absence of HMPA. [l] Lit. mp 117°: P. A. Levene and F. A. Taylor, *J. Biol. Chem.*, **54**, 351 (1922). [m] Oily product purified by chromatography on a silica gel column gave satisfactory elemental analysis.

showed no change in position of the double bond on the basis of the following analyses. The acids were oxidatively cleaved and the resulting mono- and dibasic acids obtained were quantitatively analyzed by glpc. Trans absorption of the double bond at 965 cm^{-1} was absent in both examples, indicating neither migration nor isomerization of the double bond.

Following confirmation of the integrity of the double bond in the dianions of 10-undecenoic and *cis*-9-octadecenoic acids, butylation gave their respective α-butyl unsaturated acids (Table II).

Linoleic acid (*cis*-9-*cis*-12-octadecadienoic acid) reacts with lithium diisopropylamide to give a highly colored anion solution. Butylation of this anion solution resulted in a complicated glpc pattern of alkylated and nonalkylated products.

Discussion

α Metalations.—Lithium salts of straight-chain carboxylic acids (monoanions) have low solubilities in THF; for example, lithium nonanoate has a solubility of 1.5 mg/100 ml in THF that increases to only 20 mg/100 ml in solutions containing 2 molar equiv of HMPA. Despite their low concentrations in these media, the salts α lithiate in both media to the extent of 95%. The resultant solutions were colloidal (milky) in THF and homogeneous (clear) in the presence of HMPA. Carboxylate salts at the extreme ends of the series, namely lithium acetate and lithium octadecanoate, metalated poorly in THF solutions, but high conversions were obtained in HMPA solutions.

HMPA participates in the metalation process by solubilizing the dianions. Organolithium compounds

TABLE IV

PREPARATIONS OF TRIALKYL ACETIC ACIDS[a]

Reactant acid	Product[b,c]	Registry no.	Yield, % 25°[d]	Yield, % 50°[e]	Bp, °C (mm)
2-Methylhexanoic	2-Methyl-2-butylhexanoic	17306-50-2	85		97 (0.1)
2-Ethylhexanoic	2-Ethyl-2-butylhexanoic	32970-62-0	78		136–137 (1)
2-Propylhexanoic	2-Propyl-2-butylhexanoic	33021-12-4	72	93	142 (0.5)
2-Butylheptanoic	2,2-Dibutylheptanoic	32970-63-1	68	93	140–142 (0.5)
2-Butylnonanoic	2,2-Dibutylnonanoic	32970-64-2	66	92	160–161 (0.2)

[a] α-Butylation of the α-branched acids using butyl bromide. [b] Separation of product from unreacted acid is effected by shaking the mixture with 10% $NaHCO_3$ solution (see Experimental Section). [c] All compounds gave acceptable C and H analyses (±0.4). The data were made available to the referees and to the Editor. [d] Preparation of dianion in THF without HMPA at 25° for 30 min before alkylation. [e] Preparation of dianion in THF without HMPA at 50° for 2 hr before alkylation.

EFFECTS OF CHAIN BRANCHING AND SOLVENTS

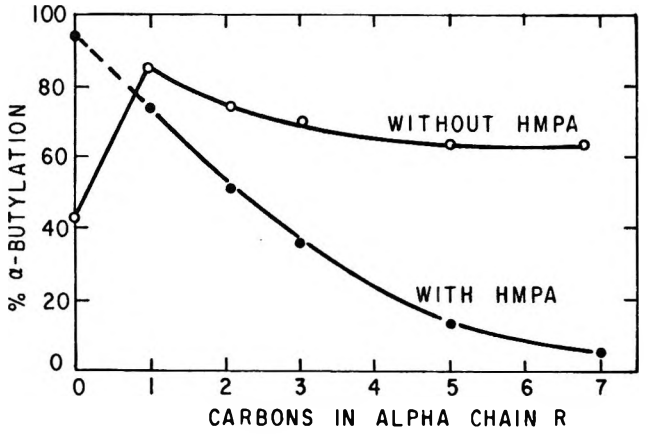
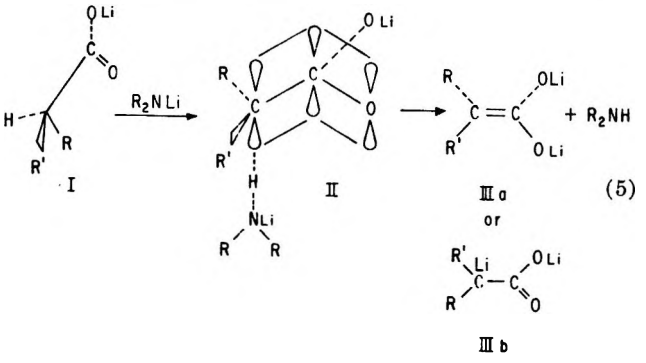


Figure 2.—Effect of HMPA on the per cent butylation of α-branched hexanoic acids. Reaction at 26° using 1 mol of HMPA per mol of acid.

are known to associate to higher molecular weight aggregates, their degrees of polymerization (n = 2–6) varying with solvent and structure.[11] The polymeric structures are altered by polar solvents by interactions that lengthen or cleave the electrostatic bond of the ion pair.[12] The interaction between certain organolithium compounds has been described as an association between one molecule of HMPA and the counterion in the solvent-separated ion pair.[13] From the limited data acquired, the behavior of α-lithiated lithium salts of carboxylic acids may be explained in these terms. They exhibit high degrees of association in THF (n = 65–250) based on molecular weight averages for dianions prepared from α and β olefinic acids).[14] These extensively high associations would account for their colloidal state in THF. It may be inferred from their solubilization in HMPA solutions that the aggregations are disrupted to simpler species by a molecular association with the dipolar solvent. Although the plot in Figure 1 was derived to determine the optimum HMPA–dianion relationship for alkylating dianions (at a prescribed set of conditions), the attainment of maximum yield where HMPA and dianion are present in equimolar amounts suggests a 1:1 correspondence in their association.

The lithium salts of α-branched chain acids, in contrast to straight-chain acids, are completely soluble in THF. The rate of dianion formation of the α-branched acids in comparison with the straight-chain members under similar reaction conditions (25°, quenched after 30 min) is slower and depends upon the size of their alkyl branchings, *e.g.*, yields diminished from α-methyl (78%) to α-octyl (31%) (Table III and Figure 2). Longer times were required to complete the metalations at room temperature as observed with α-butylnonanoic acid, which produced 86% dianion in 6 hr. Proton abstraction from the α position in the branched-chain acids is apparently hindered by classical steric effects, although these may possibly include stereoelectronic factors related to the type noted for α deprotonation of cyclic ketones.[15] The α-alkyl substituents attached to the acetate moiety in salt I (eq 5) hinder formation of the transition state



(5)

II in which the p orbitals are in contiguous overlap. The activation energy of this barrier is surmounted by a small elevation in temperature to 50°. Under these conditions α metalations are approximately quantitative (94%) in 2 hr.

The formation of carbanions from their "carbon acid" in metalation reactions may be simply treated as an equilibrium process.[16] Accordingly, α metalation of carboxylate salts may be formulated as an equilibrium in accordance with eq 6. Our efforts to improve

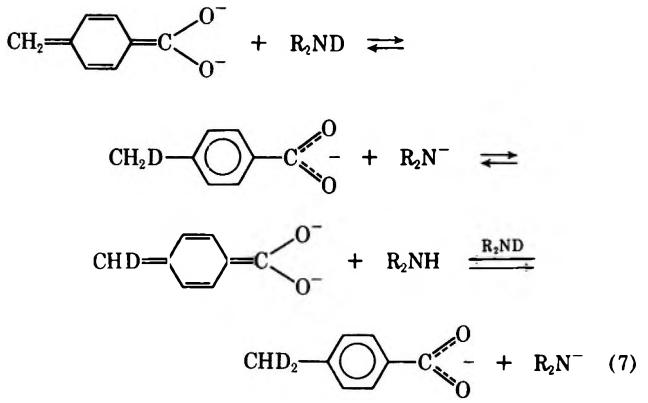
$$RR'CHCOO^- + R_2N^- \rightleftharpoons RR'C^-COO^- + R_2NH \quad (6)$$

metalations of α-branched acids at ambient temperature by treatment of the reaction as an equilibrium phenomenon gave only limited success. In accord-

(11) J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).
(12) H. E. Zaugg and A. D. Schaefer, *J. Amer. Chem. Soc.*, **87**, 1857 (1965).
(13) L. L. Chan and J. Smid, *ibid.*, **90**, 4654 (1968).
(14) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **36**, 3290 (1971).
(15) E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6269 (1956).
(16) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.

ance with the mass law, removal of the volatile diisopropylamine is expected to shift the reaction to completion. The removal of the amine and solvent at 25° *in vacuo* did indeed increase the α anion content from about 43 to 68%, although prolonged evacuation gave no further improvement in dianion content. Increasing the relative concentration of reactants on either side of the equilibrium was not successful. On the left side of the equation, increasing the concentration of lithium diisopropylamide from 2 to 6 mol per mol of acid decreased the dianion content to 15%, a result that is contrary to expectation; on the right side of the equation addition of the large excess of diisopropylamine (6 mol per mol of acid) to a solution of dianion (94% content based on carbonation) had no effect on the dianion content. The extent of formation of α-branched dianion exceeds 90% but the reaction is evidently not prescribed by simple equilibrium considerations.

Additional but incomplete evidence for an equilibrium process was suggested from our lithiation studies carried out on the aromatic acids, *o*- and *p*-toluic acids.[17] Proton abstraction from the methyl substituent leads to dianion formation by extensive conjugation. Deuteration of the dianions by *N*-deuteriodiisopropylamine results in multiple exchange with the methyl protons as indicated by eq 7 for two stages of exchange.

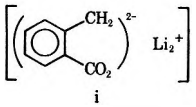


(7)

α Alkylations.—In view of the nearly quantitative conversions of straight-chain acids to dianions in either solvent system, α alkylations would be expected to be essentially quantitative in both systems. Quantitative conversion was observed in HMPA solution in which alkylation was completed in 90 min at 25° with 1.5 mol of butyl bromide per mol of carboxylic acid. In THF alone under the same conditions, conversions were only 30–50%. Attempts to quantitate alkylations in THF by imposing more forceful conditions, *e.g.*, conducting alkylations with 3 mol of butyl bromide per mol of acid at 50° for 5 hr, did not improve yields beyond 87%. These comparative experiments illustrate that HMPA, in addition to solubilizing dianions, also accelerates the alkylation rates. A preliminary kinetic investigation of the alkylations was attempted to determine the rates in THF and THF–HMPA solutions but the complexity of the kinetics precluded their continuation for our purpose. The examination, nevertheless, confirmed a rate enhancement in HMPA relative to THF: it was observed that the dianion of nonanoic acid (0.163 *M*) in THF at 10° is half butylated by butyl bromide (0.393 *M*) in 140 min compared to only 20 min in THF containing HMPA (0.163 *M*). The largest alkylation rate occurred when HMPA and dianion are equimolar (Figure 1).

Detailed studies on organolithium reagents underscore the complexity of their reactions.[11,19] In the reported cases, the reactions are described by fractional orders which are in accord with the aggregation state of the organolithium. The aggregation state is disrupted by complexation with polar solvents in formation of a solvent-separated ion pair of higher reactivity than the original aggregate. A strong dipolar solvent like HMPA (μ = 4.30 D[20]) should accordingly be more efficient in associations with metalated carboxylates than THF (μ = 1.7 D[21]) by forming a complex of higher reactivity, presumably a solvent-separated ion pair.

Straight-chain acids are cleanly monoalkylated in HMPA solutions, since the gas chromatograms show no significant evidence of dialkylated products. For example, propionic acid gave only 0.4% dialkylation in comparison with 14% dialkylation obtained from the mixed lithium–sodium salts of the dianions.[10] Even acetic acid may be primarily monoalkylated to the straight-chain homolog, if extensive conversion of acetate to dianion is obtained before alkyl halide is added (eq 8a). In THF α metalation of lithium acetate is slow and incomplete so that alkylation to the straight-chain homolog (primary product) encounters competition by metalation (eq 8b) and alkylation of the homolog to α-branched acid (secondary product). The combined effects of HMPA and temperature on controlling acetate conversion to dianion is made evident by the following observations. Metalation and butylation of acetic acid at 25° in THF containing 1 molar equiv of HMPA gave a mixture of 34% *n*-hexa-



$$\bar{C}H_2COO^- + RBr \longrightarrow RCH_2COO^- + Br^- \quad (8a)$$

$$[(CH_3)_2CH]_2\bar{N} + RCH_2COO^- \longrightarrow [(CH_3)_2CH]_2NH + R\bar{C}HCOO^- \quad (8b)$$

(17) Unpublished studies: Prior to completing this work, Creger[18] had reported the α-lithiation of *o*-, *m*- and *p*-toluic acids and dimethylbenzoic acid. He prepared lithiated lithium *o*-toluate (i) and, after removal of volatile components, obtained nmr evidence for the retention of diisopropylamine in the ratio of one molecule of amine per molecule of *o*-toluic acid. Treatment of the dianion resulted in no incorporation of deuterium in the isolated *o*-toluic acid. This was explained by his proposal of a molecular complex formed between the dianionic species and diisopropylamine wherein the amino proton is exclusively transferred in a noncompetitive process. In our limited study, we α-lithiated *o*- and *p*-toluic acids and by carbonation determined that 25 and 75% dianions, respectively, had formed. After quenching the dianions with deuterium oxide, analysis of the isolated acids showed 6 and 32% deuterium (d_1 only) incorporation in *o*- and *p*-toluic acids, respectively. These experiments did indicate the occurrence of a competitive proton-transference process, although it is less extensive than in an aliphatic dianion. The evidence of exchange was acquired on the *p*-toluate dianion and was obtained by the sequence of operations involving removal of all volatile components after dianion formation, injection of *N*-deuteriodiisopropylamine, reevacuation for removal of volatile components, and finally quenching with H_2O. Deuterium incorporation (mass spectral analysis) was observed in 52% of the molecules in a distribution consisting of 31.7% d_1, 15.9% d_2, and 4.8% d_3.

(18) P. L. Creger, *J. Amer. Chem. Soc.*, **92**, 1396 (1970).

(19) P. West, R. Waack, and J. I. Purmort, *ibid.*, **92**, 840 (1970).

(20) J. P. Fayet, *C. R. Acad. Sci., Ser. C*, **270**, 9 (1970).

(21) C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill, New York, N. Y., 1955, p 299.

noic and 17% α-butylhexanoic acids, whereas in 3 molar equiv of HMPA, the primary product increased to 58% and the secondary product diminished to 7%. Reaction at 50° in 3 molar equiv of HMPA gave a mixture of 82% *n*-hexanoic and 8% α-butylhexanoic acids that together represent 98% alkylation.

α-Metalated α-branched acids are slowly alkylated in THF at 25° in formation of trialkyl acetic acids in moderate yields [65–75% for the series with the exception of the α-methyl branch (85%)]. Because the yield of alkylated product (Table IV) is about twice the initial carbanion concentration at room temperature (Table III), it is apparent that α anion is progressively generated during the course of alkylation. Since the formation of tertiary carbanions is accelerated at 50° and approaches completion at this temperature, alkylations to trialkyl acetic acid derivatives are correspondingly rapid and complete.

In HMPA solutions, the yields of α-butylated products derived from a series of α-alkyl hexanoic acids sharply decline as the alkyl branch is increased from methyl (75%) to heptyl (9%) (Figure 2). The decline in yield is accompanied by the formation of olefin which stems from attack on alkyl bromide by unreacted diisopropylamide and tertiary carbanion and which occurs to a greater extent in HMPA. The evidence for the participation of both bases in the elimination reaction is indicated by the following results. (i) In solutions without carboxylic acid, elimination from alkyl halide by amide base in THF–HMPA was about twice the elimination noted in THF without cosolvent. In the butylation of 2-butylheptanoic acid in THF–HMPA, (ii) the dianion preparation of 34% content gave only 15% alkylation but approximately 80% elimination, whereas (iii) the dianion preparation of 94% content gave 50% alkylation and 50% elimination. (iv) The dianion preparation of 94% content in THF–HMPA, stripped free of diisopropylamine to eliminate the possibility of amide reformation, also on butylation gave 50:50 alkylation–elimination. The results of i and ii demonstrate elimination through the agency of amide base and those of iii and iv by α-branched dianion. The mechanism of the elimination reaction is unclear but it is unquestionably assisted by HMPA, which seems to amplify the steric effect of branching in the dianion.

Effect of Mixed Cations. –The low solubilities of sodium and potassium carboxylates illustrated by potassium nonanoate (1.5 mg/100 ml THF and 17 mg/100 ml THF containing 2 molar equiv of HMPA) are comparable to the low solubilities of lithium carboxylates. The poorly solubilized sodium and potassium salts α-lithiate in THF in 2 hr to the extent of 25 and 1% dianion, respectively (Table V), compared to 95% in 30 min for lithium salts. After metalation of the potassium salt, the dianion content was determined by carbonation and alkylation on the separate solution and solid phases of the heterogeneous mixtures and observed to be present only in the solution phase. HMPA (2 molar equiv) increased metalation from 1 to 14% (Table V). Efforts to increase dianion formation by heating to 40° resulted in considerable loss of dianion by reaction with solvent. Apparently, dianions associated with higher atomic weight counterions are more ionic and more reactive with solvents than dianions associated exclusively with lithium counterions.

TABLE V

REACTIONS OF α-METALATED SALTS OF NONANOIC ACID IN THF.[a] EFFECT OF COUNTERION ON YIELDS

	Yield, %		
Counterions	D_2O	CO_2	RBr
$[Li_2]^{2+}$	95	98	~50, 95 (HMPA)[b]
$[LiNa]^{2+}$	23[c]	10,[c] 27[d]	86[d]
$[LiK]^{2+}$	0[c,e]	1,[c,f] 14 (HMPA)[c,g]	100,[c] 15 (HMPA)[c,g]

[a] Reactions in THF solution except where indicated. [b] 1 molar equiv of HMPA. [c] Sodium and potassium nonanoates were prepared by neutralization in methanol and the isolated salts were dried over P_2O_5 prior to use. [d] Sodium salt prepared *in situ* by NaH neutralization of nonanoic acid. [e] Extent of formation too small for reliable determination. [f] Determined by glpc analysis. [g] 2 molar equiv of HMPA.

Because of the limited metalation of potassium salts, lithium diisopropylamide is largely unreacted and potentially available to dehydrohalogenate alkyl halides. Nevertheless, α alkylations of potassium salts are quantitative in THF when solutions contain excess amide and alkyl halide. The surprising quantitative nature of this reaction indicates the continuous generation of dianion during alkylation and the dianion's relatively greater reactivity toward halide. In the presence of HMPA, dehydrohalogenation by amide predominates, since dianion formation is insufficiently increased.

Analytical and Preparative Utility of Quenching Agents.[22]—Alkylations provide useful information on dianions but cannot be used for quantitative measurements of dianion content. The metalated carboxylate salts are not quenched by alkyl halides but metalation continues simultaneously with alkylation of the dianions. On the other hand, the results of carbonation and deuteration of α-lithioalkanoates (Tables I and III) indicate the utility of these methods for dianion analyses. Reliance on carbonation and deuteration as measures of dianion content was based on the nearly quantitative metalations obtained from straight-chain carboxylates in THF–HMPA at −5° and from α-branched chain carboxylates in THF at 50°.

Carbonation and deuteration have some limitations in dianion analyses, although carbonation is generally more sensitive. A striking difference between these methods of analysis is revealed by α-lithiated *p*-toluate, which carbonated to the extent of 75% compared to 32% deuteration.[17] In some instances, deuteration may provide a more reliable index of dianion content; for example, other workers have shown that carbonation values of sodium α-sodioacetate were about half those of deuteration.[23,24] In that case, complications inherent in the technique were evident since the carbonations of a heterogeneous solid phase system were forced at high temperatures. By comparison, carbonations of the analogous α-lithiated acetate were mild when carried out in liquid media below room temperature, the results (Table I) being in reasonable accord with alkylations (Table III).

(22) The authors are indebted to one reviewer for his thorough review and comments that encouraged a more comprehensive examination of this work.

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Quantitative carbonations and deuterations of dianions should be advantageous in synthesis for preparations of alkyl malonic acids and α-deuterioalkanoic acids, respectively. The method is particularly valuable for preparations of α-deuterio acids compared to alternative methods that require high temperatures and long reaction times and are less specific for monodeuteration.[25-27]

Olefinic Acids.—Isolated double bonds in olefinic acids such as 10-undecenoic and *cis*-9-octadecenoic acids are not altered positionally or geometrically in formation of their dianions by lithium diisopropylamide. These olefinic acids are alkylated to good yields of α-branched unsaturated acids (see Table II).

A highly colored solution is produced when linoleic acid is metalated. Alkylation of the dianion results in a complicated mixture of products. The reactive double bonds of this acid are altered by strong basic media, since it is well established that skipped double bonds in this acid conjugate and isomerize geometrically by proton abstraction from the reactive 11-carbon position.[28] The products from this reaction were not further characterized but are expected to be mixtures of α-branched and chain-branched diolefinic acids containing isomerized double bonds.

Experimental Section

Materials.—Tetrahydrofuran was obtained dry and oxygen free by distillation from a solution of ketyl (benzophenone and sodium). Hexamethylphosphoramide was distilled from sodium hydride at reduced pressure and stored over molecular sieves under a nitrogen atmosphere. *n*-Butyllithium (1.6 *M* in hexane solution) was obtained from Foote Mineral Co. Diisopropylamine was distilled and stored over 5A molecular sieves prior to use.

Equipment.—Analyses by glpc were conducted on an F & M Model 500 gas chromatograph equipped with a thermal conductivity detector and disc integrator and using the following columns: 6 ft × 1/4 in. 25% DEGA, 2% H_3PO_4; 6 ft × 3/16 in. 10% Dow Corning 710 silicone oil, 2% H_3PO_4.

α-Anion Preparation.—The following procedure described for the preparation of *n*-nonanoic acid in THF–HMPA solution is typical of the general method used for both straight-chain and α-branched-chain acids. The method was appropriately modified, where warranted, for variations in temperature and use or concentration of HMPA.

Anhydrous THF (65 ml) and diisopropylamine (9.8 g, 0.098 mol) were added to a dry flask purged with nitrogen and maintained under a nitrogen atmosphere. After cooling the mixture to −20°, *n*-butyllithium in *n*-hexane solution (60 ml of 1.6 *M*, 0.098 mol) was added in a controlled manner to prevent the temperature from exceeding 0°. *n*-Nonanoic acid (6.95 g, 0.044 mol) was added dropwise while maintaining the temperature of the reaction below 0°. A milky white solution formed that turned homogeneous after the addition of HMPA (9 ml, 0.05 mol). The reaction was completed by stirring at room temperature for 30 min.

α-Anion Analysis.—THF and THF–HMPA solutions (50 ml each) containing the dianion of a carboxylic acid (0.0125 mol) were prepared from carboxylic acid (0.0125 mol) and lithium diisopropylamide (0.0265 mol) by the above procedure.

A. D_2O Quenching.—An aliquot (10 ml) was sampled, quenched in D_2O (9 ml, 0.45 mol), and stirred for 5 min. After acidification with 10% HCl and three extractions of the aqueous phase with petroleum ether (bp 30–60°) (10-ml portions), the petroleum ether solutions were combined and extracted with 10% HCl to facilitate removal of HMPA and with five portions of water to reestablish the protium content of the carboxylic acid grouping. The organic layer was dried, the solvent was evaporated, and the residue was distilled. Methyl esters of the acids were prepared by means of diazomethane and passed through a preparative gas chromatograph (3 ft × 3/8 in. column, 10% DEGS), and the trapped samples were examined for their deuterium content by mass spectrometry. Methyl esters of the original nondeuterated acids were used as standards for examination of their P + 1 peak contribution.

B. CO_2 Quenching.—The remainder of the dianion solution was treated with CO_2 (bone dry) for 1 hr at −10° in preparation of the malonic acid derivatives. Because of the low solubility of several dioic acids in petroleum ether, diethyl ether was used as the solvent in the work-up and for isolation of the acids. The malonic acid derivatives and unreacted acid were esterified with diazomethane and the methyl ester mixture was examined by glpc.

Preparation of α-Alkyl Carboxylic Acids from Straight-Chain Acids. A. With HMPA.—The following preparation of 2-butylnonanoic acid in THF solution containing HMPA illustrates the general procedure.

n-Butyl bromide (6.05 g, 0.044 mol) was added rapidly at 0° to the dianion of nonanoic acid prepared in HMPA solution (see α-Anion Preparation). The exothermicity of the reaction elevated the temperature to 18°. The reaction was completed by stirring the mixture for 1.5 hr at room temperature. The product was isolated by neutralization with ice-cold 10% HCl (150 ml) and two extractions with petroleum ether (175-ml portions). (Note: sufficient HCl should be present to neutralize HMPA as well as the alkali.) The combined organic layers were washed three times with 10% HCl (100-ml portions), water, and saturated sodium chloride solutions. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated after filtration to obtain the crude product (9.1 g, 97% yield) consisting of 2-butylnonanoic acid (99%) and nonanoic acid (1%) by glpc analysis. Pure 2-butylnonanoic acid (8.5 g, 90% yield) was obtained by distillation, bp 128–130° (0.2 mm).

B. Without HMPA.—The procedure is identical with the above method except for the omission of HMPA in the reaction. The anion solution remained cloudy and heterogeneous. The addition of *n*-butyl bromide was not accompanied by a significant, exotherm due to the slow rate of reaction. After work-up, distillation of the resulting product gave pure 2-butylnonanoic acid (3.2 g, 34%).

Lithiation and Alkylation of Potassium Nonanoate.—The following reaction described for potassium nonanoate may be applied to other potassium and sodium salts of monocarboxylic acids.

Potassium nonanoate (8.6 g, 0.044 mol) on addition to a solution of lithium diisopropylamide (0.066 mol) in THF (65 ml) at 25° formed the dianion in association with mixed lithium–potassium counterions. Butylation with butyl bromide (13.7 g, 0.1 mol), was monitored by glpc analysis and was quantitatively completed in 2 hr.

Preparation of Trialkyl Acetic Acids From α-Alkyl Carboxylic Acids. A. General Method.—Solutions of metalated α-branched carboxylic acids were prepared as described under α-Anion Preparations. Formation of these dianions was completed by heating at 50° for 2 hr. The alkylations and general work-up were carried out as described above. Final separation of the trialkyl acetic acid from unreacted dialkyl acetic acid was effected by preferential aqueous sodium bicarbonate extraction of the latter acid from a petroleum ether solution of the mixture.

B. "Equilibrium" Method *via* Removal of Diisopropylamine.—A solution of 2-propylnonanoic acid (1 g, 0.005 mol) was metalated with lithium diisopropylamide (1.06 g, 0.01 mol) in THF (20 ml) by the described procedure. After stirring the solution at room temperature for 30 min, the solvent and liberated diisopropylamine were removed at room temperature *in vacuo* (0.1 mm) in a film evaporator and the volatile components were recovered in an acetone–Dry Ice trap. The crystalline salts were redissolved in anhydrous THF and carbonated at −10° for 1 hr. The products were isolated by elementary work-up procedures and esterified by diazomethane. Analysis by glpc indicated that the ester mixture consisted of 2-propyl-2-heptyl dimethyl malonate (67.8%) and 2-propyl methyl pelargonate (32.2%).

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Acidification with dilute HCl of the trapped volatile solution, evaporation of solvent and water by azeotropic distillation, and drying for 5 hr at 120° yielded diisopropylamine hydrochloride (1.12 g) equivalent to 65% metalation.

A control experiment was carried out on diisopropylamine (1 g, 0.01 m) as a check on the method for the quantitative isolation of the amine salt and to ensure the absence of water of hydration after drying. Acidification, isolation of the salt, and drying gave a dry salt weighing 1.31 g (theory 1.35 g).

C. Isolation of Olefin.—A dianion solution prepared from 2-butylheptanoic acid (3.0 g, 0.016 mol) was alkylated at 25° with 1-bromooctane (3.08 g, 0.016 mol) in THF–HMPA in the manner formerly described. After reaction (1.5 hr), the solution was acidified and extracted with petroleum ether and the extracts were reextracted sequentially with dilute HCl, water, and 5% sodium hydroxide solution. The solvent was removed by distillation and the residue was carefully distilled (bp 120–121°) to give a colorless liquid fraction (1.45 g, 80% yield) which was confirmed to be 1-octene by glpc retention time, ir, and nmr. The same procedure carried out at 25° in the absence of HMPA gave 0.54 g of 1-octene (30% yield).

α Metalation of Oleic Acid. Analysis for Double Bond Migration (von Rudloff Method).[29]—Oleic acid was α metalated in the prescribed manner and regenerated from the salt by acidification.

Samples (0.035 g each) of the treated oleic acid and of untreated oleic acid as a control were separately weighed into Erlenmeyer flasks (50 ml capacity). To each flask were added the oxidant solution [7 ml of an aqueous solution comprised of sodium periodate (21 g) and potassium permanganate (25 ml of 0.1 *N*) diluted to 1 l.], potassium carbonate (0.009 g in 1.4 ml of water), and *tert*-butyl alcohol (8.5 ml). The solutions were stirred (72 hr) until clear. A pellet of potassium hydroxide was added to each solution, the alcohol was removed on a steam bath under a stream of nitrogen, and the solutions were acidified with several drops of concentrated HCl. The materials were extracted three times with chloroform (25 ml portions) and dried, and the combined solutions were evaporated to the organic acid residues under a nitrogen stream. These were each esterified to the methyl esters and analyzed *via* glpc. The samples gave identical chromatograms consisting of only two products, dimethyl azelate and methyl pelargonate, in agreement with the retention times for the authentic compounds.

Registry No.—2-Butyloctadecanoic acid, 33021-13-5; 2-butyl-10-undecenoic acid, 32970-65-3; 2-butyl-*cis*-9-octadecenoic acid, 33016-09-0; ethylheptylmalonic acid, 32970-66-4; actylheptylmalonic acid, 32970-67-5.

Acknowledgment.—The authors express their appreciation to S. F. Osman and C. J. Dooley for the mass spectral analyses.

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Metal Ion Promoted Dehydrohalogenation of Secondary Alkyl Halides

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Orientation in dehydrohalogenation of 2-alkyl iodides and bromides by silver nitrate, perchlorate, acetate, and nitrite and mercuric nitrate in aprotic and protic solvents under conditions of kinetic control has been determined. Strong preference for formation of internal olefins and *trans*- to *cis*-2-alkene ratios of 1.1–2.8 were observed. In aprotic solvents, metal halide catalysis was negligible, and orientation was somewhat affected by variation of the metal ion, the metal counterion, the leaving group, the solvent, and the 2-alkyl group. Reactions in protic solvents were complicated by metal halide catalysis. The mechanism of metal ion promoted dehydrohalogenation of 2-alkyl halides is discussed.

Electrophilic assistance by mercuric and silver ions in replacement reactions of alkyl halides has been the subject of numerous investigations in recent years.[3-16] Kinetic and stereochemical studies have revealed that silver salt catalyzed substitutions of 2-alkyl halides do not proceed by a simple carbonium ion mechanism.[5,6,12-14] Such conclusions raise questions concerning the mechanism of the competing elimination reactions, about which little is known. An investigation of metal ion promoted dehydrohalogenation from 2-alkyl halides therefore seemed warranted.

Of the available methods for studying β eliminations from 2-substituted alkanes, determination of the effect of experimental variables upon positional and geometrical orientation[17,18] of the olefinic products appeared most suitable for an initial examination.

In only two instances has orientation in metal ion assisted elimination from 2-alkyl halides been considered. Unfortunately, in the reported olefin-forming reaction of 2-bromobutane with silver nitrate in water and *tert*-butyl alcohol,[20] possible complication due to catalysis by silver bromide[16,21] was apparently ignored. In the second study, reaction of 2-octyl bromide with silver nitrate in acetonitrile produced approximately 2% 1-octene and 14% 2-octenes.[12] The isomeric 2-octenes were not separated.

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(2) Presented by G. M. P. at the 26th Annual Northwest Regional Meeting of the American Chemical Society, Bozeman, Mont., June 1971.

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(17) For 2-substituted alkanes, positional orientation refers to the relative proportions of 1- and 2-alkenes formed, whereas geometrical orientation compares the relative amounts of *trans*-2-alkene and *cis*-2-alkene produced.

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TABLE I

OLEFINIC PRODUCTS FROM REACTIONS OF 2-BUTYL HALIDES WITH SILVER NITRATE[a] IN DMSO AT 50°

Run	X of 2-BuX	Reaction time, min	Butene yield, %	Total butenes, % 1-Butene	*trans*-2-Butene	*cis*-2-Butene	*trans*-2-Butene: *cis*-2-butene
1	I	2	18	8.5 ± 0.3[b]	59.4 ± 0.2	32.1 ± 0.2	1.85
2	I	10	36	8.3 ± 0.3	58.8 ± 0.2	32.9 ± 0.1	1.79
3	I	10	30	8.5 ± 0.1	58.5 ± 0.1	33.0 ± 0.2	1.77
4	Br	2	1	7.5 ± 0.1	62.5 ± 0.2	30.0 ± 0.1	2.08
5	Br	3	2	7.4 ± 0.2	62.3 ± 0.2	30.2 ± 0.2	2.06
6	Br	10	10	7.4 ± 0.2	61.7 ± 0.1	30.9 ± 0.1	2.00

[a] [2-BuX] = 0.22 *M*, [$AgNO_3$] = 0.30 *M*. [b] Standard deviation from repetitive analysis of trapped butene mixture.

TABLE II

OLEFINIC PRODUCTS FROM REACTIONS OF 2-BUTYL HALIDES WITH METAL SALTS IN APROTIC SOLVENTS AT 50°

Run	Silver salt[a]	X of 2-BuX[b]	Solvent	Butene yield, %[c]	Total butenes, % 1-Butene	*trans*-2-Butene	*cis*-2-Butene	*trans*-2-Butene: *cis*-2-butene
3	$AgNO_3$	I	DMSO	36	8.3 ± 0.3[d]	58.8 ± 0.2	32.9 ± 0.1	1.79
6	$AgNO_3$	Br	DMSO	10	7.4 ± 0.2	61.7 ± 0.1	30.9 ± 0.1	2.00
7	$AgNO_3$	I	DMF	50	9.5 ± 0.2	55.4 ± 0.1	35.1 ± 0.2	1.58
8	$AgNO_3$	Br	DMF	20	8.2 ± 0.2	57.5 ± 0.1	34.3 ± 0.1	1.68
9	$AgNO_3$	I	MeCN	24	8.4 ± 0.1	57.8 ± 0.1	33.8 ± 0.1	1.71
10	$AgNO_3$	Br	MeCN	2	7.6 ± 0.4	60.4 ± 0.5	32.0 ± 0.1	1.89
11	$AgClO_4$	I	DMSO	63	8.3 ± 0.3	58.9 ± 0.3	32.8 ± 0.3	1.80
12	$AgClO_4$	Br	DMSO	11	7.0 ± 0.2	61.7 ± 0.1	31.2 ± 0.2	1.98
13	$AgNO_3$	I	DMAC[e]	48	9.0 ± 0.2	57.8 ± 0.3	33.1 ± 0.3	1.74
14	$AgNO_3$	I	NMP[f]	52	9.4 ± 0.5	57.2 ± 0.8	33.3 ± 0.4	1.72
15	$AgNO_3$	I	Pyridine	6	6.8 ± 0.3	67.9 ± 0.4	25.4 ± 0.4	2.68
16	AgOAc[g]	I	DMSO	9	8.4 ± 0.1	57.7 ± 0.1	34.0 ± 0.1	1.70
17	$AgNO_2$[g]	I	DMSO	12	7.2 ± 0.1	60.6 ± 0.1	32.2 ± 0.3	1.88
18	$Hg(NO_3)_2$[g]	I	DMSO	46	9.2 ± 0.1	54.1 ± 0.1	36.6 ± 0.2	1.48

[a] [$AgNO_3$], [$AgClO_4$] = 0.30 *M*. [b] [2-BuX] = 0.22 *M*. [c] Ten-minute reaction period. [d] Standard deviation from repetitive analysis of trapped butene mixture. [e] *N*,*N*-Dimethylacetamide. [f] *N*-Methyl-2-pyrrolidone. [g] Saturated solution.

Results

Reactions were carried out, at 50.0°, in an apparatus continuously bubbled with nitrogen gas and volatile products were collected in a trap cooled in liquid nitrogen. Because of the low stability of silver–olefin complexes,[22] interference by complexation of the liberated alkenes was deemed unlikely. A uniform 10-min reaction period was employed, unless otherwise noted. The relative proportions of the three isomeric olefins were determined by gas–liquid partition chromatography (glpc). Alkene yields were estimated by comparison of the olefin peak areas with those from reaction of 2-bromobutane with potassium *tert*-butoxide in DMSO. Reactions of 2-bromoalkanes with potassium *tert*-butoxide in DMSO produce nearly quantitative yields of alkenes.[23]

Isomerization of product olefins under the reaction conditions was shown to be negligible. As described in the Experimental Section, the isomeric composition of synthetic mixtures of butenes was unaffected by silver nitrate or a mixture of silver iodide and silver nitrate in DMSO or in *tert*-butyl alcohol.

Reactions with Metal Salts in Aprotic Solvents.— Olefinic products from reactions of silver nitrate with 2-butyl iodide and bromide in DMSO are presented in Table I. Under the reaction conditions, 2-butyl chloride produced no olefins when treated with silver nitrate in DMSO.[24] Runs 2 and 3, which were conducted by different researchers with a 1-year time interval, demonstrate the reproducibility of the measured relative olefinic proportions and butene yields. The virtual constancy of the relative butene proportions with varying reaction time indicates little catalytic activity of precipitated silver halides.[25] Kinetic evidence for the relative unimportance of catalysis by silver bromide in reactions of 2-octyl bromide with silver nitrate in acetonitrile has been previously reported.[12]

The effect of leaving groups upon orientation in reactions of 2-butyl iodide and bromide with silver nitrate and perchlorate in aprotic solvents is depicted in Table II. The variations in relative olefinic proportions with change of leaving groups are small, but are outside of experimental error. A consistently lower percentage of 1-butene and higher *trans*- to *cis*-2-butene ratio is observed when the iodide leaving group is replaced by bromide (compare runs 3 and 6, 7 and 8, 9 and 10, 11 and 12).

The consequence of varying the metal cation, the metal anion, and the aprotic solvent may also be inferred from the data in Table II.[26] In DMSO, the relative olefinic proportions in eliminations from 2-butyl iodide are somewhat affected by a change of metal ion from silver(I) to mercury(II) (runs 3 and 18) and exhibit slight sensitivity to variation of the silver counterion (runs 3, 11, 16, 17). A small effect of solvent upon orientation in silver nitrate induced eli-

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(24) (a) Small amounts of olefin resulted from treatment of 2-chlorobutane with silver nitrate in pyridine at 68.8° for 27.1 days.[15] (b) Reaction of 2-octyl bromide with silver nitrate in acetonitrile is 450 times more rapid than that of 2-octyl chloride.[12]

(25) In contrast, reactions of 2-butyl halides with silver nitrate and perchlorate in tetramethylene sulfone (sulfolane) were found to be strongly catalyzed by silver halides, producing olefinic proportions markedly different from those in reactions performed in other aprotic solvents.

(26) Lead and thallium nitrates in DMSO were ineffectual in promoting elimination from 2-iodobutane at 50°.

TABLE III

OLEFINIC PRODUCTS FROM REACTIONS OF 2-ALKYL BROMIDES WITH SILVER NITRATE IN DMSO AT 50° [a,b]

Run	Registry no.	R of RBr	Total alkenes, % 1-Alkene	Total alkenes, % *trans*-2-Alkene	Total alkenes, % *cis*-2-Alkene	*trans*-2-alkene: *cis*-2-alkene
6		2-Butyl	7.4 ± 0.2[c]	61.7 ± 0.1	30.9 ± 0.1	2.00
19	107-81-3	2-Pentyl	7.5 ± 0.2	68.3 ± 0.9	24.2 ± 1.1	2.82
20	3377-86-4	2-Hexyl	8.8	64.7	26.5	2.44

[a] Ten-minute reaction period. [b] [2-RBr] = 0.22 *M*, [$AgNO_3$] = 0.3 M. [c] Standard deviation from repetitive analysis of trapped alkene mixture.

TABLE IV

OLEFINIC PRODUCTS FROM REACTIONS OF 2-BUTYL HALIDES WITH SILVER AND MERCURIC NITRATE IN PROTIC SOLVENTS AT 50°

Run	X of 2-BuX	Salt	Solvent	Reaction time, min.	Butene yield, %	Total butenes, % 1-Butene	Total butenes, % *trans*-2-Butene	Total butenes, % *cis*-2-Butene	*trans*-: *cis*-2-Butene
21	I[a]	$AgNO_3$	H_2O	0.5	4	4.9 ± 0.1[b]	54.1 ± 0.2	41.0 ± 0.2	1.32
22				1.5	28	5.0 ± 0.1	53.7 ± 0.1	41.3 ± 0.1	1.30
23				10	38	5.2 ± 0.1	53.3 ± 0.2	41.6 ± 0.3	1.28
24	I[c]	$AgNO_3$	*tert*-BuOH	0[d]		8.7	47.8	43.5	1.12
25				0.5	10	8.5 ± 0.2	47.7 ± 0.5	43.8 ± 0.4	1.09
26				1.5	19	8.0 ± 0.3	47.3 ± 0.3	44.8 ± 0.1	1.06
27				10	89	7.5 ± 0.1	46.3 ± 0.1	46.2 ± 0.1	1.00
28	Br[a]	$AgNO_3$	H_2O	0[d]		3.6	57.2	39.2	1.46
29				1.5	1	3.6 ± 0.2	56.4 ± 0.2	40.0 ± 0.3	1.42
30				3	2	3.6 ± 0.2	55.5 ± 0.2	40.9 ± 0.3	1.36
31				10[f]	9	4.1 ± 0.1	53.0 ± 0.1	42.9 ± 0.1	1.23
32	Br[e]	$AgNO_3$	*tert*-BuOH	0[d]		7.6	56.8	35.6	1.60
33				1.5	1	7.5 ± 0.5	55.1 ± 0.5	37.5 ± 0.2	1.47
34				3	6	6.9 ± 0.2	54.3 ± 0.2	38.9 ± 0.2	1.40
35				10	25	7.0 ± 0.2	46.4 ± 0.1	46.7 ± 0.1	1.00
36	Br[g]	$Hg(NO_3)_2$	*tert*-BuOH	1.5	6	0.8 ± 0.1	70.0 ± 0.4	29.2 ± 0.4	2.40
37				3	32	1.1 ± 0.1	65.2 ± 0.2	33.7 ± 0.2	1.94
38				10	36	3.0 ± 0.1	60.5 ± 0.1	36.5 ± 0.1	1.66
39	Br[e]	$AgNO_3$	*tert*-BuOH	10	24	6.6 ± 0.2	47.4 ± 0.2	46.0 ± 0.1	1.03
40	Br[h]	$AgNO_3$	*tert*-BuOH	10	50	11.6 ± 0.1	29.2 ± 0.3	59.2 ± 0.3	0.49

[a] [2-BuX] = 0.22 *M*, [$AgNO_3$] = 0.30 *M*. [b] Standard deviation from repetitive analysis of trapped alkene mixture. [c] [2-BuI] = 0.10 *M*, [$AgNO_3$] = 0.11 *M*. [d] Extrapolated. [e] [2-BuBr] = [$AgNO_3$] = 0.11 *M*. [f] Reference 20 reports a 29% yield of butenes after 4 hr at 70°. [g] [2-BuBr] = 0.22 *M*, [$Hg(NO_3)_2$] = saturated solution. [h] [2-BuBr] = 0.11 *M*, [$AgNO_3$] = 0.10 *M*, AgBr present.

minations from 2-butyl iodide is also noted (runs 3, 7, 9, 13, 14, 15).

The relative olefinic proportions from reactions of a homologous series of 2-bromoalkanes with silver nitrate in DMSO are displayed in Table III. Variation of the 2-alkyl group affects geometrical orientation with the *trans*- to *cis*-2-alkene ratio increasing in the order 2-butyl < 2-hexyl < 2-pentyl.

Reactions with Metal Salts in Protic Solvents.— In order to assess possible catalytic activity of precipitated metal halides in reactions of 2-butyl iodide and bromide with silver and mercuric nitrates in water and *tert*-butyl alcohol, the effect of reaction time variation upon relative olefinic proportions was examined. The results, which are recorded in Table IV, demonstrate significant metal halide catalysis in four of the five reactions investigated. Such effects are particularly evident in *tert*-butyl alcohol. The apparent order of catalytic activity is AgI < AgBr ~ $HgBr_2$.[27]

For the silver nitrate promoted eliminations, the olefinic products derived solely from the silver nitrate induced reaction may be estimated by extrapolation of the product proportions to zero time. Comparison of the present extrapolated results for reaction of 2-butyl bromide with silver nitrate in *tert*-butyl alcohol (run 32) with those previously reported[20] reveals large discrepancies in both the per cent of 1-butene and *trans*- to *cis*-2-butene ratio. Such variance may be ascribed to complicating silver bromide catalysis in the earlier study.

Examination of the reaction of 2-butyl bromide with silver nitrate in *tert*-butyl alcohol in the presence of silver bromide (run 40) provides confirmation of metal halide catalysis in reactions between 2-alkyl halides and silver or mercuric nitrates in protic solvents. The presence of a small amount of *in situ* generated silver bromide (a milky suspension) strongly affects both the relative proportions of isomeric olefins and the butene yield (compare runs 39 and 40). It is noteworthy that a *trans*- to *cis*-2-butene ratio of much less than unity was observed. Treatment of 2-butyl bromide with externally synthesized silver bromide in *tert*-butyl alcohol in the absence of silver nitrate produced no olefins.

Discussion

Since the observed olefinic proportions for metal ion promoted elimination from 2-butyl halides are similar to the thermodynamic butene distribution from acid-catalyzed butene isomerization,[28] it was necessary to establish the stability of product olefins to the reaction conditions. The relative olefinic proportions of synthetic butene mixtures with composition far from the

(27) Walton and Spiro have noted greater catalysis by AgI than AgBr in reactions of ethyl iodide with silver nitrate in water.[16]

(28) Sulfuric acid catalyzed equilibration of butenes yields the following butene proportions: 1-butene, 6 ± 1%; *trans*-2-butene, 68 ± 1%; *cis*-2-butene, 26 ± 1%; and *trans*,*cis*-2-butene, 2.6.[20]

TABLE V

Synthetic mixture	Injected into	% 1-Butene	% *trans*-2-Butene	% *cis*-2-Butene
A		31.0 ± 0.7	52.5 ± 0.2	16.4 ± 0.1
A	$AgNO_3$ in DMSO at 50°	31.0 ± 0.5	53.2 ± 0.3	15.8 ± 0.5
A	AgI–$AgNO_3$ in DMSO at 50°	30.8 ± 0.4	52.9 ± 0.2	16.2 ± 0.4
B		30.3 ± 0.2	52.8 ± 0.2	16.8 ± 0.1
B	$AgNO_3$ in *t*-BuOH at 50°	29.4 ± 0.5	53.8 ± 0.2	16.8 ± 0.4
B	AgI–$AgNO_3$ in *t*-BuOH at 50°	29.2 ± 0.2	53.3 ± 0.3	17.5 ± 0.1

thermodynamic distribution were unaffected by silver nitrate or a mixture of silver iodide and silver nitrate in DMSO or *tert*-butyl alcohol. Therefore, the observed olefinic products are those of kinetic control.

Orientation in Aprotic Solvents.—Before discussion of metal ion promoted eliminations from 2-alkyl halides in aprotic solvents, it is pertinent to establish the orientation anticipated for β eliminations proceeding by concerted and free carbonium ion mechanisms. A characteristic feature of base-catalyzed β elimination from 2-alkyl halides in dipolar aprotic solvents is high *trans*- to *cis*-2-alkene ratios.[19] Thus, ratios of 3.0–4.0 are observed for eliminations from 2-butyl halides induced by a wide variety of bases in DMSO and DMF.[19] For a free 2-alkyl cation, *trans*- to *cis*-2-alkene ratios of unity are anticipated.[20,29,30]

It is immediately apparent from the data presented in Tables II and III that in the metal ion promoted dehydrohalogenation of 2-alkyl halides in aprotic solvents geometrical orientation obtains which is intermediate between that observed in concerted, base-catalyzed elimination and that expected for a free carbonium ion intermediate.

From product and kinetic studies of the reaction of 2-octyl halides with silver nitrate in acetonitrile, Pocker has proposed rate-determining formation of a carbonium nitrate silver halide ion quadruplet which subsequently decomposes to form substitution and elimination products.[12] The observed strong preference for formation of Saytzeff alkenes in the present study is indicative of olefin-forming transition states with a high degree of carbonium ion character.[31] The small but significant variation of orientation with change in the metal ion, the leaving group, the silver counterion, and the 2-alkyl group (Tables II and III) rule out a free carbonium ion intermediate or even a carbonium–metal counterion ion pair. However, these results are consistent with slight encumbrance of a carbonium ion intermediate by the other members of an ion quadruplet in the olefin-forming transition states. The limited sensitivity of the olefinic proportions to variation of the metal counterion and dipolar aprotic solvent (Table II) indicates that proton loss from the high-energy carbonium ion intermediate is quite unselective. Nevertheless, the change in orientation observed for the basic solvent pyridine suggests that proton removal by the solvent obtains.

Orientation in Protic Solvents.—For reactions of 2-butyl iodide and bromide with silver and mercuric nitrates in water and, particularly, in *tert*-butyl alcohol, the relative proportions of the three isomeric olefins change with time (Table IV). Complication due to metal halide produced in the reactions is evident. Graphical extrapolation to zero time produces estimates of the relative olefinic proportions for reactions of silver nitrate with 2-butyl iodide and bromide in water and *tert*-butyl alcohol. Such extrapolated values should be considered more reliable than those previously reported for dehydrohalogenation of 2-butyl bromide with silver nitrate.[20]

In general, the results for silver nitrate promoted elimination from 2-iodo- and 2-bromobutane in water and *tert*-butyl alcohol roughly parallel those in aprotic solvents. Thus, orientation varies with change in leaving group; the ratio of geometric isomers is greater than unity; and strong preference for formation of internal olefins is found (Table IV). Such observations again suggest an ion quadruplet intermediate. The greater sensitivity of orientation to change of leaving group in *tert*-butyl alcohol than in water or the aprotic solvents may be due to a "tighter" ion quadruplet in solvents of low polarity.

It is interesting to speculate briefly concerning the effect of insoluble metal halide upon metal-promoted elimination from 2-alkyl halides. A small amount ($AgNO_3$:AgBr = 10:1) of *in situ* generated silver bromide profoundly influences orientation and olefin yield in reactions of 2-butyl bromide with silver nitrate in *tert*-butyl alcohol (compare runs 39 and 40, Table IV). However, externally synthesized silver bromide in the absence of silver nitrate was ineffectual in inducing elimination. These observations indicate a heterogeneous reaction of alkyl halide with silver ions adsorbed onto the silver bromide surface. The strikingly different geometrical orientation (preferential formation of *cis*-2-butene) observed in the presence of silver bromide is characteristic of contact eliminations.[33]

Experimental Section

Materials.—Reagent grade aprotic solvents were used directly from freshly opened bottles. *tert*-Butyl alcohol was purified as before.[23] 2-Alkyl halides were available from earlier studies.[19,23]

Procedure.—The apparatus, procedure, and glpc analysis previously utilized for study of base-catalyzed dehydrohalogenation of 2-alkyl halides in aprotic solvents were used.[19,23] Solvolytic elimination from 2-butyl iodide in DMF and DMSO was shown to be negligible under the employed conditions. A nitrogen sweep rate of 60 ml/min was used. Olefin yields were estimated by glpc comparison of amounts of butenes derived from a given reaction with that from reaction of 2-bromobutane with potassium *tert*-butoxide in dimethyl sulfoxide. Nearly quantitative olefin yields are anticipated for the latter reaction.[23] Estimated uncertainty in butene yield is ±0.1 times the reported value.

Stability of Olefinic Products to Reaction Conditions.—To test for isomerization of olefinic products under the conditions of silver ion promoted eliminations from 2-alkyl halides, a synthetic

(29) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Amer. Chem. Soc.*, **79**, 2888 (1957).

(30) In the sulfuric acid catalyzed isomerization of butenes, *trans*- and *cis*-2-butene are formed from the 2-butyl cation at the same rate.[29]

(31) In the solvolysis of 2-butyl iodide in DMSO in the presence of 2,6-lutidine at 50 . 97% of the product olefins are 2-butenes.[32]

(32) R. A. Bartsch, unpublished results.

(33) H. Noller, P. Andreu, and M. Hunger, *Angew. Chem., Int. Ed. Engl.*, **10**, 172 (1971).

mixture of butenes was injected into (1) a 0.30 *M* solution of silver nitrate in DMSO; (2) a mixture of silver iodide and silver nitrate in DMSO which resulted from the reaction of 0.22 *M* 2-butyl iodide with 0.30 *M* silver nitrate in DMSO; (3) a 0.11 *M* solution of silver nitrate in *tert*-butyl alcohol; and (4) a mixture of silver iodide and silver nitrate in *tert*-butyl alcohol which resulted from the reaction of 0.10 *M* 2-butyl iodide with 0.11 *M* silver nitrate in *tert*-butyl alcohol. The results which follow (Table V) demonstrate the stability of olefinic products to the reaction conditions.

Reaction of 2-Butyl Bromide with Silver Nitrate in *tert*-Butyl Alcohol in the Presence of Silver Bromide.—To 5 ml of a 0.11 *N* solution of silver nitrate in *tert*-butyl alcohol in the reaction apparatus was injected 0.2 ml of 0.5 *N* solution of HBr in slightly aqueous *tert*-butyl alcohol. Into the resulting milky white suspension was immediately injected 0.08 g of 2-butyl bromide. The reaction was then carried out in the customary fashion.

It was subsequently demonstrated that reaction of 2-butyl bromide with HBr in *tert*-butyl alcohol produced negligible yields of butenes under the reaction conditions.

Registry No.—$AgNO_3$, 7761-88-8; 2-BuI, 513-48-4; 2-BuBr, 78-76-2; $AgClO_4$, 7783-93-9; AgOAc, 563-63-3; $Hg(NO_3)_2$, 10045-94-0; AgI, 77883-96-2; AgBr, 7785-23-1; $HgBr_2$, 7789-47-1.

Reactions of π-Allylic Nickel(II) Bromide with Organic Halides. A Novel Synthesis of Monoterpenoid Compounds[1]

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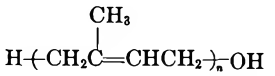
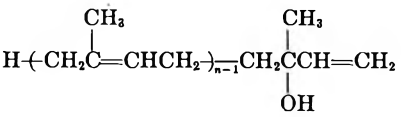
A novel synthesis of monoterpenoid compounds from isoprene as a major starting material is described. Reaction of isoprene with *N*-bromosuccinimide in ethanol or glacial acetic acid gives 1-bromo-4-ethoxy-2-methyl-2-butene and 4-acetoxy-1-bromo-2-methyl-2-butene, respectively. The two allylic bromides react in benzene with 1,1-dimethyl-π-allylnickel bromide prepared by reacting prenyl bromide with excess nickel carbonyl to give geranyl ethyl ether and geranyl acetate, respectively. Under similar condition, ethyl γ-bromosenecioate and 1,1-dimethyl-π-allylnickel bromide give ethyl geranate in a moderate yield.

The synthesis of polyprenyl alcohols **1** and **2**, which are not only naturally occurring terpenes but also serve as important materials for synthesis, is achieved by a five-carbon (isoprene skeleton) homologation involving successive two- and three-carbon elongation reactions.[2] This method suffers from low over-all yields in the synthesis of higher analogs of **1** and **2**.

Previously we have reported[3] that such a C-5 homologation can be achieved in one step by using an organophosphorus compound, 4-pentyn-1-ylidenetriphenylphosphorane. This reacted with a isoprenoid ketone to afford its higher analogs *via* the intermediate γ,δ-unsaturated acetylene. In the present paper we describe another method for the desired chain extension, using π-allylnickel complexes.

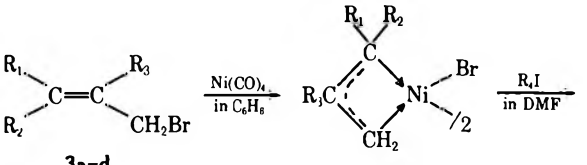


1



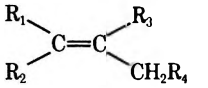
2

During the last decade, organo-transition metal compounds have been shown to be interesting and useful substances in synthetic chemistry. For instance, an efficient and useful method for the attachment of an allylic group **3** to an alkyl, vinyl, or aryl unit by means of π-allylnickel reagents has recently been described by Corey and Semmelhack.[4] However, because these π-allylnickel halides **4**, which can be obtained expeditiously by the reaction of allylic halides **3** with nickel carbonyl in benzene are somewhat unstable and air-sensitive, the purification of these π-allylic complexes must be conducted below room temperature with rigorous exclusion of oxygen. In a preliminary experiment we found that this troublesome purification can be omitted without any noticeable diminution of yields to give **5a–d** (See Experimental Section).



3a–d **4a–d**

a, $R_1 = H$; $R_2 = H$; $R_3 = H$
b, $R_1 = H$; $R_2 = H$; $R_3 = CH_3$
c, $R_1 = CH_3$; $R_2 = H$; $R_3 = H$
d, $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$



5a–d, $R_4 = C_6H_5$
e, $R_1 = R_2 = R_3 = H$; $R_4 = (CH_3)_2CHCH_2CH_2$

We intended at first to generate the π-allylnickel complex from an allylic halide possessing a functionalized carbon substituent which can be elaborated to an allylie halide function. Thus, ethyl *trans*-γ-bromocrotonate (**6a**) was heated with nickel carbonyl in benzene, the progress of the reaction being evidenced by evolution of carbon monoxide and the appearance

(1) A portion of this paper was presented at the 23rd Annual Meeting of the Chemical Society of Japan, Tokyo, April 1970.

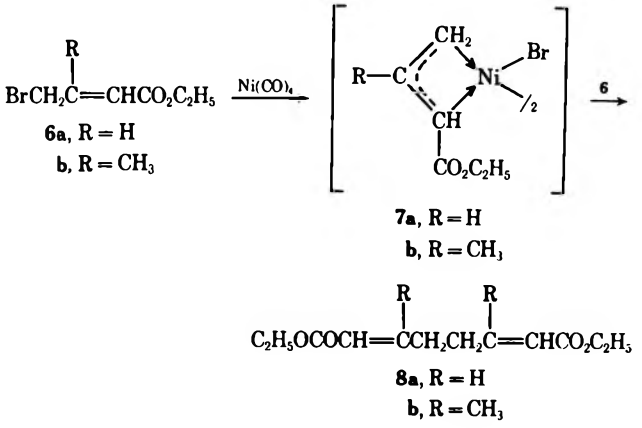
(2) (a) W. Kimel and A. C. Cope, *J. Amer. Chem. Soc.*, **65**, 1992 (1943); (b) O. Isler and K. Doebel, *Helv. Chim. Acta*, **37**, 225 (1954); (c) G. Saucy and R. Marbet, *ibid.*, **50**, 2091 (1967).

(3) K. Sato, S. Inoue, and S. Ota, *J. Org. Chem.*, **35**, 565 (1970).

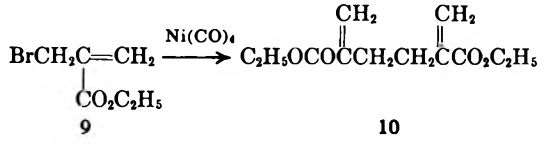
(4) (a) E. J. Corey and M. F. Semmelhack, *J. Amer. Chem. Soc.*, **89**, 2755 (1967); (b) E. J. Corey and E. K. Wat, *ibid.*, **89**, 2757 (1967); (c) E. J. Corey and E. Hamanaka, *ibid.*, **89**, 2758 (1967).

of characteristic red color. However, treatment of the mixture with iodobenzene in *N*,*N*-dimethylformamide (DMF) resulted in the isolation of the self-condensation product of **6a**, diethyl 2,6-octadiene-1,8-dioate (**8a**) as a mixture of trans,trans and trans,cis isomers, but no cross-coupled product, ethyl γ-phenylcrotonate. Iodobenzene was recovered almost quantitatively.

To determine the manner in which the dimerization product **8a** was formed, the reaction mixture was quenched with hydrogen bromide before being treated with iodobenzene. By this operation **8a** was also obtained. This indicates that the rate of the coupling reaction of **6a** with the π complex **7a** formed by the initial interaction of **6a** and nickel carbonyl is very rapid even in nonpolar solvent such as benzene, in which coupling of π-allylnickel bromide with allyl bromide proceeds to only a slight degree (*vide supra*), although the corresponding methyl ester of **6a** has been reported[5] to undergo dimerization in ethyl ether, acetone, or methyl acetate in the presence of nickel carbonyl.

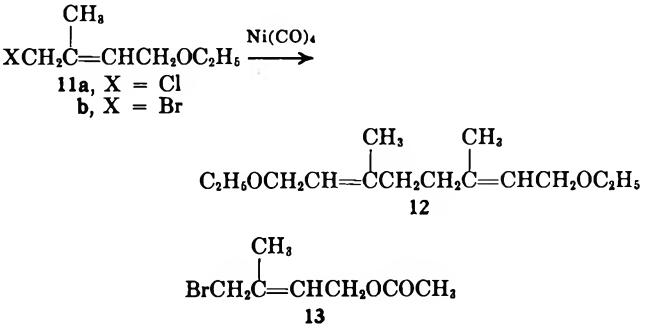


A similar result was obtained with ethyl γ-bromosenecioate (**6b**). Because these results might reflect an activating effect of the ethoxycarbonyl group on the allylic bromide function of 4-bromo-2-butenoate esters **6a** and **6b**, it became of interest to study ethyl α-bromomethylacrylate (**9**), a positional isomer of **6a**. When **9** was reacted with nickel carbonyl in benzene at 50°, the dimer of **9**, diethyl 2,5-dimethylene-1,6-hexanedioate, was obtained in 70% yield.[6]



We were thus unable to isolate ethoxycarbonyl-substituted π-allylnickel bromides irrespective of the position of substitution. Hence, we considered the use of another series of allylic halides, *i.e.* allyl halides substituted with a protected hydroxymethyl radical. Thus, *trans*-1-chloro-4-ethoxy-2-methyl-2-butene[7] (**11a**) was heated with nickel carbonyl in benzene at 50°; the mixture gradually exhibited a pink coloration, indicating very slow reaction of the substrate with nickel carbonyl. Heating for 3 hr, followed by the usual work-up resulted in almost quantitative recovery of the starting chloride **11a**.

On the other hand the bromo analog of **11a**, *trans*-1-bromo-4-ethoxy-2-methyl-2-butene (**11b**) reacted with nickel carbonyl in benzene at 50° with evolution of carbon monoxide, but the corresponding π complex could not be isolated and the self-coupled dimer, 1,8-diethoxy-3,6-dimethyl-2,6-octadiene (**12**) was obtained instead in 72% yield as a mixture of trans,trans and trans,cis isomers.



In contrast to **11a** and **11b**, *trans*-4-acetoxy-1-bromo-2-methyl-2-butene (**13**) was found to react clearly with nickel carbonyl under similar condition. However, neither the starting bromide **13** nor the self-coupled dimer was obtained from the reaction mixture. It seems most probable that isoprene was generated in this reaction by analogy to what was observed in the use of 1-acetoxy-4-chloro-2-butene.[8]

The results described so far led to the conclusion that allylic bromides **6a**, **6b**, **9**, and **11b** are so reactive that they react easily with the π complexes generated by the reaction of the bromide itself with nickel carbonyl to afford self-coupled dimers. These results suggested in turn that these reactive bromides would readily react with a simple π-allylnickel bromide under the present reaction conditions.

Thus, the investigation was extended to the reactions of the π-allylnickel complexes **4** with allylic bromides **6b**, **9**, etc. As expected, dropwise addition of ethyl γ-bromosenecioate (**6b**) to the solution of 1,1-dimethyl-π-allylnickel bromide (**4d**) in benzene at 50° resulted in the formation of ethyl 3,7-dimethyl-2,6-octadienoate (ethyl geranate) (**14**) in 40% yield. Surprisingly, however, similar reaction of ethyl α-bromomethylacrylate (**9**) with **4d** in benzene at 50° for 3 hr afforded 70% ethyl 2,5-dimethylene-1,6-hexanedioate (**10**), which had previously been obtained by the direct reaction of **9** with nickel carbonyl. On the other hand, the reaction of **11b** and **13** with **4d** gave geranyl ethyl ether (**15**) and geranyl acetate (**16**), respectively, in moderate yields.

The distinct course of the reaction of **9** with **4d** can be interpreted as follows: the cross-coupling reaction of **9** and **4d** to give ethyl 2-methylene-6-methyl-5-heptenoate is slower than the ligand-exchange reaction[9]

(5) G. P. Chiusoli and G. Cometti, *Chim. Ind. (Milan)*, **45**, 401 (1963).

(6) E. J. Corey and M. F. Semmelhack [*Tetrahedron Lett.*, 6237 (1966)] reported that the corresponding π-allylic complex of **9** was obtained by the reaction of bis(1,5-cyclooctadiene)nickel or nickel carbonyl with **9** in benzene, but the experimental detail was not described.

(7) W. Oroshnik and R. A. Mallory, *J. Amer. Chem. Soc.*, **72**, 4608 (1950).

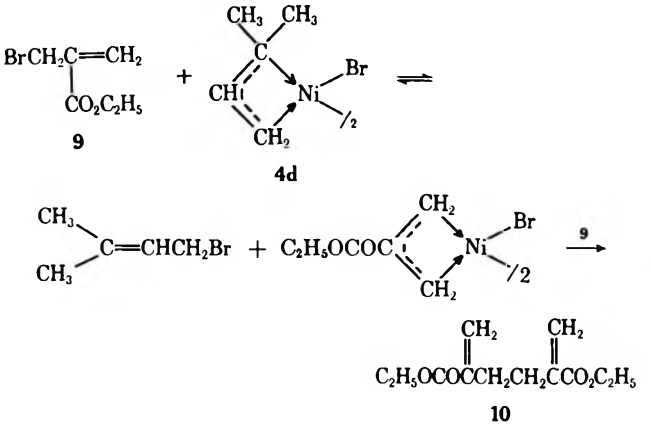
(8) J. B. Mettalia and E. H. Specht, *J. Org. Chem.*, **32**, 3941 (1967).

(9) E. J. Corey, *et al.* [*J. Amer. Chem. Soc.*, **90**, 2417 (1968)], reported the occurrence of rapid exchange reactions according to the equation (A = allyl)

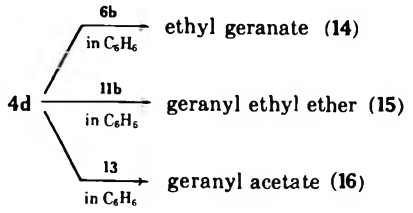
$$(\pi\text{-A}^1\text{NiBr})_2 + 2\text{A}^2\text{Br} \rightleftharpoons (\pi\text{-A}^2\text{NiBr})_2 + 2\text{A}^1\text{Br}$$

under several solvent systems including tetraglyme, DMF, and toluene. The present observation is an another example of rapid exchange reaction occurring in hydrocarbon solvent.

between **9** and **4d** which generates prenyl bromide (**3d**) and 2-carbethoxy-π-allylnickel bromide. The latter compound then reacts rapidly with **9** to afford **10**.



All the other reactions afforded mainly cross-coupling products. The formation of dimers **8b** and **12** was minimal indicating that the exchange reactions[9] occur only to a very small extent, if at all.



It is evident that the present reaction provides a highly convenient procedure for achieving a C-4 or C-5 homologation. At the same time extension of this reaction provides a facile route for the synthesis of polyprenyl alcohols **1** and other acyclic terpenes using isoprene as the sole starting material. The realization of this synthesis as well as the examination of the stereochemical course of the reaction including π-allylic nickel complex is in progress in these laboratories.

Experimental Section

General.—Boiling points are uncorrected. Infrared spectra were recorded with a Hitachi Model EPI-S2 spectrophotometer. Nmr spectra were obtained on a JEOL Model C-60 spectrometer in carbon tetrachloride solution with tetramethylsilane as an internal reference. Gas chromatography was carried out on a Shimadzu GC-4A gas chromatograph using a 3-mm, 300-cm column of 25% silicone DC-200 or 3-mm, 190-cm of 15% Carbowax 20M on Celite 545 with He as the carrier gas.

Allyl bromide,[10] methallyl bromide,[11] crotyl bromide,[12] prenyl bromide,[13] isoamyl iodide,[14] ethyl γ-bromocrotonate,[15] ethyl γ-bromosenecioate,[15] ethyl α-bromomethylacrylate,[16] and 4-acetoxy-1-chloro-2-methyl-2-butene[7,17] were prepared by the methods described in the literature. The other chemicals were commercially available and purified by usual procedures before use. All reactions of π-allylnickel complexes were carried out in a nitrogen atmosphere.

Allylbenzene (5a). The Typical Procedure of the Reaction of Iodobenzene with Simple π-Allylic Nickel Bromide.—Allyl bromide (6.8 g, 50 mmol) and nickel carbonyl (14.5 g, 85 mmol) in benzene (85 ml) were heated with stirring at 50° for 3 hr. Benzene and any remaining nickel carbonyl were removed under reduced pressure at room temperature and the residue was dissolved in DMF (40 ml) with cooling in an ice-water bath. To this solution was added iodobenzene (8.6 g, 42 mmol) in DMF (40 ml) at 22° over 1 hr. Stirring was continued further for 2 hr. The mixture was then poured into ice-water, acidified by hydrochloric acid, and extracted with petroleum ether (bp 40–60°). The organic layer was washed with saturated brine and dried with magnesium sulfate. Distillation gave allylbenzene (**5a**) (4.1 g, 82%): bp 74–77° (46 mm), n^{20}D 1.5103 (lit.[18] bp 158–159°, n^{20}D 1.5104).

A similar procedure afforded methallylbenzene [**5b**, 81%, bp 77–78° (32 mm), n^{20}D 1.5094], crotylbenzene [**5c**, 75%, bp 72–76° (23 mm), n^{20}D 1.5221],[19] and prenylbenzene [**5d**, 75%, bp 74–77° (8 mm), n^{20}D 1.5165] by using methallyl bromide, crotyl bromide, and prenyl bromide, respectively, instead of allyl bromide.

6-Methyl-1-heptene (5e).—Allyl bromide (4.5 g, 37 mmol) and nickel carbonyl (8.5 g, 50 mmol) were allowed to react by the procedure described above. Solvent was removed under reduced pressure, DMF (30 ml) was added in return, and isoamyl iodide (5.3 g, 27 mmol) in DMF (30 ml) solution was added at 22°, and the mixture was allowed to react for 19 hr. Distillation gave 6-methyl-1-heptene (0.9 g, 30%): bp 110–113.5° (676 mm), n^{20}D 1.4052 (lit.[20] bp 113.2°, n^{20}D 1.4068).

This compound was identified by comparison of ir, nmr, and vpc retention time with those of an authentic sample obtained from allyl magnesium chloride and isoamyl chloride in tetrahydrofuran.[20]

Diethyl 2,6-Octadiene-1,8-dioate (8a).—Ethyl *trans*-γ-bromocrotonate (5.8 g, 30 mmol) in benzene (32 ml) was added dropwise to a solution of nickel carbonyl (8.5 g, 50 mmol) in benzene (48 ml) at 50° during 1.5 hr, and the mixture was stirred at 50° for 1.5 hr. The solvent was evaporated under reduced pressure (10–20 mm); the residue was dissolved in 25 ml of DMF. To this solution was added iodobenzene (51g, 25 mmol) over 1 hr. The mixture was stirred at 22° for 3 hr, poured into ice-water, acidified with diluted hydrochloric acid, and extracted with petroleum ether (bp 35–50°). The organic layer was washed with aqueous sodium bicarbonate, dried over magnesium sulfate, and distilled, giving iodobenzene (4.4 g, 86% recovery) and 3.0 g (76%) of diethyl 2,6-octadiene-1,8-dioate: bp 115–118° (0.45 mm); n^{20}D 1.4725 [lit.[21] bp 97–99° (0.3 mm); n^{20}D 1.4606]; ir (neat) 1715, 1650, 1265, 1175, 975 cm^{-1}; nmr δ 1.26 (t, CH_3, 6 H, J = 7 Hz), 2.37 and 2.80 (each dt, CH_2CH_2, total 4 H), 4.11 (q, OCH_2, 2 H, J = 7 Hz), 5.72 and 5.75 (each d, C=CHCOO, total 2 H), 6.18 and 6.88 (each dt, CH_2CH=C, total 2 H).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.54; H, 8.25.

Vpc analysis of the product on a 15% Carbowax 20M on Celite 545 column (1.9 m) at 225° showed two peaks (4.7 and 6.4 min) in the ratio of 65:35. The relative integrals at δ 2.37, 6.88 (dt, J = 7 and 17 Hz), and 5.75 (d, J = 17 Hz) (*trans*-CH_2CH=CH-COO) and 2.80, 6.18 (each dt, J = 7 and 12 Hz), and 5.72 (d, J = 12 Hz) (*cis*-CH_2CH=CHCOO) were measured and the product ratio was determined as *trans,trans*-**8a** (35%) and *trans,cis*-**8a** (65%).

Diethyl 3,6-Dimethylocta-2,6-diene-1,8-dioate (8b).—A solution of ethyl γ-bromosenecioate (mixture of stereoisomers, 6.2 g 30 mmol), and nickel carbonyl (8.5 g, 50 mmol) in benzene (85 ml) was stirred at 50° for 2 hr, and then, after remaining nickel carbonyl was removed under reduced pressure, acidified with 0.8 *N* HBr–benzene solution, washed with water, dried, and distilled to give diethyl 3,6-dimethylocta-2,6-diene-1,8-dioate (2.1 g, 73%): bp 119° (0.45 mm); n^{20}D 1.4810 [lit.[22] bp 105–106° (0.1

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mm); n^{20}D 1.4762]; ir (neat) 1715, 1220, 1155, 860 cm^{-1}; nmr δ 1.24 (t, CH_3, 6 H, J = 7 Hz), 1.89 (s, *trans*-CH_3, 3 H), 2.17 (s, *cis*-CH_3, 3 H), ~2.07–2.37 and ~2.59–2.90 (m, CH_2CH_2, 4 H), 4.06 (q, OCH_2, 4 H, J = 7 Hz), 5.62 (s, =CH, 2 H).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.24; H, 8.87.

The product showed only one peak on vpc, using a 3 mm × 190 cm column of Carbowax 20M, and was shown to be *trans,cis*-**8b** by analysis by nmr spectra.

Diethyl 2,5-Dimethylene-1,6-hexanedioate (10).—Ethyl α-bromomethylacrylate (9) (5.2 g, 28 mmol) was treated with nickel carbonyl (6.67 g, 39 mmol) in benzene (81 ml) at 50° for 3 hr. The usual work-up described above afforded diethyl 2,5-dimethylene-1,6-hexanedioate (2.2 g, 70%): bp 134–138° (0.75 mm); n^{20}D 1.4527 [lit.[23] bp 81–82° (0.1 mm); $n^{25.5}$D 1.4470]; ir (neat) 1720, 1629, 1195, 1140, 940, 920 cm^{-1}; nmr δ 1.30 (t, CH_3, 6 H, J = 7.2 Hz), 2.42 (s, CH_2CH_2, 4 H), 4.15 (q, OCH_2, 4 H, J = 7.2 Hz), 5.48 and 6.08 (each s, $=CH_2$, 4 H).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.98; H, 8.09.

1-Bromo-4-ethoxy-2-methyl-2-butene (11b).—Isoprene (34 g, 0.5 mol) was dissolved in 200 ml of absolute ethanol at 10°, and *N*-bromosuccinimide (36 g, 0.2 mol) was added at 10° to react for 5 hr, then at 30° for 3 hr. Products were extracted with ether and dried with magnesium sulfate. Distillation gave 22 g (56%) of 4-bromo-3-ethoxy-3-methyl-1-butene, bp 63–64° (20 mm), n^{20}D 1.4720 [lit.[17] bp 60–62.2° (20 mm)], and 5 g (13%) of *trans*-1-bromo-4-ethoxy-2-methyl-2-butene, bp 62–63° (8 mm), n^{20}D 1.4852 (lit.[17] bp 100–104.5° (50 mm)]. The former product showed the following spectra: ir (neat) 1640, 1440, 1410, 1390, 1370, 1105, 1065, 995, 930 cm^{-1}; nmr δ 1.15 (t, CH_3, 3 H, J = 7 Hz) 1.38 (s, CH_3, 3 H), 3.32 (s, $BrCH_2$, 2 H), 3.39 (q, OCH_2, 2 H, J = 7 Hz), 5.19 and 5.27 (each d, $=CH_2$, total 2 H, J = 18 and 11 Hz, respectively), 5.90 (dd, CH=C, 1 H, J = 18 and 11 Hz).

Anal. Calcd for $C_7H_{13}BrO$: C, 43.54; H, 6.78. Found: C, 43.92; H, 6.88.

The latter (**11b**) had the following spectra: ir (neat) 1655, 1430, 1368, 1192, 1090, 1000, 970 cm^{-1}; nmr δ 1.17 (t, CH_3, 3 H, J = 7 Hz), 1.90 (s, CH_3, 3 H), 3.41 (q, OCH_2, 2 H, J = 7 Hz), 3.91 (s, $BrCH_2$, 2 H), 3.93 (d, OCH_2, 2 H, J = 10 Hz), 5.72 (t, CH=C, 1 H, J = 10 Hz).

Anal. Calcd for $C_7H_{13}BrO$: C, 43.54; H, 6.78. Found: C, 42.98; H, 6.23.

4-Acetoxy-1-bromo-2-methyl-2-butene (13).—Isoprene (34 g, 0.5 mol) was dissolved in 200 ml of glacial acetic acid at 10°, *N*-bromosuccinimide (36 g, 0.2 mol) was added, and the mixture was allowed to react for 8 hr. The reaction mixture was extracted with ether and dried with magnesium sulfate. Distillation gave 18.6 g (45%) of 3-acetoxy-4-bromo-3-methyl-1-butene, bp 41–43° (5 mm), n^{20}D 1.4942, and 6.5 g (16%) of 4-acetoxy-1-bromo-2-methyl-2-butene, bp 95–100° (6 mm), n^{20}D 1.4902 [lit.[17] bp 108° (12 mm), $n^{24.3}$D 1.4906]. The former ester showed the following spectra: ir (neat) 1735, 1640, 1445, 1410, 1250, 1170, 1020, 990, 930 cm^{-1}; nmr δ 1.61 (s, CH_3, 3 H), 2.01 (s, CH_3CO_2–, 3 H), 3.75 (s, $BrCH_2$, 2 H), 5.22 and 5.25 (each d, $=CH_2$, total 2 H, J = 10 and 17 Hz, respectively), 6.11 (dd, CH=C, 1 H, J = 10 and 17 Hz).

Anal. Calcd for $C_7H_{11}BrO_2$: C, 40.59; H, 5.37. Found: C, 40.35; H, 5.26.

The latter ester showed the following spectra: ir (neat) 1735, 1668, 1440, 1385, 1230, 1030, 964 cm^{-1}; nmr δ 1.88 (s, CH_3, 3 H), 2.02 (s, CH_2COO, 3 H), 3.95 (s, $BrCH_2$, 2 H), 4.58 (d, CH_2O, 2 H, J = 7 Hz), 5.73 (t, =CH, 1 H, J = 7 Hz).

Anal. Calcd for $C_7H_{11}BrO_2$: C, 40.59; H, 5.37. Found: C, 40.28; H, 5.21.

The latter compound **13** was also obtained by another method, starting from *trans*-1,4-dibromo-2-methyl-2-butene.[24] The mixture of *trans*-1,4-dibromo-2-methyl-2-butene (8.6 g, 33 mmol) and 3.2 g (33 mmol) of dry potassium acetate in 80 ml of *N*,*N*-dimethylformamide (DMF) was stirred at 0–1° for 18 hr, and the product was extracted with petroleum ether (bp 35–50°) and dried with magnesium sulfate. Distillation of the product gave only *trans*-4-acetoxy-1-bromo-2-methyl-2-butene (3.2 g, 46%), bp 73–74° (0.3 mm), n^{20}D 1.4896.

This compound was identified by comparison of ir, nmr, and retention time by vpc with those of an authentic sample obtained from the previous method.

1,8-Diethoxy-3,6-dimethyl-2,6-octadiene (12).—The method was the same as that described before. The mixture of 1-bromo-4-ethoxy-2-methyl-2-butene (4.8 g, 25 mmol) and nickel carbonyl (6.8 g, 40 mmol) in benzene (85 ml) was stirred at 50° for 3 hr, after substitution of solvent, 4.1 g (20 mmol) of iodobenzene in 30 ml of DMF, solution was added at 22°, and the mixture was allowed to react for 3 hr. A similar work-up as described before afforded 3.8 g (92% recovery) of iodobenzene, and 2.1 g (72%) of 1,8-diethoxy-3,6-dimethyl-2,6-octadiene: bp 64–65° (0.3 mm); n^{20}D 1.4631; ir (neat) 1660, 1440, 1338, 1100, 1030 cm^{-1}; nmr δ 1.17 (t, CH_2, 3 H, J = 7 Hz), 1.68 (s, CH_3, 6 H), ~2.05–2.57 (m, CH_2CH_2, 4 H), 3.40 (q, OCH_2, 4 H, J = 7 Hz), 3.92 (d CH_2O, 4 H, J = 11 Hz), 4.73 and 5.30 (each broad s, =CH, total 2 H).

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 73.88; H, 11.41.

Vpc analysis of the product on a 15% Carbowax 20M on Celite 545 column (1.9 m) at 170° showed two peaks (7.2 and 8.3 min) in the ratio of 60:40, respectively. The former peak (60%) was thought to be *trans,cis*-**12** and the latter (40%) to be *trans,trans*-**12**.

Ethyl 3,7-Dimethyl-2,6-octadienoate (14).—Prenyl bromide (5.4 g, 36 mmol) was allowed to react with nickel carbonyl (8.5 g, 50 mmol) in benzene (80 ml) at 50° for 2.5 hr. Excess nickel carbonyl was removed under reduced pressure, and 6.2 g (30 mmol) of ethyl γ-bromosenecioate in benzene (34 ml) was added at 50° during 1.5 hr. Reaction was continued for 3 hr more, and the reaction mixture was extracted with ether and dried with magnesium sulfate. Distillation gave ethyl 3,7-dimethyl-2,6-octadienoate (2.3 g, 40%): bp 102–104° (10 mm); n^{20}D 1.4716 [lit.[25] bp 112–114° (10 mm); n^{20}D 1.4667]; ir (neat) 1740, 1660, 1455, 1384, 1220, 1150, 1060, 1040, 850 cm^{-1}; nmr δ 1.25 (t, CH_3, 3 H, J = 7 Hz), 1.62, 1.69, and 1.88 (each s, CH_3, 9 H), ~2.02–2.37 and ~2.48–2.75 (m, CH_2CH_2, 4 H), 4.08 (q, OCH_2, 2 H, J = 7 Hz), 5.10 (broad s, =CH, 1 H), 5.58 (s, CH=, 1 H).

The product showed two peaks on vpc in the ratio of 70:30. The first (70%) peak was identified as ethyl *cis*-geranate and the latter as ethyl *trans*-geranate by comparison of nmr spectra and vpc retention time with those of the authentic samples prepared by oxidizing citral with silver oxide[25] to geranic acid followed by esterification.

Reaction of Ethyl α-Bromomethylacrylate with 4d.—To the solution of 1,1-dimethyl-π-allylnickel bromide [prepared from 7.5 g (50 mmol) of prenyl bromide and 12 g (70 mmol) of nickel carbonyl in 80 ml of benzene] was added 7.9 g (40 mmol) of ethyl α-bromomethyl acrylate in 30 ml of benzene at 50° over 30 min, and the mixture was stirred at 50° for 5 hr, cooled, poured into ice-water, extracted with ether, and dried. Distillation gave 3.1 g (70%) of diethyl 2,5-dimethylene-1,6-hexanedioate (**10**): bp 87–91° (0.7 mm); n^{20}D 1.4492 [lit.[23] bp 81–82° (0.1 mm); $n^{25.5}$D 1.4470].

This compound was identified by comparison of ir, nmr, and vpc retention time with those of an authentic sample obtained by reaction of ethyl α-bromomethylacrylate and nickel carbonyl as described before.

Geranyl Ethyl Ether (15).—To a solution of 1,1-dimethyl-π-allylnickel bromide (prepared from 7.5 g of prenyl bromide and 12 g of nickel carbonyl as described above) was added 5.8 g (30 mmol) of 1-bromo-4-ethoxy-2-methyl-2-butene in benzene (23 ml) solution at 50° over 1.5 hr, and the mixture was stirred at 50° for 5 hr. The usual work-up described above afforded 2.4 g (45%) of geranyl ethyl ether: bp 115–118° (20 mm); n^{20}D 1.4665 [lit.[26] bp 115° (19 mm); n^{20}D 1.4662].

This compound was identified as *trans*-geranyl ethyl ether, containing below 5% of cis form (neryl ethyl ether) by comparison of ir, nmr, and vpc retention time with those of an authentic sample obtained from the reaction of *trans*-geranyl bromide and sodium ethoxide in absolute ethanol at 35–40°.

Geranyl Acetate (16).—A solution of 1,1-dimethyl-π-allylnickel bromide prepared as described previously and 4-acetoxy-1-bromo-2-methyl-2-butene (6.2 g, 30 mmol) in benzene (100 ml) was stirred at 50° for 6 hr. After cooling, the solution was poured into ice-water and acidified with hydrochloric acid, and the aqueous phase was extracted with ether. The combined

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(24) (a) R. C. Krug and T. F. Yen, *J. Org. Chem.*, **21**, 1082 (1956). (b) V. L. Heasley, G. E. Heasley, S. K. Taylor, and C. L. Frye, *ibid.*, **35**, 2967 (1970).

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(26) M. O. Forster and D. Cardwell, *J. Chem. Soc.*, **103**, 1338 (1913).

layer was washed with water and dried over magnesium sulfate. Removal of solvent and distillation of the product gave 3.5 g (60%) of geranyl acetate: bp 92–94° (3.5 mm); n^{20}D 1.4645 (lit.[27] bp 242; n^{20}D 1.4628). Vpc and nmr spectra analysis showed that the product was *trans*-geranyl acetate contaminated with a minor amount (below 5%) of the cis isomer (neryl acetate).

(27) "The Merck Index," 8th ed, Merck & Co., Rahway, N. J., 1968, p 487.

Registry No.—**4a**, 12012-90-7; **4b**, 12145-58-3; **4c**, 32650-03-6; **4d**, 32650-02-5; *trans,trans*-**8a**, 32829-97-3; *trans,cis*-**8a**, 32829-98-4; *trans,cis*-**8b**, 32829-99-5; **10**, 32670-57-8; *cis*-**11b**, 32659-09-9; *trans*-**11b**, 32659-10-2; *trans,trans*-**12**, 32659-11-3; *trans,cis*-**12**, 32659-12-4; *cis*-**13**, 32659-13-5; *trans*-**13**, 32659-14-6; *cis*-**14**, 32659-20-4; *trans*-**14**, 32659-21-5.

Studies on Chrysanthemic Acid. VIII.[1] Syntheses of 1-Vinyl-2-isobutenyl- and 1,2-Diisobutenyl-3,3-dimethylcyclopropanes. Their Thermal Behavior in Comparison with *cis*-2,2-Dimethyl-3-isobutenylcyclopropyl Isocyanate and *cis*-2,2-Dimethyl-3-isobutenylcyclopropanecarboxaldehyde

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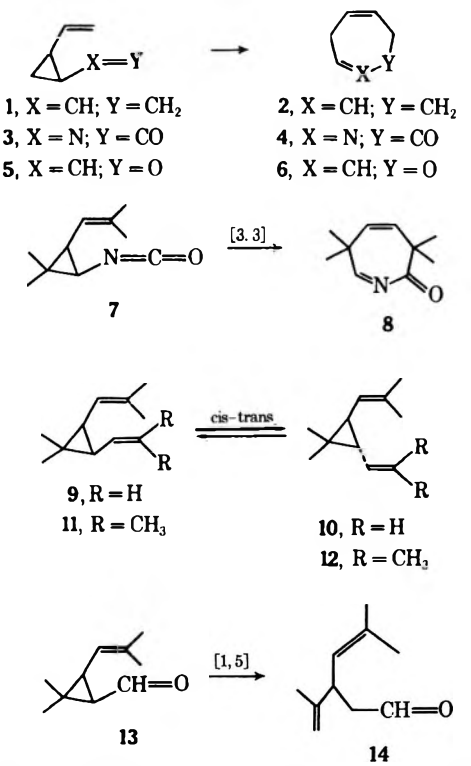
cis- (**9**) and *trans*-1-vinyl-2-isobutenyl- (**10**) and *cis*- (**11**), and *trans*-1,2-diisobutenyl-3,3-dimethylcyclopropanes (**12**) were prepared by the Wittig reaction of *cis*- (**13**) and *trans*-2-isobutenyl-3,3-dimethylcyclopropanecarboxaldehyde (**19**) with methylene- and isopropylidenetriphenylphosphoranes in 52–85% yields, respectively. Cis olefins **9** and **11** were both very stable at room temperature. However, heating the substances neat under nitrogen resulted exclusively in cis–trans isomerization but no Cope rearrangement; the ratio of **9** to **10** was 1:3 after 3 hr at 180° and that of **11** to **12** was 1:2.6 after 3 hr at 170°. From the first-order rate constants for the **11** → **12** isomerization, the kinetic parameters, E_a, log A, and $\Delta S^{\ddagger}$, were calculated as 33 kcal/mol, 12.4 sec^{-1}, and −3.8 eu (443°K), respectively. Similarly, from the rate constants for the Cope rearrangement of 2,2-dimethyl-3-isobutenylcyclopropyl isocyanate (**7**), E_a, log A, and $\Delta S^{\ddagger}$ were calculated as 23 kcal/mol, 7.06 sec^{-1}, and −29 eu (450°K), respectively. Thermal rearrangement of cis aldehyde **13** proceeded rapidly at 173° (the half-life = 14 min) affording exclusively 5-methyl-3-isopropyl-4-hexenal (**14**) by a homo[1,5]sigmatropic rearrangement. The characteristic thermal behavior of **7**, **9**, **11**, and **13** was explained in terms of the steric repulsion between the face to face methyl groups in the cis-like quasiboat transition state required for the Cope rearrangement, in comparison with the simple *cis*-divinylcyclopropane systems, **1**, **3**, and **5**.

It is well known that *cis*-divinylcyclopropane (**1**) cannot be isolated even at −45° because of its extremely facile Cope rearrangement to 1,4-cycloheptadiene (**2**).[2-4] Similar facile concerted bisallylic rearrangements have been recorded for the *cis*-vinylcyclopropyl isocyanate (**3**) → 3,6-dihydro-2*H*-azepin-2-one (**4**) system and the *cis*-vinylcyclopropanecarboxaldehyde (**5**) → 2,5-dihydrooxepin (**6**) system.[5-7] In a previous communication,[8] we reported that *cis*-2,2-dimethyl-3-isobutenylcyclopropyl (chrysanthemyl) isocyanate (**7**) was quite stable and that Cope rearrangement to **8** occurred only under drastic conditions at 144°. We now wish to report syntheses of *cis*- (**9**) and *trans*-1-vinyl-2-isobutenyl- (**10**) and *cis*- (**11**) and *trans*-1,2-diisobutenyl-3,3-dimethylcyclopropanes (**12**) and their thermal behavior in comparison with **7** and *cis*-2,2-dimethyl-3-isobutenylcyclopropanecarboxaldehyde (**13**).



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(2) (a) E. Vogel, K. H. Ott, and K. Gajek, *Justus Liebigs Ann. Chem.*, **644**, 172 (1961); (b) W. v. E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

(3) For a theoretical treatment, see M. Simonetta, G. Favini, C. Mariani, and P. Gramaccioni, *J. Amer. Chem. Soc.*, **90**, 1280 (1968).

(4) For a recent review on the thermal unimolecular reactions of hydrocarbons, see H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969).

(5) E. Vogel, R. Erb, G. Lenz, and A. A. Bothner-By, *Justus Liebigs Ann. Chem.*, **682**, 1 (1965); I. Brown, O. E. Edward, J. M. McIntosh, and D. Vocelle, *Can. J. Chem.*, **47**, 2751 (1969).

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(7) For the rearrangement of Schiff bases of 1,2-diaminocyclopropane to 2,3-dihydro-1,4-diazepins, see H. A. Staab and F. Vögtle, *Chem. Ber.*, **98**, 2701 (1965).

(8) T. Sasaki, S. Eguchi, and M. Ohno, *J. Amer. Chem. Soc.*, **92**, 3192 (1970).

Results

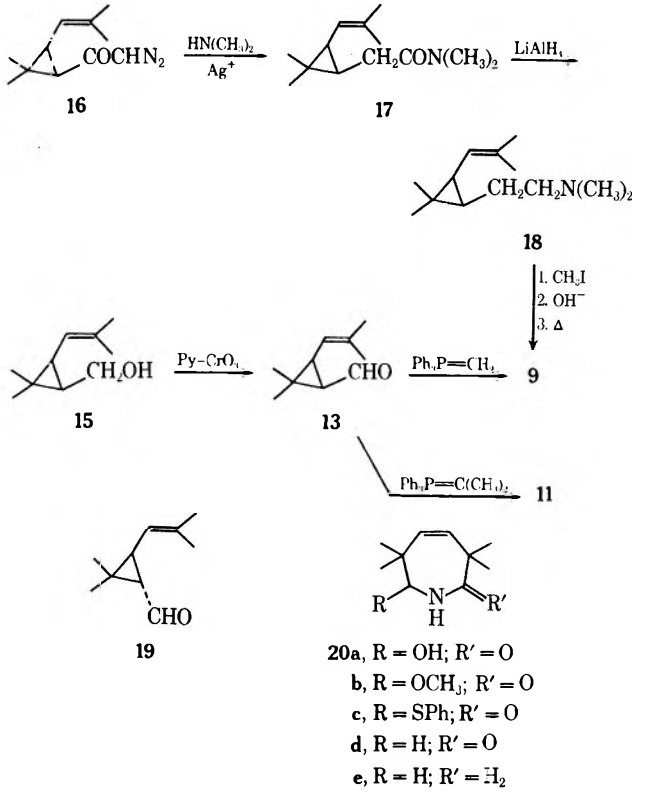
cis-Chrysanthemyl alcohol (**15**) was converted to cis aldehyde **13** in 71% yield by oxidation with pyri-

TABLE I
SPECTRAL DATA OF 9–12

Compd	Ir,[a] cm⁻¹ HC=CH₂	Ir,[a] cm⁻¹ HC=C(CH₃)₂	Uv,[b] nm (log ε)	Nmr, τ[c,d] (J, Hz) C=CH	Nmr, τ[c,d] (J, Hz) Ring H	Nmr, τ[c,d] (J, Hz) CH₃		Mass spectrum,[e] m/e (rel intensity, %)
9	1635	840	198 (4.28)	4.3–5.3	8.5–9.2	8.32	8.89	150 (M⁺, 22)
	990			(m)	(m)	8.37	9.02	107 (100)
	910					(s)	(s)	
10	1630	850	200 (4.20)	4.1–5.3	8.6–9.1	8.33	8.91	
	990			(m)	(m)	(s)	8.93	
	890						(s)	
11		850	202 (4.18)	5.22	8.67	8.30	8.87	178 (M⁺, 11)
				(d, 8.0)	(d, 8.0)	8.37	9.10	121 (100)
						(s)	(s)	
12		840	206 (4.23)	5.19	8.84	8.38	8.98	
				(d, 8.0)	(d, 8.0)	(s)	(s)	

[a] Neat. [b] In cyclohexane. [c] In CCl_4 at 60 MHz. [d] Area of each signal was compatible with the assigned structures. [e] At 80 eV.

dine–CrO_3 complex.[9] The Wittig reaction of **13** with methylenetriphenylphosphorane afforded **9** in 52% yield after purification on a silica gel column and by preparative vpc. The structure of **9** was determined as *cis*-1-vinyl-2-isobutenyl-3,3-dimethylcyclopropane by the spectral data (Table I) and by an alternative synthesis *via* the Hofmann degradation of *cis*-*N*,*N*-dimethylhomochrysanthemylamine (**18**); the silver ion catalyzed decomposition of *cis*-chrysanthemoyldiazomethane (**16**) in aqueous dioxane–dimethylamine afforded *cis*-*N*,*N*-dimethylhomochrysanthemamide (**17**), which was converted to the corresponding amine **18**.



16 17 18 15 13 9 11 19

20a, R = OH; R′ = O
b, R = OCH_3; R′ = O
c, R = SPh; R′ = O
d, R = H; R′ = O
e, R = H; R′ = H_2

The Hofmann degradation of **18** methiodide yielded an olefin **9**, which was identical with a sample prepared by the Wittig reaction by ir, nmr, and vpc inspections, indicating no cis–trans isomerization during the Wittig reaction of **13** even under the strongly alkaline conditions employed.

Similarly, trans (**10**), cis (**11**), and trans olefins (**12**) were prepared in 75–85% yields by the Wittig reactions of **13** and trans aldehyde **19** with the corresponding alkylidenetriphenylphosphoranes, respectively. The structures of these olefins were evidenced by the spectral data (Table I).

Both cis olefins **9** and **11** were stable at room temperature; no nmr spectral changes were observed after 1 week. Heating of **9** and/or **11** neat under dry nitrogen resulted exclusively in cis–trans isomerization, but, unexpectedly, no Cope rearrangement: **9** afforded a *ca.* 1:3 mixture of **9** and **10** after 3 hr at 180° (nmr analysis) and **11**, a 1:2.6 equilibrium mixture of **11** and **12** after 3 hr at 170° (vpc and nmr analyses).

The isomerization of **11** to **12** followed first-order kinetics with the rate constants shown in Table II.

TABLE II
FIRST-ORDER RATE CONSTANTS OF 7 → 8 REARRANGEMENT AND 11 → 12 ISOMERIZATION (VPC)

Temp, °C	k, sec^{-1} (7 → 8)	k, sec^{-1} (11 → 12)
140		1.6×10^{-5}
150		4.0×10^{-5}
160	3.0×10^{-5}	1.0×10^{-4}
170	5.3×10^{-5}	2.1×10^{-4}
180	1.3×10^{-4}	
190	1.7×10^{-4}	
200	3.5×10^{-4}	

The kinetic parameters were calculated as E_a = 33 kcal/mol, log A = 12.4 sec^{-1}, and $\Delta S^{\pm}$ = −3.8 eu at 443°K.

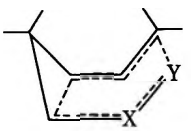
cis-Chrysanthemyl isocyanate (**7**) was prepared by thermal decomposition of the corresponding carbonylazide at the refluxing temperature of benzene.[10] The Cope rearrangement of **7** at the refluxing temperature of *o*-xylene[11] afforded a 1:7 equilibrium mixture of **7** and 3,6-dihydro-3,3,6,6-tetramethyl-2*H*-azepin-2-one (**8**). From the kinetic study on the **7** → **8** rearrangement, the first-order rate constants were obtained in the temperature range of 160–200° (Table II, vpc analysis). The kinetic parameters were calculated as E_a = 23 kcal/mol, log A = 7.06 sec^{-1}, and $\Delta S^{\pm}$ = −29 eu at

(9) T. Sasaki, S. Eguchi, M. Ohno, and T. Umemura, unpublished work. This oxidation method seems superior to those reported using either active manganese dioxide or Jones reagent: L. Crombie and J. Crossley, *J. Chem. Soc.*, 4983 (1963); W. G. Dauben and G. W. Shaffer, *J. Org. Chem.*, **34**, 2301 (1969).

(10) T. Sasaki, S. Eguchi, and M. Ohno, *Tetrahedron*, **25**, 2145 (1969).

(11) At the same temperature, *trans*-chrysanthemyl isocyanate was thermostable.

CHART I



7, X = N; Y = CO
9, X = CH; Y = CH_2
11, X = CH; Y = $C(CH_3)_2$
13, X = CH; Y = O

450°K. The E_a value is more or less similar to those reported for the Cope rearrangement of *cis*-1,2-divinylcyclobutane to cycloocta-1,5-diene,[12] of 2-vinylbicyclo[3.1.0]hex-4-ene to bicyclo[3.2.1]octa-2,6-diene,[13] and of **5** to **6**.[6] However, the $\Delta S^{\ddagger}$ shows a much larger negative value compared with −11.7 eu for *cis*-1,2-divinylcyclobutane[12] and those reported for other related systems.[4]

The thermal behavior of cis aldehyde **13** was different from that of isocyanate **7** and olefins **9** and **11**: rearrangement of **13** occurred at 173° and afforded a single product **14**, which was demonstrated to be known 3-isopropenyl-5-methyl-4-hexenal[14,15] produced by a homo[1,5]sigmatropic rearrangement of **13**.

Discussion

The facile Cope rearrangement aptitude of simple *cis*-vinylcyclopropyl systems such as **1**, **3**, and **5** was in contrast with the present methyl-substituted systems **7**, **9**, **11**, and **13**. Considerable steric repulsion between a vinylic methyl group and one of the *gem*-dimethyl groups on a cyclopropane ring might exist in the quasiboat transition state (Chart I, X = N, Y = C=O) for the [3,3]sigmatropic (Cope) rearrangement of **7**.[8,16] This was evidenced clearly by the kinetic data of the **7** → **8** rearrangement: the $\Delta S^{\ddagger}$ value was extraordinarily large and negative compared to those reported for other related systems (*vide supra*). This large negative value indicates the presence of a methyl–methyl interaction at the transition state for **7** → **8** conversion; *i.e.*, the interaction leads to prohibition of the free rotation of the face-to-face methyl groups in the transition state with a cis-like quasiboat geometry (Chart I).

The complete prohibition of the Cope rearrangement in **9** and **11** could be explained in terms of greater steric repulsion between the methyl groups on the cyclopropane ring and the two side chains in the transition state with such a geometry [Chart I, X = CH, Y = CH_2; X = CH, Y = $C(CH_3)_2$].[17] The homolytic ring cleavage of **9** and **11** can be facilitated by the formation of two allylic radicals and also by the strain relief (*ca.* 27.6 kcal/mol) of a cyclopropane ring,[18,19] resulting in the cis–trans isomerization. In fact, the observed E_a value for **11** → **12** isomerization seems to be one of the lowest for a homolytic cleavage.[4,19]

The preference of **13** for the homo[1,5]sigmatropic rearrangement over the [3,3]sigmatropic rearrangement and the cis–trans isomerization could be explained also by the steric hindrance in the transition state (Chart I, X = CH, Y = O) for the Cope rearrangement; the 1,5-H shift is favored by the ease with which a cyclopropylcarbonyl moiety takes the s-cis-like conformation,[20] and by the large C=O polarity.[21,22]

Experimental Section[23]

***cis*-1-Vinyl-2-isobutenyl-3,3-dimethylcyclopropane (9). A. By the Wittig Reaction.**—*cis*-Chrysanthemylaldehyde (**13**)[9] (1.3 g, 8.6 mmol) in dry ether (10 ml) was added to a stirred solution of methylenetriphenylphosphorane prepared from triphenylmethyl phosphonium bromide (8.8 g, 28 mmol) and *n*-butyllithium (16 ml of 15% w/w *n*-hexane solution) in dry ether (70 ml) under a dry nitrogen stream, and the mixture was stirred at room temperature for 2 hr. The excess Wittig reagent was decomposed by addition of water and the organic layer was separated. The water layer was extracted once with ether (20 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give an oily residue which was purified on a silica gel (Mallinckrodt, 100 mesh) column eluting with petroleum ether (bp 47–52°) to obtain **9** (0.74 g, 52%) as a volatile, colorless oil. An analytical sample was obtained by preparative vpc (silicone SE-30, 130°). Mass spectral analysis of the molecular ion gave *m/e* 150.1398 (calcd for $C_{11}H_{18}$: 150.1409).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.08. Found: C, 88.05; H, 12.17.

B. By the Hofmann Degradation of the 18 Methiodide.—To a solution of *cis*-chrysanthemoyl diazomethane prepared from *cis*-chrysanthemoyl chloride (10 g, 53.6 mmol)[24] in dioxane (60 ml) was added aqueous dimethylamine (40%, 100 ml) and aqueous silver nitrate (10%, 30 ml). The mixture was heated at 60° overnight and was concentrated to *ca.* 100 ml. After cooling, the mixture was extracted with ether (five 30-ml por-

(12) G. S. Hammond and C. D. DeBoer, *J. Amer. Chem. Soc.*, **86**, 899 (1964).

(13) J. M. Brown, *Chem. Commun.*, 226 (1965).

(14) The same rearrangemnet has been reported on a mixture of **13** and **19** at 300°: G. Ohloff, *Tetrahedron Lett.*, 3795 (1965).

(15) The half-life of **13** at 173° was calculated as 14 min and that of **19** at 172° as 15 min (vpc analysis). During the rearrangement of **13**, the formation of **19** was negligibly small, indicating that the **13** → **14** rearrangement has occurred prior to the cis–trans isomerization.

(16) Recently, the Cope rearrangement of tetramethylhomotropilidene has been shown to proceed *via* a bishomobenzene type (cis-like) transition state: L. Birladeanu, D. L. Harris, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 6387 (1970); see also ref 2b.

(17) It is reported that *cis,cis*-1-hexenyl-2-vinylcyclopropane (Dictyopterene) is stable at room temperature, but its Cope rearrangement to 1-*n*-butyl-1,4-cycloheptadiene occurs smoothly even at 75°: G. Ohloff and W. Pickenhagen, *Helv. Chim. Acta*, **52**, 880 (1969). See also K. C. Das and B. Weinstein, *Tetrahedron Lett.*, 3459 (1969).

(18) For a cyclopropane ring cleavage *via* the trimethylene diradical mechanism, see R. J. Crawford and T. R. Lynch, *Can. J. Chem.*, **46**, 1457 (1968), and ref 4, p 120. For the ring cleavage of ethyl chrysanthemate, see T. Hanafusa, M. Ohnishi, M. Mishima, and Y. Yukawa, *Chem. Ind. (London)*, 1050 (1970).

(19) For a recent review on ring strain, see L. N. Ferguson, *J. Chem. Educ.*, **47**, 46 (1970).

(20) For the conformational study of cyclopropylaldehyde, see G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.*, **87**, 2864 (1965); L. S. Bartell, B. L. Carroll, and J. P. Guillory, *Tetrahedron Lett.*, 705 (1964). For the conformation of ethyl chrysanthemate, see J.-L. Pierre, R. Perraud, and P. Arnaud, *Bull. Soc. Chim. Fr.*, 1539 (1970).

(21) It should be mentioned that a higher temperature is required for **5** → **6** rearrangement compared to those for **1** → **2** and **3** → **4**, and that a N=C=O group possesses a linear geometry different from nonlinear ones for C=O and C=C groups.

(22) The activation energy for the 2,2-dimethyl-1-acetylcyclopropane → 5-methyl-5-hexen-2-one rearrangement is known to be smaller than that for the 1-vinyl-2,2-dimethylcyclopropane → 2-methyl-1,4-hexadiene rearrangement: R. M. Roberts, R. G. Landolt, R. N. Greene, and E. W. Heyer, *J. Amer. Chem. Soc.*, **89**, 1404 (1967); H. M. Frey and R. K. Solly, ref 4.

(23) All melting points were obtained on a hot-stage type micro melting point apparatus and are uncorrected. Nmr spectra were recorded on a JEOL JNM-C-60HL spectrometer at 60 MHz, and ir spectra on a JASCO IR-S ir spectrophotometer, and uv spectra on a JASCO ORD/UV-5 spectrophotometer. High-resolution mass spectra were obtained with a JEOL JMS-01SG mass spectrometer at 75 eV and others with a Hitachi RMS-4 mass spectrometer at 80 eV. Vpc analyses were performed on a K-23 Hitachi gas chromatograph and a Varian gas chromatograph Model 1400, and preparative vpc on a Varian Aerograph Model 700 (silicone SE-30). Microanalyses were carried out with a Perkin-Elmer 240 elemental analyzer.

(24) L. Crombie, J. Crossley, and D. A. Mitchard, *J. Chem. Soc.*, 4957 (1963).

tions) and the combined extracts were washed with water (50 ml), dried (Na_2SO_4), and evaporated to give an oil which was distilled to afford *N*,*N*-dimethylhomochrysanthemamide (**17**) (6.9 g, 63%): bp 107–114° (1 mm); ir (neat) 1655 cm^{-1} (C=C).

A solution of **17** (6.5 g, 31.1 mmole) in dry ether (20 ml) was added under ice cooling to a stirred suspension of $LiAlH_4$ (1.5 g, 40 mmol) in ether (50 ml). After stirring was continued for 15 hr at room temperature, the excess $LiAlH_4$ was decomposed by adding water (50 ml) and the organic layer was separated and dried. Removal of the solvent afforded an oily residue which was distilled to give *cis*-*N*,*N*-dimethylhomochrysanthemylamine (**18**) (4.5 g, 75%): bp 72–75° (1 mm); $n^{22}D$ 1.4656; ir (neat) 845 cm^{-1} (CH=C); nmr (CCl_4) τ 5.22 (broad d, 1, J = 8.5 Hz, CH=C), 7.78 (t, 2, J = 4.0 Hz, CH_2N), 7.90 (s, 3, NCH_3), 8.32 and 8.35 [each s, 6, $C{=}C(CH_3)_2$], 8.63 (d, d, 1, J = 8.0 and 7.0 Hz, C_3-H), 8.98 (d, d, 2, J = 8.0 and 4.0 Hz, C_1-CH_2), 8.94 and 9.08 [each s, 6, $C(CH_3)_2$], and 9.40 (t, d, 1, J = 8.0 and 7.0 Hz, C_1-H). Amine **18** afforded a crystalline methiodide quantitatively, mp 198–201°.

Anal. Calcd for $C_{14}N_{28}NI$: C, 49.84; H, 8.37; N, 4.16. Found: C, 49.56; H, 8.16; N, 4.15.

To an ice-cooled solution of the methiodide (3.4 g, 10 mmol) in water (25 ml) was added silver oxide freshly prepared from silver nitrate (8.5 g) and sodium hydroxide (2.2 g). After the mixture was stirred at room temperature for 15 hr, water was removed under reduced pressure to give a brownish residue, which was heated gradually in a flask fitted with a cold trap (−73°). The decomposition occurred rapidly at 77° to give an olefin **9** (0.68 g, 45%) as a volatile oil which was identical with a sample prepared by the Wittig reaction.

***cis*-1,2-Diisobutenyl-3,3-dimethylcyclopropane (11).**—*cis*-Chrysanthemyl aldehyde **13** (1.0 g, 6.6 mmol) was added to a stirred solution of isopropylidenetriphenylphosphorane prepared from triphenylisopropylphosphonium bromide (5.0 g, 13 mmol) and *n*-butyllithium (9 ml of 15% w/w in *n*-hexane) in ether (50 ml) under a nitrogen stream. After stirring was continued for 2 hr at room temperature, water (50 ml) was added and the organic layer was separated. Work-up as above afforded **11** (0.88 g, 75%) as a colorless oil. An analytical sample was obtained by preparative vpc. Mass spectral analysis of the molecular ion gave *m*/*e* 178.1716 (calcd for $C_{13}H_{22}$: 178.1722).

Anal. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.44. Found: C, 87.49; H, 12.54.

***trans*-1-Vinyl-2-isobutenyl-3,3-dimethylcyclopropane (10).**—This was prepared similarly from trans aldehyde **19** (1.0 g, 6.6 mmol) in 84% yield (0.84 g) as a colorless oil. Mass spectral analysis of the molecular ion gave *m*/*e* 150.1398 (calcd for $C_{11}H_{18}$: 150.1409).

***trans*-1,2-Diisobutenyl-3,3-dimethylcyclopropane (12).**—This was obtained similarly in 85% yield (1.0 g) from the trans aldehyde **19** (1.0 g, 6.6 mmol). Mass spectral analysis of the molecular ion gave *m*/*e* 178.1707 (calcd for $C_{13}H_{22}$: 178.1722).

3,6-Dihydro-3,3,6-tetramethyl-2*H*-azepin-2-one (8) and Its Derivatives 20a–e.—A solution of *cis*-chrysanthemyl isocyanate[10] (3.5 g, 21.2 mmol) in dry *o*-xylene (30 ml) was refluxed under a dry nitrogen atmosphere for 60 hr. After evaporation of *o*-xylene, the residue was distilled under a nitrogen stream to give **8** (2.1 g, 60%) as a colorless oil, bp 79° (2 mm), and recovered **7** (0.3 g, 8.6%), bp 50–55° (2 mm). Since **8** was very hygroscopic, it was characterized by the spectral data[8] and by the chemical conversion to **20a**, **20b**, and **20c** with water, methanol, and thiophenol, respectively, in *n*-hexane or without solvent; **20a** was obtained as colorless crystals from *n*-hexane, mp 144–145°.

Anal. Calcd for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.79; H, 9.12; N, 7.94.

20b was an oil.

Anal. Calcd for $C_{11}H_{19}O_2N$: C, 66.97; H, 9.71; N, 7.10. Found: C, 6.71; H, 9.51; N, 6.81.

20c was obtained as colorless crystals from *n*-hexane, mp 102–103°.

Anal. Calcd for $C_{16}H_{21}ONS$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.80; H, 7.69; N, 5.12.

Catalytic hydrogenation of **8** (0.45 g, 2.7 mmol) in *n*-hexane (50 ml) over Adams catalyst (0.1 g) under atmospheric pressure gave **20d** (0.46 g, 100%) as colorless crystals, mp 113–114°.

Anal. Calcd for $C_{10}H_{17}ON$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.60; H, 10.29; N, 8.29.

$LiAlH_4$ (0.12 g) reduction of **8** (0.45 g, 2.7 mmol) in dry ether (30 ml) and work-up as usual gave an oily product which was dissolved in *n*-hexane and left standing overnight in a refrigerator to precipitate **20d** as colorless crystals (0.20 g, 40%). From the mother liquor, 2,3,6,7-tetrahydro-3,3,6,6-tetramethyl-1*H*-azepine (**20e**) was obtained as an oil (0.25 g, 60%), which gave crystalline picrate, mp 142–143°.

Anal. Calcd for $C_{16}H_{22}O_7N_4$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.22; H, 5.80; N, 14.39.

Kinetic Measurements.—All kinetic measurements were carried out using vpc analyses on a column packed with silicone SE-30 (5%) on Chromosorb G NAW at 140° for **7** → **8**, and on a column packed with silicone SE-30 (3%) on Varaport 30 at 80° for **11** → **12** and **13** → **14**. The samples (1–10 mg) were introduced in a Pyrex glass tube (0.6 cm diameter and 5.0 cm length) under a dry nitrogen atmosphere and the tube was sealed under evacuating by aspirator. The rate constants were calculated each from the peak area ratio of the starting material and the products. The kinetic parameters were calculated from the rate constants over a 30° temperature range (413–443°K) for **11** → **12**, and over a 40° temperature range (443–473°K) for **7** → **8**.

Registry No.—**7**, 22823-32-1; **8**, 28830-13-9; **9**, 32658-99-4; **10**, 32659-00-0; **11**, 32659-01-1; **12**, 32659-02-2; **13**, 20104-06-7; **17**, 32653-68-2; **18**, 32653-69-3; **18** MeI, 32653-70-6; **20a**, 28830-14-0; **20c**, 28830-16-2; **20d**, 28830-17-3; **20e** picrate, 28830-18-4.

Interconversions of Hexofuranosyl Nucleosides. I. Synthesis of 9-β-L-Gulofuranosyladenine from 9-α-D-Mannofuranosyladenine[1]

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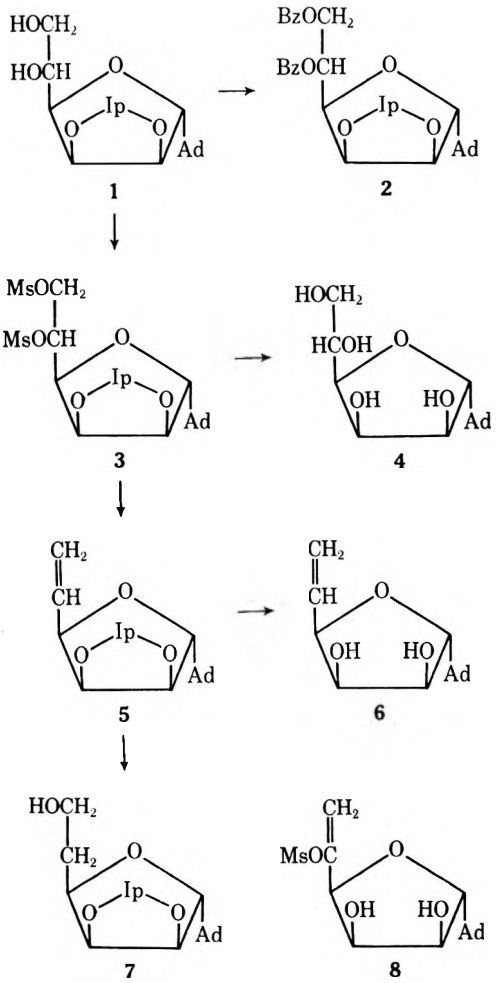
9-β-L-Gulofuranosyladenine (**4**) has been prepared from 9-α-D-mannofuranosyladenine by epimerization at C-5′. This was accomplished by formation of the 5′,6′-di-*O*-methanesulfonyl ester of 9-(2,3-*O*-isopropylidene-α-D-mannofuranosyl)adenine (**3**), followed by inversion of configuration at C-5′ in a boiling mixture of sodium benzoate in *N*,*N*-dimethylformamide. Removal of the blocking groups gave **4**. Several other derivatives prepared from **3** included the 5′,6′-dideoxy nucleoside (**5**), which was formed by elimination of the vicinal dimesyl esters, and an exocyclic enol sulfonate (**8**), which was isolated after inadvertent removal of one molecule of methanesulfonic acid. Hydroboration of **5** gave 9-(5-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosyl)adenine (**7**) and acid hydrolysis of **5** gave the free nucleoside, 9-(5,6-dideoxy-α-D-*lyxo*-hex-5-enofuranosyl)adenine (**6**).

A number of hexofuranosyl nucleosides have been prepared by the author and his colleagues as biologically interesting analogs of naturally occurring nucleosides.[2,3] Such compounds have a potential use as antitumor or antimicrobial agents. Some of the rare hexose sugars required as starting materials in the synthesis of other hexofuranose-containing nucleosides are tedious to prepare in quantities which are large enough to work with. Therefore, the decision was made to prepare hexofuranosyl nucleosides from commercially available inexpensive sugars. A change in the configuration of a hydroxyl group at one or more carbon atoms could then be undertaken and would result in the desired nucleoside. This procedure offered the advantage of use of synthetic methods in nucleoside synthesis which are known to give good yields in the coupling reaction, whereas many of the rare hexose derivatives used previously have yielded low amounts of the desired products. Results such as these would not be unexpected in further experiments with rare hexoses, and the preparation of such rare hexose derivatives as are needed for these experiments would be a less than worthwhile undertaking. Hence, an investigation was begun with a study of the change in configuration at C-5′ of preformed hexofuranosyl nucleosides.

It has previously been reported that the coupling of 2,3,5,6-tetra-*O*-benzoyl-L-gulofuranosyl chloride with 6-benzamidochloromercuripurine gave a 10% yield of 9-β-L-gulofuranosyladenine.[2] This was accomplished by synthesis of the required glycosyl halide in a rather extensive series of reactions starting with D-glucuronic acid.[4,5] Furthermore, it has been demonstrated that the use of isopropylidene blocking groups in place of ester groups in nucleoside coupling reactions has resulted in increased yields[6] but the large number of steps in the reaction sequence still discouraged the use of this pathway. 9-(2,3-*O*-Isopropylidene-α-D-mannofuranosyl)adenine (**1**) is a nucleoside intermediate which can be obtained in good yield in a few, relatively simple steps.[3] What will be described below is the inversion of configuration at C-5′ of **1** as a simple method for the preparation of **4** (Scheme I).

SCHEME I[a]



[a] Ad = adeninyl; Ms = CH_3SO_3; Ip = $(CH_3)_2C$; Bz = benzoyl.

Some years ago Baker and his colleagues demonstrated that benzoate ion became a powerful nucleophile in solutions of moist *N*,*N*-dimethylformamide.[7] This reaction has since had wide application in carbohydrate chemistry.[8] To use this procedure in the preparation of **4** from **1** it was necessary to prepare the 5′,6′-di-*O*-

(1) This work was supported, in part, by Grant No. T-442 from the American Cancer Society.

(2) P. Kohn, R. H. Samaritano, and L. M. Lerner, *J. Org. Chem.*, **31**, 1503 (1966).

(3) L. M. Lerner and P. Kohn, *J. Org. Chem.*, **31**, 339 (1966); P. Kohn, L. M. Lerner, and B. D. Kohn, *ibid.*, **32**, 4076 (1967).

(4) F. Erlich and K. Rehorst, *Ber.*, **62**, 628 (1929); M. L. Wolfrom and K. Anno, *J. Amer. Chem. Soc.*, **74**, 5583 (1952).

(5) P. Kohn, R. H. Samaritano, and L. M. Lerner, *ibid.*, **87**, 5475 (1965).

(6) L. M. Lerner, B. D. Kohn, and P. Kohn, *J. Org. Chem.*, **33**, 1780 (1968).

(7) E. J. Reist, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 5775 (1958).

(8) D. H. Ball and F. W. Parrish, *Advan. Carbohyd. Chem.*, **24**, 139 (1969).

p-toluenesulfonyl ester of **1**. However, the usual conditions of synthesis of tosyl esters[9] failed to give complete tosylation of **1**. When forcing reaction conditions were used which involved an excess of *p*-toluenesulfonyl chloride and heat, as many as six products were detectable on thin layer chromatograms, all of which could be approximated to be in nearly equal amounts. The lack of ease of reactivity of the hydroxyl groups of **1** may be, in part, a steric property, as ascertained by a study of molecular models and from experiments on the benzoylation of **1**. Although complete benzoylation of **1** could be achieved, a great excess of benzoyl chloride and a temperature of 100° was necessary, and the yield was still relatively low. Tosylation of **1** was abandoned in favor of methanesulfonylation, which proceeded satisfactorily under mild conditions to give **3**. When **3** was treated with an excess of sodium benzoate in moist *N*,*N*-dimethylformamide at 100°, or for 6 hr at reflux, 9-α-D-mannofuranosyladenine and **4** were isolated in a ratio of about 10:1 after removal of the blocking groups and chromatography on a Dowex 1 (OH) resin.[10] When the reaction mixture was heated at reflux for 24 hr and the blocking groups were removed, the major product was **4** in a 12% yield. Reaction mixtures became nearly black within minutes after the application of heat, a sign which is probably indicative of extensive decomposition when one considers the small yield of **4** and the inability to recover any 9-α-D-mannofuranosyladenine. Also, it is necessary to consider the often difficult problem of the removal of the isopropylidene group under conditions which will frequently hydrolyze the acid labile C–N nucleoside bond.[11] Nevertheless, the yield seems respectable enough when these results are compared to the 16% yield obtained for a similar inversion of 3-deoxy-1,2-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-α-D-galactofuranose to 3-deoxy-5,6-di-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-mannofuranose.[12] Buss, *et al.*,[13] have shown that the tosyloxy group at C-6 of 3-*O*-acetyl-1,2-*O*-isopropylidene-5,6-di-*O*-*p*-toluenesulfonyl-α-D-glucofuranose is displaced much more easily and at a lower temperature than the one at C-5, and raising the temperature to the boiling point of *N*,*N*-dimethylformamide transforms this compound into 3-*O*-acetyl-5,6-di-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose in 50% yield. The better yield in this case may be due to the ability of the tosyloxy group to act as a better leaving group than the mesyloxy.[8,9] Goodman[14] has suggested that the reaction of sodium benzoate in *N*,*N*-dimethylformamide proceeds under SN2 displacement conditions at the exocyclic carbons of hexofuranose derivatives even under situations where a neighboring group participation would be expected. No clear reason for this was offered, but the recovery of 9-α-D-mannofuranosyladenine as the principal product in some of the reactions run in the present work may indicate that only the mesyloxy group at C-6 was displaced, and that the expected participation of the benzoyloxy group at that stage never occurred. Davidson and coworkers[15] have recently been studying the effects of solvent on the ability of potassium acetate to effect a displacement at C-5 of sugar derivatives possessing a benzoyloxy group at C-6 and they have concluded that both direct displacement and neighboring group participation take place in *N*,*N*-dimethylformamide.

Prior to the publication of papers by Davidson and colleagues[15,16] and by Chalk, *et al.*,[17] which demonstrated that reactions of acetate ion in boiling acetic anhydride proceeded by neighboring group participation reactions, **3** was treated with Dowex 1 (acetate) resin in acetic anhydride under the expectation that a simple displacement would occur.[18] Removal of the blocking groups gave, instead of **4**, what appeared to be an unsaturated enol mesylate (**8**). The structure shown is only tentatively assigned on the basis of elemental analysis, stability of the compound under conditions where allylic mesylates (4′,5′-olefinic bond) would be expected to be highly reactive, a characteristic infrared band at 885 cm^{-1} for a *gem*-vinyl group, and the expectation that the mesyl group at C-6′ would be more labile than the one at C-5′. Similarly, enol tosylates and mesylates in the rings of sugars[19a] and cyclitols[19b] have been isolated after reactions with sodium benzoate in *N*,*N*-dimethylformamide, and in one case a straight-chain enol tosylate of an alditol was prepared.[19c]

Dimesylate **3** was next subjected to reaction conditions which are known to give unsaturated products in compounds containing acyclic vicinal sulfonyloxy groups.[20] When **3** was treated with sodium iodide in acetone at 100° for only 1.5 hr,[20a] very little happened and what was recovered was primarily the starting material. It was found necessary to increase the reaction time to at least an overnight reaction, whereupon a substantial yield of 9-(5,6-dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranosyl)adenine (**5**) was obtained. That **5** had a double bond between carbons 5′ and 6′ and not between carbons 4′ and 5′ was supported by an nmr spectrum which showed no C-6′ methyl peak near τ 8.4. Acid hydrolysis of the isopropylidene of **5** gave compound **6**. Application of hydroboration reactions[21] to **5** were not very successful under the various conditions employed,[22] but one of the reactions yielded a very small quantity of what is believed to be 9-(5-deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosyl)adenine (**7**). The position of the deoxy carbon was based upon the known course of this addition reaction, which yields anti-Markovnikoff products.[21,22]

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(22) (a) M. L. Wolfrom, K. Matsuda, F. Komitsky, Jr., and T. E. Whitely, *J. Org. Chem.*, **28**, 3551 (1963); (b) H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 74 (1964).

Experimental Section[23]

9-(5,6-Di-*O*-benzoyl-2,3-*O*-isopropylidene-α-D-mannofuranosyl)adenine (2).—To a suspension of 9-(2,3-*O*-isopropylidene-α-D-mannofuranosyl)adenine (1)[3] (0.75 g, 2.2 mmol) in 14 ml of dry pyridine was added 1.8 ml of benzoyl chloride. The mixture was stirred at room temperature for 15 min, and then kept on a steam bath for 4.5 hr, protected from moisture. After allowing the mixture to cool to room temperature, it was poured into a mixture of ice and saturated sodium bicarbonate and stirred for 1 hr. The insoluble gum was extracted into chloroform and the chloroform solution was washed with saturated sodium bicarbonate and water, dried, and evaporated. The gum was dissolved in 15 ml of warm absolute ethanol, treated with 10 ml of 10% ethanolic picric acid,[24] and heated at reflux for 20 min, whereupon crystallization began. The flask was kept at room temperature for 2 hr, and the yellow crystals were filtered off and thoroughly washed with ethanol, giving 0.55 g (32%) of the picrate of **2**, mp 225–227° dec. Recrystallization of a portion of this from methanol gave fine needles: mp 229–230° dec; ir (KBr) 1722 (benzoate C=O), 1548 (NO_2), 1360 (*gem*-dimethyl), 1316 (NO_2), and 712 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{34}H_{30}N_8O_{14}$: C, 52.72; H, 3.88; N, 14.48. Found: C, 53.48; H, 3.98; N, 14.75.

The picrate was dissolved in 80% aqueous acetone and treated with Bio-Rad AG 1-X8 (CO_3^{-2}) resin to remove the picrate ion.[25] The resin was removed by filtration and the solvents were evaporated off. Crystallization of **2** was not achieved, but a hard foam was obtained by evaporation of absolute ethanol and dried at 64° under high vacuum. The product appeared homogeneous on tlc plates,[26] R_f 0.74 in 1:1 ethyl acetate–methanol: ir (film, NaCl) 1720 (benzoate C=O), 1370 (*gem*-dimethyl), and 710 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{28}H_{27}N_5O_7$: C, 61.64; H, 4.99; N, 12.84. Found: C, 61.55; H, 5.10; N, 12.30.

9-(2,3-*O*-Isopropylidene-5,6-di-*O*-methanesulfonyl-α-D-mannofuranosyl)adenine (3).—A solution of 3.03 g (9 mmol) of **1** in 150 ml of dry pyridine was chilled in an ice bath and 4.3 ml of methanesulfonyl chloride was added dropwise. The mixture was stirred for 1 hr, kept at room temperature for 48 hr, and poured into an ice-saturated sodium bicarbonate mixture. The product was extracted with chloroform, washed with saturated sodium bicarbonate and water, and dried. Evaporation left a hard gum: 2.9 g (64.5%); ir (film, NaCl) 1360, 1333 sh (*gem*-dimethyl and sulfonate) and 1174 cm^{-1} (sulfonate). Tlc revealed that there were two trace components contaminating the main substance, which had R_f 0.53 in 1:1 ethyl acetate–methanol. Preparations such as this were found to be sufficiently pure for the reactions described below.

9-β-L-Gulofuranosyladenine (4).—To a solution of **3** (2.9 g, 5.8 mmol) in 290 ml of *N*,*N*-dimethylformamide was added 12.8 g of sodium benzoate and the mixture was stirred and heated at reflux for 24 hr.[7,12] During the first few minutes at reflux the reaction mixture became nearly black. It was cooled to room temperature, 150 ml of water was added, and the solution was extracted several times with chloroform (total volume, 400 ml). The organic layer was washed with saturated sodium bicarbonate (two 200-ml portions) and water (200 ml), dried, and evaporated to yield a thick, dark brown syrup weighing 2.6 g. Tlc in 1:1 methylene chloride–ethyl acetate revealed a major spot at R_f 0.17 and trace components at R_f 0.24 and 0.03. A similar pattern occurred on tlc in 9:1 ethyl acetate–methanol, R_f 0.37 for the major component and R_f 0.57 and 0.28 for the minor components.

The syrup was treated with 70 ml of 0.25 *N* methanolic sodium methoxide at room temperature for 19 hr and brought to neutrality with Dowex 50 (H) resin. The solvent was evaporated off and the residue was dissolved in 214 ml of hot 25% aqueous acetic acid and kept on a steam bath for 3.5 hr. Evaporation to dryness was followed by several coevaporations with absolute ethanol and then the brown residue was dissolved in hot water and decolorized with Darco G-60. The water was evaporated off and the residue was dissolved in 10 ml of 60% aqueous methanol and placed on top of a column (30 × 2 cm) of Bio-Rad AG 1-X2 (OH, 200–400 mesh)[10] which had been packed in the same solvent. Fractions were collected which were 10 ml in volume and tubes 175–250, the only tubes containing substantial uv absorption, were collected and the contents pooled. The solvents were removed by evaporation and **4** was crystallized from ethanol–water to give 211 mg (12%): mp 231–233°; $[\alpha]^{26}D$ +56.3° (*c* 1.13, 1 *N* HCl). Admixture with an authentic sample[2] of **4** gave no depression of melting point. The ir spectra and mobilities on paper chromatograms in two solvent systems were identical.

9-(5,6-Dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranosyl)adenine (5).—Dimesylate **3** was prepared from 3 g of **1** and was dissolved in 50 ml of acetone. Sodium iodide (10.5 g) was added and the solution was placed in a stainless steel bomb and kept at 100° for 16 hr.[20] The bomb was cooled to room temperature and the contents were diluted with chloroform. The organic solution was washed with water, three times with a mixture of sodium thiosulfate and aqueous sodium bicarbonate, once more with water, and dried. The solvent was evaporated, leaving a light brown syrup which solidified after an hour. Crystallization from methanol over several days gave pink-colored crystals. These were dissolved in chloroform, silicic acid[27] was added, and the solvent was removed by evaporation. The silicic acid was placed on top of a column (26 × 3.5 cm) of silicic acid[27] which had been packed in benzene and the column was washed with 600 ml of ethyl acetate. The product was eluted with 1:1 ethyl acetate–methanol. The first 400 ml was discarded and the next 300 ml contained **5**. Evaporation of the solvents and crystallization of **5** as hemispherical colonies from ethyl acetate–petroleum ether (bp 60–110°) gave 1.3 g (48%) in several crops; mp 180.5–181° with a change in form to needles above 165°; $[\alpha]^{24}D$ −76° (*c* 1.2, $CHCl_3$); ir (KBr) 3080 (CH=CH_2), 1730, 1671, 1598, 1565 (C=C and purine ring), 1372 (*gem*-dimethyl), 995 cm^{-1} (CH=CH_2); nmr ($CDCl_3$) τ 3.96 (s, 1, H-1′), 4–5.3 (m, CH=CH_2 and unresolved H-2′, H-3′, H-4′), 8.42 and 8.58 (both s, 6, *gem*-dimethyl); tlc in 95:5 ethyl acetate–methanol, R_f 0.30.

Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.47; H, 5.65; N, 23.09. Found: C, 55.39; H, 5.61; N, 23.02.

9-(5,6-Dideoxy-α-D-*lyxo*-hex-5-enofuranosyl)adenine (6).—A solution of 317 mg of **5** in 18 ml of 0.1 *N* sulfuric acid was kept at room temperature for 5 days.[6] It was neutralized with barium carbonate, heated at 90° for 1 hr, filtered by suction through a pad of Celite, and evaporated to a small volume. Two days later the crystals were filtered off. This turned out to be a mixture of spherical colonies (**6**) and tiny needles (**5**). The large spheres were easily separated with a tweezers to give 168 mg (61%), mp 237–240° dec. Two recrystallizations from water gave 116 mg: mp 245–246.5° dec; $[\alpha]^{26}D$ +53° (*c* 0.92, 1 *N* HCl); uv max (H_2O) 259 mμ (ε 15,100); Rad[28] 1.49 in 5% aqueous disodium hydrogen phosphate; Rad 1.09 in 86:14 *n*-butyl alcohol–water; tlc in 95:5 ethyl acetate–methanol, R_f 0.10.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 50.47; H, 4.80; N, 26.87.

Recrystallization of the tiny needles obtained above and comparison against a sample of **5** (mixture melting point, ir, tlc) verified its identity.

9-(5-Deoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hexofuranosyl)adenine (7).—Compound **5** (415 mg) was dissolved in 35 ml of tetrahydrofuran, 268 mg of sodium borohydride was added, and the mixture was stirred in a nitrogen atmosphere.[22b] A solution

(23) Elementary analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich., or by the Baron Consulting Co., Orange, Conn. Melting points were determined on a Kofler hot stage and correspond to corrected values. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer and ultraviolet spectra on a Beckman DK-2 spectrophotometer. Molar extinction coefficients were checked on a Beckman DU equipped with a Gilford digital readout attachment. Optical rotations were obtained on a Rudolph polarimeter and nmr spectra were recorded on a Perkin-Elmer 20A by Dr. Harry Agahigian of the Baron Consulting Co. Evaporations were performed *in vacuo* in a rotary evaporator at a bath temperature of 40–45°. All moist organic solutions were dried over anhydrous magnesium sulfate. Spots on tlc plates or on paper chromatograms were visualized with a Mineralight lamp which produced ultraviolet radiation at 254 mμ.

(24) J. R. Parikh, M. E. Wolff, and A. Burger, *J. Amer. Chem. Soc.*, **79**, 2778 (1957).

(25) M. L. Wolfrom, A. B. Foster, P. McWain, W. von Bebenburg, and A. Thompson, *J. Org. Chem.*, **26**, 3095 (1961).

(26) Tlc was performed on silica gel HF plates (E. Merck A.G., Darmstadt) of 0.25 mm thickness which were prepared with Desaga equipment.

(27) Mallinckrodt 100 mesh; dried at 150° for 16 hr prior to use.

(28) Paper chromatograms were run by a descending technique on Whatman No. 1 paper. The expression Rad refers to the ratio of the distance the nucleoside migrated to the distance which adenine migrated.

of boron trifluoride ethyl etherate [1.32 g, freshly distilled at 44° (9 mm)] in 10 ml of tetrahydrofuran was added dropwise over a period of 15 min. After 2 hr, water was carefully added to destroy excess reagent and the solution was treated with 30% hydrogen peroxide while maintaining the pH at 9 with 3 *N* sodium hydroxide. This was stirred for 1.5 hr, the solvents were evaporated, and the residue was extracted with chloroform which was washed with water and dried. Evaporation left a syrup which crystallized slowly over the next 4 months. The syrup–crystal mixture was triturated with methanol to give 22 mg (5%) of crystals which were recrystallized from methanol. Tiny, colorless prisms weighing 6 mg were obtained: mp 220–220.5°; ir (KBr) 3320 (NH, OH), 1680, 1600, 1572 ($NH_2C{=}N$, purine ring), 1384–1364 (multiplet, *gem*-dimethyl), 1092, 1064 (COC, CO).

Anal. Calcd for $C_{14}H_{19}N_5O_4$: C, 52.33; H, 5.96; N, 21.80. Found: C, 52.04; H, 5.73; N, 21.90.

Enol Mesylate (8).—A mixture of 5.1 g of **3**, Dowex 1-X10 (acetate, 200–400 mesh) resin, and 200 ml of acetic anhydride was heated at reflux for 8 hr. The resin was removed by filtration and the filtrate was evaporated to a brown foam which was coevaporated five times with a mixture of ethanol and toluene. The foam (5.4 g) was dissolved in methanol and treated with 13 ml of 1 *N* methanolic sodium methoxide at reflux for 1 hr. After neutralization with Dowex 50 (H) resin and a Darco G-60 treatment, the methanol was removed by evaporation, leaving a tan foam which was dissolved in 0.1 *N* sulfuric acid and kept at room temperature for 6 days. The neutralization step was carried out as described above for **6**. The aqueous solution was washed with chloroform and evaporated, and the residue was dissolved in a minimum amount of 30% aqueous methanol. This was applied to the top of a column of Bio-Rad AG 1-X2 (OH, 200–400 mesh)[10] (30 × 2.3 cm), the column was eluted with the same solvent, and 12 ml fractions were collected. Fractions 136–225 represented the only major uv-absorbing component. The contents of these tubes were pooled and evaporated to dryness and crystallization was achieved from ethanol–water (644 mg, 16%). Two recrystallizations yielded 380 mg of feathery platelets: mp 160°; $[\alpha]^{27}D$ +143° (*c* 0.71, 1 *N* HCl); ir (KBr) 1702, 1643, 1618, 1575 ($CH{=}CH_2$ and purine ring), 1360, 1175 (sulfonate), and 885 cm^{-1} (*gem*-vinyl); Rad 1.58 in 5% aqueous disodium hydrogen phosphate and 0.57 in 86:14 *n*-butyl alcohol–water.

Anal. Calcd for $C_{12}H_{15}N_5O_6S$: C, 40.33; H, 4.23; N, 19.60; S, 8.97. Found: C, 40.31; H, 4.21; N, 19.56; S, 8.99.

Registry No.—**1**, 32659-04-4; **2**, 32659-05-5; **2** (picrate), 32829-93-9; **3**, 32659-06-6; **4**, 10279-88-6; **5**, 32659-07-7; **6**, 32829-95-1; **7**, 32659-08-8; **8**, 32829-96-2.

Interconversions of Hexofuranosyl Nucleosides. II. Preparation of 9-α-L-Idofuranosyladenine and 5′,6′-Unsaturated Derivatives[1]

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9-(2,3-Di-*O*-acetyl-5,6-di-*O*-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine (**3**) was prepared from 1,2-*O*-isopropylidene-5,6-di-*O*-*p*-toluenesulfonyl-α-D-glucofuranose (**1**) in a four-step synthesis. Inversion of configuration at C-5′ was not possible without extensive degradation and cyclonucleoside (**4**) formation. 9-(2,3-Di-*O*-acetyl-6-*O*-benzoyl-5-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine successfully underwent inversion to the L-idose nucleoside (**8**) but in too small of a yield to be of preparative value. Therefore, 9-α-L-idofuranosyladenine (**8**) was synthesized starting from 3,6-di-*O*-acetyl-5-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose (**9**) and proceeded by condensation of the acetate **10**, prepared by acetolysis of **9**, with 6-benzamidochloromercuripurine and titanium tetrachloride. An 5′,6′-olefinic blocked nucleoside **12** was prepared from **3** in hot sodium iodide–acetone or by a pathway starting from the known unsaturated sugar derivative, 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-glucofuranose. This derivative was converted in two steps to an acetate **15** which was coupled to adenine by the titanium tetrachloride method. Removal of the blocking groups of **12** gave 9-(5,6-dideoxy-β-D-*xylo*-hex-5-enofuranosyl)adenine, a noncrystalline, unstable compound.

The aims of the present investigation were set forth in the previous paper of this series.[2] 9-α-L-Idofuranosyladenine (**8**) appeared to be an interesting compound to prepare because of its structural relationship to 9-β-D-xylofuranosyladenine, a compound of biological interest because of its ability to inhibit growth of some forms of animal tumors.[3] It was of interest to see if epimerization of C-5′ of a preformed D-glucofuranosyl nucleoside derivative could be effected, thereby giving the nucleoside with the L-ido configuration. To do this it was necessary to prepare a derivative of 9-β-D-glucofuranosyladenine which had a group at C-5′ that could easily be displaced by an SN2 reaction or assisted by neighboring group participation. 9-(2,3-Di-*O*-acetyl-5,6-di-*O*-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine (**3**) seemed like such a compound.

The preparation of **3** started from 1,2-*O*-isopropylidene-5,6-di-*O*-*p*-toluenesulfonyl-α-D-glucofuranose[4] (**1**) and the route used is illustrated in Scheme I. Acetolysis of **1** converted it to tri-*O*-acetate **2**, which was immediately coupled, without further purification, with 6-benzamidochloromercuripurine using the titanium tetrachloride method of nucleoside synthesis.[5] The product of this condensation was treated with picric acid,[6] and a crystalline picrate of **3** was obtained in excellent yield. Removal of the picrate ion with an ion exchange resin[7] gave **3**.

Buss, *et al.*,[8] were able to convert 3-*O*-acetyl-1,2-*O*-isopropylidene-5,6-di-*O*-toluenesulfonyl-α-D-glucofuranose to 3-*O*-acetyl-5,6-di-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose in a yield of 50% using the hot sodium benzoate–dimethylformamide system first de-

(1) This work was supported, in part, by Grant No. T-442 from the American Cancer Society.

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(3) D. B. Ellis and G. A. LePage, *Cancer Res.*, **26**, 893 (1966).

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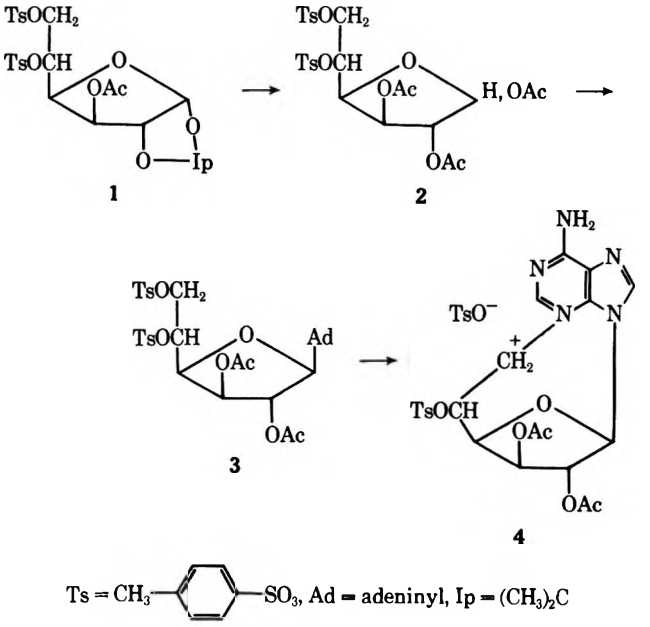
(6) J. R. Parikh, M. E. Wolff, and A. Burger, *J. Amer. Chem. Soc.*, **79**, 2778 (1957).

(7) M. L. Wolfrom, A. B. Foster, P. McWain, W. von Bebenburg, and A. Thompson, *J. Org. Chem.*, **26**, 3095 (1961).

(8) D. H. Buss, L. D. Hall, and L. Hough, *J. Chem. Soc.*, 1616 (1965).

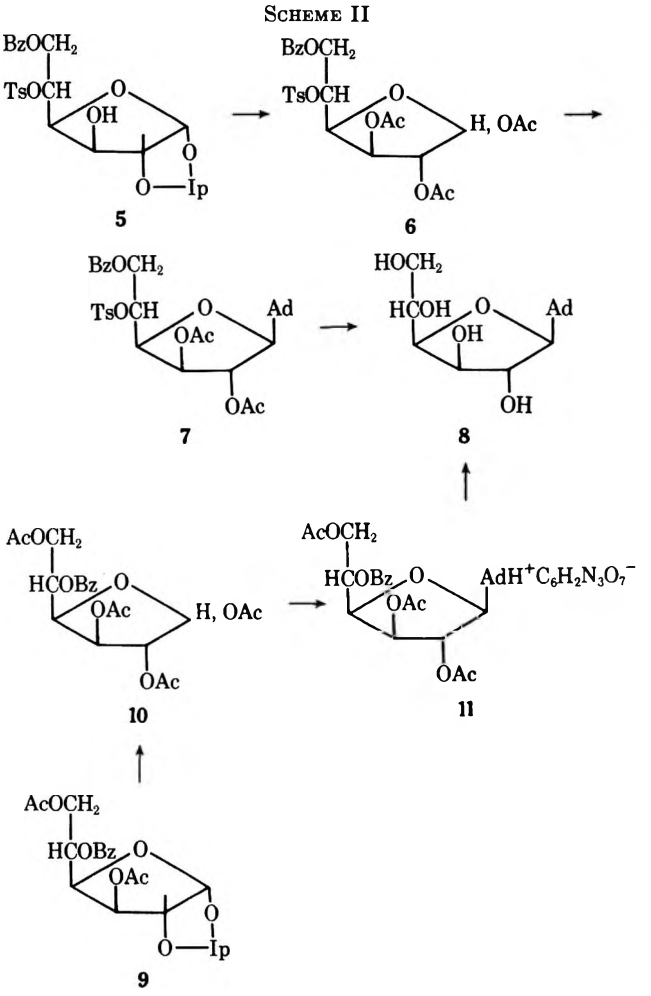
SCHEME I



scribed by Baker and his colleagues.[9] When **3** was allowed to react in a boiling mixture of sodium benzoate and moist *N*,*N*-dimethylformamide, extensive degradation ensued in minutes as the mixture became black. After work-up, hardly any organic-soluble material could be isolated from the organic phase and this appeared to consist of decomposed tarry residues. On the assumption that a cyclonucleoside had formed which had passed into the aqueous phase during work-up, confirmatory evidence was sought by scanning the water layer in the ultraviolet. Cyclonucleosides derived from adenine nucleosides are internal salts which are very water-soluble even when the hydroxyl groups are blocked with organic-soluble residues.[10] An absorption peak near λ_{max} 272 mμ confirmed this as a strong possibility. Therefore, a sample of **3** was heated at reflux alone in *N*,*N*-dimethylformamide and although the cyclonucleoside **4** would not crystallize, its structure was evident from the absorption maximum at 274 mμ and from two new bands at 1010 and 685 cm^{-1} in the infrared. This is believed to be the first report of an N-3,6′ cyclonucleoside and acts as a proof of the β configuration of **3**. Stereomodels confirmed that, if **3** had the α configuration, then it would not have been possible to form the cyclonucleoside. Problems such as cyclonucleoside formation during attempts to carry out reactions at the primary carbons of pentose nucleosides are not uncommon or unexpected.[11] Similarly, a substitution to yield the N-3,6′ cyclonucleoside (**4**) rather than the N-3,5′ cyclonucleoside would be expected due to the greater reactivity of the primary carbon.

Failure of the reaction pathway proposed above to give the desired product **8** prompted the investigation of another route starting from 6-*O*-benzoyl-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose[12] (**5**) and this is shown in Scheme II. Acetolysis of **5**

SCHEME II



gave **6**, which was coupled with 6-benzamidochloromercuripurine and this was converted to the picrate as described in the preparation of **3**. The blocked nucleoside obtained after removal of the picrate ion failed to crystallize, but was believed to be 9-(2,3-di-*O*-acetyl-6-*O*-benzoyl-5-*O*-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine (**7**). It was hoped that the use of a benzoyl group block at position 6′ would prevent the undesirable effect which occurred with compound **3**. Because Goodman had stated in a recent review article[13] that the exocyclic carbons of aldofuranose derivatives undergo displacement only by an SN2 mechanism and it was believed that the products of the reaction of acetate ion in acetic anhydride with 6-*O*-benzoyl-5-*O*-tosylhexofuranosyl derivatives were the inverted 5-*O*-acetate derivatives,[14,15] **7** was treated with Dowex 1 (acetate) in boiling acetic anhydride.[15] Some decomposition was evident and only a very small yield of **8** occurred after removal of the blocking groups. It is now known that the 6-benzoyloxy group participates in these reactions and the yields of C-5 inverted prod-

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(10) V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951); W. Anderson, D. H. Hayes, A. M. Michelson, and A. R. Todd, *ibid.*, 1882 (1954).

(11) See, for example, W. Jahn, *Chem Ber.*, **98**, 1705 (1965); M. Hubert-Habart and L. Goodman, *Can. J. Chem.*, **48**, 1335 (1970); J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, **35**, 2319 (1970); and ref 10.

(12) J. Kovar, *Can. J. Chem.*, **48**, 2383 (1970).

(13) L. Goodman, *Advan. Carbohyd. Chem.*, **22**, 119 (1967).

(14) L. Vargha, *Chem. Ber.*, **87**, 1351 (1954); M. A. Miljkovic and E. A. Davidson, Abstract of Papers, 155th Meeting of the American Chemical Society, San Francisco, Calif., 1968, C-7.

(15) P. Perchemlides, T. Osawa, E. A. Davidson, and R. W. Jeanloz, *Carbohyd. Res.*, **3**, 463 (1967).

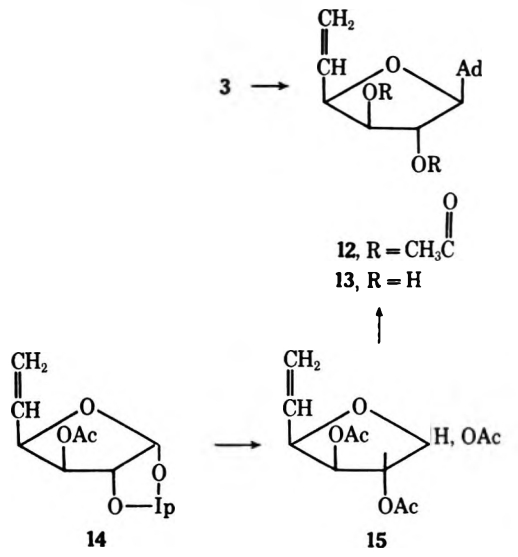
ucts are very high with sugar derivatives.[16] It is therefore not inconceivable that the nitrogen at N-3 of the purine ring was capable of competing with acetate ion in attacking the 6′ position as the benzoate migrated. This matter was not pursued further and a completely new synthesis of 9-α-L-idofuranosyladenine (**8**) was achieved as described below.

The decision to make **8** by condensation of L-idose derivatives with the base was due to recent publications of improved methods for their synthesis from D-glucose.[12,17] 3,6-Di-*O*-acetyl-5-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose[12,18] (**9**) was converted to tri-*O*-acetate **10**, which was coupled in the usual fashion with the base. The nucleoside was isolated *via* an intermediate picrate,[6,7] the blocking groups were removed, and the free nucleoside **8** crystallized and was found to be identical with the one prepared above from **5**. No attempts were made to deduce the configuration of C-1′ of **8**, but a strong argument can be made in favor of the α configuration from what is known about the ratio of β/α anomers obtained after nucleoside formation by the titanium tetrachloride method.[5,19,20]

Attention was drawn next to the preparation of a 5,6-olefinic nucleoside (**13**) which could be synthesized in a homologous manner to the preparation of a similar compound from the D-mannosyl nucleoside described in the preceding paper. Treatment of **3** with sodium iodide in acetone[2,21] gave 9-(5,6-dideoxy-2,3-di-*O*-acetyl-β-D-*xylo*-hex-5-enofuranosyl)adenine (**12**) in a 21% yield. It was noted that the competition from cyclonucleoside formation was not as evident in this reaction as in the formation of **4** in dimethylformamide. The stability of compound **3** in boiling acetone and dioxane was investigated and it was discovered that no change in λ_{max} from 259 mμ occurred, indicating that under these conditions no cyclonucleoside had formed. Considering the reactivity of most pentose nucleosides under such conditions,[10,11] the only explanation that can perhaps be offered here would be that the ring structure of cyclonucleoside **4** would be more difficult to form than that found in the pentose nucleosides. Formation of **4** is clearly a solvent effect for solutions in *N*,*N*-dimethylformamide and such a result as noted here would be quite typical for this dipolar aprotic solvent.[22]

It now became of interest to see if the 5,6-olefinic nucleoside **12** could be prepared directly from an unsaturated sugar. Although unsaturated nucleosides have been previously reported, these have usually been prepared from preformed nucleosides[23] or by condensation of a glycal[24] or 2-hydroxyglycal[25] with a nitrogenous base, which in the latter cases resulted in a double-bond migration. 5,6-Dideoxy-1,2-*O*-isopropylidene-α-D-hex-5-enofuranose[26] was acetylated to give the 3-*O*-acetate **14** as an oil (Scheme III). The boiling point of

SCHEME III



14 was considerably different from that recorded for this compound when it was prepared by condensation of 3-*O*-acetyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose with methylenetriphenylphosphorane;[27] however, the optical rotations agreed well and the infrared spectrum showed the required bands supporting the structure. Acetolysis converted **14** to the tri-*O*-acetate **15**. Of the methods available to couple a sugar derivative to a nitrogenous base, the most desirable ones were either the fusion method[28] or the titanium tetrachloride method;[5] other procedures require previous formation of a glycosyl halide which is usually done with a hydrogen halide in an organic solvent, conditions which will result in addition of the hydrogen halide across the double bond of **15**. Condensation of **15** with 6-benzamidochloromercuripurine and titanium tetrachloride gave a 33% yield of a picrate, which was prepared from the crude product. Removal of the picrate ion gave **12**. The acetyl groups of **12** were removed with base to give 9-(5,6-dideoxy-β-D-*xylo*-hex-5-enofuranosyl)adenine (**13**) which was an unstable substance.

Although not entirely unexpected, it is quite obvious from these experiments that interconversions of preformed hexofuranosyl nucleosides at the exocyclic carbons will be fraught with difficulties when the purine ring is on the same side of the sugar ring as the ethylene glycol side chain. Reactions that would probably be the most successful are those which would proceed by an S_N2 displacement at C-5′ and have a nonparticipating group at C-6′. The nature of the solvent and the temperature will likewise effect this to a great extent.

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(17) M. A. Miljkovic and E. A. Davidson, *Carbohyd. Res.*, **13**, 444 (1970).
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Experimental Section[29]

9-(2,3-Di-*O*-acetyl-5,6-di-*O*-*p*-toluenesulfonyl-β-D-glucofuranosyl)adenine (3).—1,2-*O*-Isopropylidene-5,6-di-*O*-*p*-toluenesulfonyl-α-D-glucofuranose[4] (1) (15.1 g, 28.5 mmol) was dissolved in a mixture of 385 ml of glacial acetic acid and 36 ml of acetic anhydride, and 21.6 ml of concentrated sulfuric acid was added dropwise. During this procedure the temperature of the reaction mixture was held between 10 and 20° by frequent immersion in an ice bath. The flask was stored overnight at room temperature and then the contents were poured into 1.1 l. of ice–water. A heavy, white gum formed, which was extracted with chloroform (*ca.* 215 ml) and washed with water, saturated sodium bicarbonate, and again with water, and dried. The chloroform was removed by evaporation and traces of acetic acid were azeotropically distilled using toluene. A clear, almost colorless syrup (2) weighing 14.7 g (83%) resulted: ir (film, NaCl) 1755 (C=O of acetate), 1594 (phenyl ring), 1363 and 1175 cm^{-1} (sulfonate). There was no band for a hydroxyl group.

From a mixture containing 2.44 g (4 mmol) of **2**, 2.4 g of 6-benzamidochloromercuripurine, 2.4 g of Celite-545, and 200 ml of 1,2-dichloroethane was distilled 25 ml of the solvent in order to remove traces of moisture. A solution of 0.55 ml of titanium tetrachloride in 10 ml of 1,2-dichloroethane was added and the mixture was stirred under reflux for 19 hr.[5] When the flask had cooled, 73 ml of saturated sodium bicarbonate solution was added and stirring was continued at room temperature for 2.5 hr. The precipitate was removed by filtration through a pad of Celite and the filter cake was washed three times with 20-ml portions of chloroform. The organic phase was separated and evaporated to dryness. The syrupy residue was dissolved in chloroform and washed three times with 45-ml portions of 30% aqueous potassium iodide and once with water. After the solution had been dried and evaporated, an orange gum remained which weighed 3.17 g. This was dissolved in warm absolute ethanol and 13 ml of 10% ethanolic picric acid was added and the solution was heated at reflux for a few minutes and then allowed to cool.[6] Crystallization yielded 2.94 g (80%) of the picrate of **3**, mp 139°. A portion of this was recrystallized from methanol to give tiny, spherical crystals, mp 141–143°.

Anal. Calcd for $C_{35}H_{34}N_8O_{19}S_2$: C, 45.75; H, 3.87; N, 12.19. Found: C, 46.14; H, 3.87; N, 11.80.

To a solution of 2.83 g (3.1 mmol) of the picrate in 145 ml of 75% aqueous acetone was added Bio-Rad AG1-X8 (CO_3^{-2}) resin and the solution was stirred until the yellow color of the picrate ion had been removed.[7] An orange-colored contaminant was removed with a Darco G-60 treatment and the clear, colorless solution was evaporated to dryness giving a white solid. This was recrystallized from chloroform–ethanol to produce 1.2 g (56%) of crystals: mp 187–187.5°; $[\alpha]^{25}D$ −36° (*c* 1.5, $CHCl_3$); uv λ_{max}^{MeOH} 259 mu; ir (KBr) 3370 (NH), 1760, 1740 (C=O), 1650, 1598 (phenyl and purine ring), 1360 and 1174 (sulfonate), 1104, 1093, 1074, 1012 cm^{-1} (COC, CO); tlc in 5:1 chloroform–methanol, R_f 0.66.

Anal. Calcd for $C_{29}H_{31}N_5O_{11}S_2$: C, 50.49; H, 4.54; N, 10.16; S, 9.30. Found: C, 50.07; H, 4.48; N, 9.80; S, 8.93.

Conversion of 3 to Cyclonucleoside 4.—A solution of 100 mg of **3** in 3 ml of *N*,*N*-dimethylformamide was heated at reflux for 1 hr. The mixture turned a dark brown and the ultraviolet absorption maximum shifted to 275 mμ. The solvent was evaporated off, but all attempts to achieve crystallization failed. The solubility of **4** in water was confirmed: λ_{max}^{MeOH} 274 mμ; ir (film, NaCl) 1010 and 685 cm^{-1} (tosylate anion). Another band expected near 1210 cm^{-1} was obscured by a broad plateau, tlc in 5:1 chloroform–methanol, R_f 0.09.

9-α-L-Idofuranosyladenine (8). From **9.**—3,6-Di-*O*-acetyl-5-*O*-benzoyl-1,2-*O*-isopropylidene-β-L-idofuranose[12] (9) (4.9 g, 12 mmol) was dissolved in a mixture containing 58 ml of glacial acetic acid and 6.6 ml of acetic anhydride. The addition of sulfuric acid (2.8 ml) and the work-up were carried out as described above for **2**. The syrup was added to a mixture of 7.1 g of 6-benzamidochloromercuripurine, 7.1 g of Celite-545, titanium tetrachloride (1.7 ml), and a final volume of 550 ml of 1,2-dichloroethane. The reaction and work-up followed the procedure described for the preparation of **3**. A picrate was prepared by reaction of a solution of the completely blocked nucleoside in 30 ml of ethanol with 28 ml of 10% ethanolic picric acid at reflux for 0.5 hr. Yellow crystals (4.56 g, 50%) were deposited upon chilling. Recrystallization from acetone–ethanol (Darco treatment) gave colonies of crystals: 2.86 g; mp 188°; $[\alpha]^{28}D$ +38° (*c* 1.1, $CHCl_3$); ir (KBr) 1748, 1738 sh (C=O), 1694 (protonated adenine ring), 1610, 1582 (phenyl and purine rings), 1550 (NO_2), 1362 (*gem*-dimethyl), 1313 (NO_2), 1098–1050 (broad CO), 710 cm^{-1} (monosubstituted phenyl).

Anal. Calcd for $C_{30}H_{28}N_8O_{16}$: C, 47.62; H, 3.73; N, 14.81. Found: C, 46.82; H, 3.94; N, 14.42.

A solution of the picrate (2.73 g) in 200 ml of 80% aqueous acetone was stirred with Bio-Rad AG1-X8 (CO_3^{-2}) resin until the solution was colorless, whereupon the resin was filtered off and the solvents were removed by evaporation. Coevaporation with ethanol to dry the product left a white foam (1.84 g) which did not crystallize from common solvents. Finally a solution of this in 50 ml of methanol was treated with 6 ml of 1 *N* methanolic sodium methoxide and refluxed for 1 hr. IR-120 (H^+) ion exchange resin was used to neutralize the solution. After removal of the resin, the methanolic solution was concentrated by boiling, whereupon crystallization began and was allowed to proceed at room temperature, affording 668 mg, mp 227°. A second crop of crystals from the mother liquor gave 96 mg: mp 226° (total yield 71%) (recrystallization raised the melting point to 228–228.5°); $[\alpha]^{26}D$ −39° (*c* 1.0, 1 *N* HCl); uv max (0.1 *N* HCl) 257.5 mμ (ε 13,800), (H_2O) 257 (14,000), (0.1 *N* NaOH) 260 (14,300); Rad 1.47 (5% aqueous disodium hydrogen phosphate), 0.43 (86:14 *n*-butyl alcohol–water).

Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.45; H, 5.09; N, 23.56. Found: C, 44.44; H, 5.09; N, 23.52.

From 5.—6-*O*-Benzoyl-1,2-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-D-glucofuranose[12] (4.13 g, 8.6 mmol) was converted to the tri-*O*-acetate **6** as described above for the preparation of **2**, yielding 5.1 g of a hard, white foam. This was coupled with 6-benzamidochloromercuripurine (5.4 g), Celite-545 (5.4 g), titanium tetrachloride (1.3 ml), and 1,2-dichloroethane (450 ml) as previously described. The picrate was prepared by boiling a 60-ml solution of the product with 23 ml of 10% ethanolic picric acid, yielding 3.29 g of yellow crystals which were probably contaminated slightly with picric acid, mp 133–136°.

Anal. Calcd for $C_{32}H_{32}N_8O_{17}S$: C, 48.37; H, 3.71; N, 12.90. Found: C, 48.14; H, 3.75; N, 14.16.

The picrate ion was removed as described above giving a yellow foam (2.17 g) of 9-(2,3,6-tri-*O*-acetyl-5-*O*-benzoyl-β-D-glucofuranosyl)adenine, which was contaminated by two trace components which moved slower than the main product on tlc in 95:5 ethyl acetate–methanol: R_f 0.35; ir (film, NaCl) 3320 (NH), 1725 (broad C=O), 1642, 1598 (phenyl and purine ring), 1368, 1175 (sulfonate), 1108–1048 (plateau CO), 712 (monosubstituted phenyl).

The foam was dissolved in 65 ml of acetic anhydride and treated at reflux with 40 ml of Dowex 1-X8 (acetate) resin for 10 hr.[15] The reaction mixture darkened rather quickly and was nearly black by the end of the reflux time. The resin was removed by filtration and the solution was evaporated to dryness. The blocking groups were removed in methanolic sodium methoxide and a picrate was prepared,[30] yield 305 mg, mp 191–195°, resolidifying as needles which melted at 242–244° dec. The free nucleoside was regenerated[30] with an anion exchange resin in hot water and was crystallized from methanol giving 94 mg, mp 226.5–228°. This substance was identical with compound **8** as prepared from **9** in every respect.

9-(5,6-Dideoxy-2,3-di-*O*-acetyl-β-D-*xylo*-hex-5-enofuranosyl)adenine (12). From 3.—A solution of 1.36 g of **3**, 3.5 g of sodium iodide, and 50 ml of acetone was heated at 100° in a stainless steel bomb for 15 hr.[2,21] The mixture was diluted with chloroform and washed with 400 ml of one-half saturated sodium bicarbonate solution containing 9 g of sodium thiosulfate and water, and dried. The chloroform was evaporated on a steam bath, whereupon crystallization occurred. Two recrystallizations from ethanol gave 147 mg (19%) of colorless platelets: mp 202.5–203° with softening of the crystals between 195 and 201°; $[\alpha]^{23}D$ +22.5° (*c* 1.12, $CHCl_3$); uv max (EtOH) 259 mμ; ir (KBr) 3240 (NH), 3080 (CH=CH_2), 1745 (C=O of acetate), 1678, 1602, 1574 (purine ring), 1090, 1058, 1045 (CO), 988 (CH=CH_2); nmr ($CDCl_3$) 1.61, 1.84 (both s, H-2 and H-8),

(29) General methods and instrumentation are given in the preceding paper.[2] Tlc was performed on precoated silica gel F_{254} plates prepared by E. Merck A.G., Darmstadt. Paper chromatography was done on Whatman No. 1 paper. Rad (adenine) = 1.00.

(30) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

3.68 (d, $J_{1,2}$ = 2.4 Hz, H-1'),[31] 4–4.8 (m, CH=CH_2 and unresolved H-2', H-3'), 5.1 (m, H-4'), 7.81, 7.90 (both s, CH_3); tlc in 95:5 ethyl acetate–methanol, R_f 0.31.

Anal. Calcd for $C_{15}H_{17}N_5O_5$: C, 51.87; H, 4.93; N, 20.16. Found C, 51.51; H, 5.01; N, 19.77.

From **14**.—To a solution of 5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose[26] (4.75 g) in 50 ml of dry pyridine was added 16 ml of acetic anhydride while the mixture was stirred and chilled in an ice bath. After remaining at this temperature for 1 hr, the mixture was kept at room temperature for 24 hr. The solution was evaporated to a small volume diluted with 100 ml of chloroform, and washed with water (100 ml), saturated sodium bicarbonate (two 100-ml portions), and water (100 ml), and dried. Evaporation gave an oil from which traces of pyridine were removed by coevaporation of toluene. Distillation gave 2.4 g (41%) of an unstable oil (**14**): bp 67–70° (0.15 mm); $[\alpha]^{24}D$ −12° (*c* 4, $CHCl_3$); ir (film, NaCl) 1745 (C=O), 1648 (C=C), 1414 (=CH_2), 1375 (*gem*-dimethyl), 994 cm^{-1} (-CH=CH_2) [lit.[27] bp 154–157° (0.7 mm), $[\alpha]D$ −13° (c 1, $CHCl_3$)].

Compound **14** (2.4 g) was converted to tri-*O*-acetate **15** in a solution of glacial acetic acid (51 ml), acetic anhydride (6.8 ml), and concentrated sulfuric acid (3.5 ml) as described above for the preparation of **2**. A yellow syrup weighing 2.52 g resulted.

The coupling reaction was performed by previously described methods. The reaction mixture consisted of 2.52 g (9.3 mmol) of **15**, 5.44 g (11.5 mmol) of 6-benzamidochloromercuripurine, 5.4 g of Celite-545, 0.7 ml of titanium tetrachloride, and 200 ml of 1,2-dichloroethane. The syrupy residue obtained was dissolved in 20 ml of warm ethanol, 22 ml of 10% ethanolic picric acid was added, and the mixture was boiled under reflux until crystals began to appear after 5 min. The picrate was allowed to crystallize at room temperature, then chilled in an ice bath to give upon filtration 1.54 g of crystals. The mother liquor deposited an additional 0.32 g (total yield 33%). Recrystallization from acetone–ethanol gave 1.2 g of tiny crystals (picrate of **12**): mp 210–214° dec; ir (KBr) 1752 (C=O), 1694 (protonated adenine ring), 1608, 1568 (purine ring), 1548, 1314 (NO_2), 1077–1042 cm^{-1} (broad CO).

Anal. Calcd for $C_{21}H_{20}N_8O_{12}$: C, 43.76; H, 3.50; N, 19.44. Found: C, 43.41; H, 3.76; N, 19.26.

(31) The low coupling constant is indicative of a *trans* relationship between C-1' and C-2' and represents additional support for the configurational assignment.

The picrate (1.06 g) was dissolved in 150 ml of 80% aqueous acetone and the yellow color was discharged with Bio-Rad AG1-X8 (CO_3^{-2}) resin. The resin was filtered off, the solvents were removed by evaporation, and the product was crystallized from ethanol in two crops to give 344 mg (54%); mp 198–201° Recrystallization produced 248 mg of colorless platelets of **12**, mp 201–203°. The mixture melting point with **12** prepared from **3** gave no depression, the ir spectra were identical, and the compounds migrated the same on tlc plates.

9-(5,6-Dideoxy-β-D-*xylo*-hex-5-enofuranosyl)adenine (**13**).—To a solution of 207 mg of **12** in 25 ml of methanol was added 1.5 ml of 1 *N* methanolic sodium methoxide and the mixture was boiled under reflux for 50 min.[32] The dark solution was cooled to room temperature, brought to neutrality with Dowex 50 (H^+) resin, and evaporated to dryness. The brown residue was dissolved in water, treated with activated charcoal (heat), and evaporated again. The compound failed to crystallize but could be obtained as a hard, gray foam by evaporation of acetone to give 63 mg (40%) of **13**. This substance was very hygroscopic and slowly decomposed upon storage in a desiccator at room temperature. It was homogeneous on paper chromatograms: Rad 1.25 (5% aqueous disodium hydrogen phosphate) and 1.40 (86:14 *n*-butyl alcohol–water); uv max (0.1 *N* HCl) 257 and (H_2O or 0.1 *N* NaOH) 259 mμ.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 50.14; H, 5.25; N, 25.26.

A picrate prepared from **13** in methanol[30] had mp 209–211° dec on recrystallization. This material was very light sensitive.

Anal. Calcd for $C_{17}H_{16}N_8O_{10}$: C, 41.47; H, 3.28; N, 22.76. Found: C, 41.46; H, 3.30; N, 22.14.

Registry No.—**2**, 32653-56-8; **3**, 32653-57-9; **3** (picrate), 32653-58-0; **4**, 32653-59-1; **7** (picrate), 32781-70-7; **8**, 32653-60-4; **11** (picrate), 32653-67-1; **12**, 32653-61-5; **12** (picrate), 32653-62-6; **13**, 32653-63-7; **13** (picrate), 32653-64-8; **14**, 17225-57-9.

Acknowledgment.—The author would like to give acknowledgment to Mr. Philip Schiffman, who performed some of the preliminary experiments connected with this work.

(32) It is better to run this reaction overnight at room temperature to prevent degradation of the product.

Interconversions of Hexofuranosyl Nucleosides. III. Synthesis of a 4',5'-Unsaturated Hexofuranosyl Nucleoside[1]

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6-Deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-L-mannofuranose (**1**) was converted to the α-L-chloride (**2**) by reaction with thionyl chloride in pyridine. Compound **2** was coupled with 6-benzamidopurine and 9-(6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine (**4**) was isolated *via* its picrate **3**. Proof of the structure of **4** was obtained by removal of the tosyl group, which gave the known isopropylidene nucleoside **5**. When **4** was allowed to react with sodium benzoate in boiling *N*,*N*-dimethylformamide, the unsaturated nucleosides, 9-(5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranosyl)adenine (**6**) and 9-(5,6-dideoxy-α-L-*lyxo*-hex-5-enofuranosyl)adenine (**7**), were unexpectedly isolated. The yield of **6** was 35% and could be raised to 54% by reaction of **4** with potassium *tert*-butoxide in hot *N*,*N*-dimethylformamide. The nucleosidic bond of **6** was extremely acid labile and attempts to remove the isopropylidene group resulted in immediate degradation and release of adenine. Interest in the unsaturated free nucleoside **10** is due to its structural relationship to the nucleoside antibiotic, decoyinine. Another nucleoside derivative, 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine (**13**), was prepared as a potentially useful starting material toward the synthesis of **10**. Reaction of **1** under acetolysis conditions gave the triacetate **12** which was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method. Removal of the *N*-benzoyl group gave **13**, whose chemical properties did not favor its transformation to **10**.

It was shown in the preceding two papers[2,3] that the transformation of a hexofuranosyl nucleoside into its 5' epimer was dependent to a great extent upon the configuration of the exocyclic group at C-4' relative to the configuration of the purine ring at C-1'. When they were both on the same side of the furan ring of the sugar, it became difficult to achieve a successful epimerization

(1) This work was supported, in part, by Grant No. T-442 from the American Cancer Society.

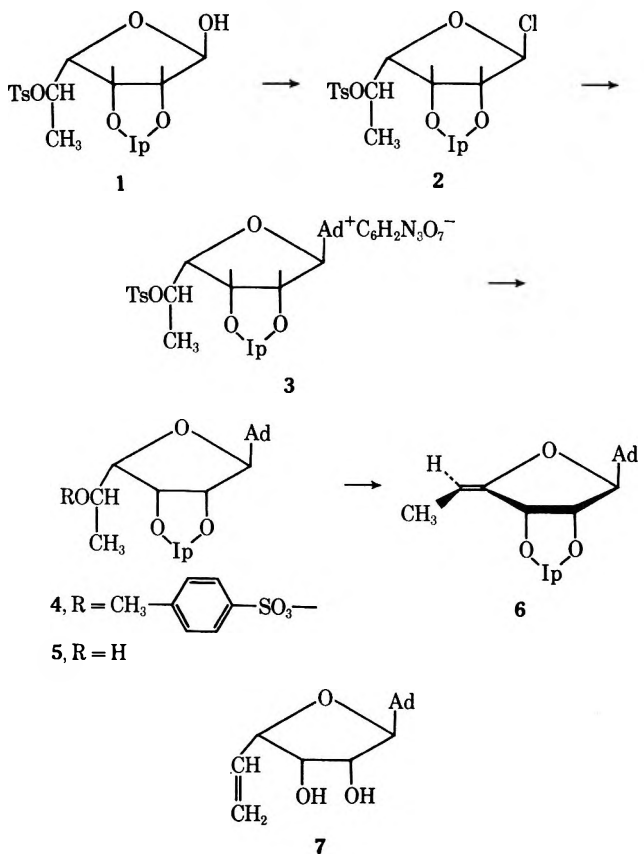
(2) L. M. Lerner, *J. Org. Chem.*, **37**, 470 (1972).

(3) L. M. Lerner, *ibid.*, **37**, 473 (1972).

at C-5′, especially if the C-6′ position was occupied by a tosyloxy group. If an acyloxy group occupied the C-6′ position, there was still the possibility of a participation and the success of this synthesis became dependent to some degree on the reaction conditions used, especially as concerned the solvent and temperature. In this paper are reported attempts at inversion of configuration at C-5′ of a hexofuranosyl nucleoside having the exocyclic carbons on the opposite side of the sugar ring from the purine and a 6′-deoxy carbon. The intention was to prepare 9-(6-deoxy-β-D-gulofuranosyl)-adenine from a nucleoside derivative of 6-deoxy-L-mannose (L-rhamnose).

It was first necessary to undertake the synthesis of 9-(6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine (**4**). The route chosen was similar to those which have been used several times before for the preparation of nucleosides having a nonparticipating acetal group blocking the hydroxyls at C-2 and C-3 (Scheme I).[4] The anomeric hydroxyl

SCHEME I



1 2 3 6 7

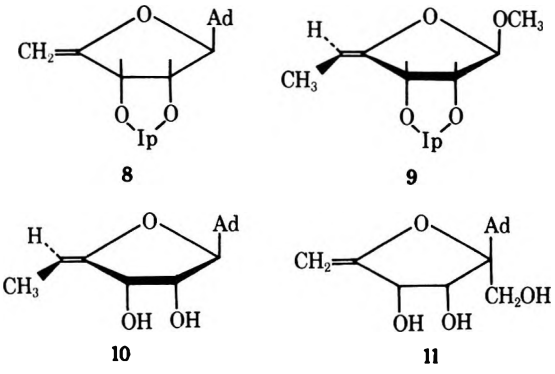
group of 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-L-mannofuranose[5] (**1**) was exchanged for a chloride by reaction with thionyl chloride in pyridine. The chloro sugar **2** was shown to have the α-L configuration by nmr spectroscopy which revealed a singlet for the anomeric hydrogen at τ 3.96. This is consistent with a trans configuration between H-1 and H-2. Condensation of **2** with 6-benzamidopurine under conditions developed by Yamaoka, Aso, and Matsuda[6] was successfully carried out and the crude product was converted to the picrate[7] **3**, which was in turn treated with an anion exchange resin[8] to give **4**. Both **3** and **4** probably contained small amounts of their β-L anomers; however, it has been demonstrated that only trace amounts of the 1′,2′-cis nucleosides are obtained from reactions of purines with glycosyl halides having nonparticipating blocking groups.[4] Proof of the structure of **4** was obtained by preparation of 9-(6-deoxy-2,3-*O*-isopropylidene-α-L-mannofuranosyl)adenine[4] (**5**) by removal of the tosyl group at C-5′ of **4** with sodium amalgam. These experiments represent further evidence that these coupling reactions proceed by an SN1 mechanism. The anomeric configuration of nucleoside **4** is the same as that of the glycosyl chloride **2** and the only effect directing the configuration appears to be steric in origin.[4]

In one of the early attempts to invert the configuration at C-5′ by reaction of **4** with sodium benzoate in boiling, moist *N*,*N*-dimethylformamide,[9] the crude product was treated directly with base, then acid, and subsequently chromatographed on an anion-exchange column.[10] All that was obtained from the column were very small amounts of two substances, one of which was identified as 9-(5,6-dideoxy-α-L-*lyxo*-hex-5-enofuranosyl)adenine (**7**) from its elemental analysis and by comparison of its melting point, ir spectrum, and specific rotation to those of the D enantiomer prepared previously.[2] Paper and thin layer chromatography of a similar preparation prior to column chromatography revealed that the nucleoside bond had broken, giving adenine as the major uv-absorbing spot. Since it was not expected that 9-(6-deoxy-2,3-*O*-isopropylidene-β-D-gulofuranosyl)adenine would be degraded under the acidic conditions used and it was known that the nucleosidic bond of the enantiomer of **7** was fairly stable to mild acid conditions,[2] it was felt that further investigation of the immediate product of the sodium benzoate–dimethylformamide reaction was warranted. When this was done, a crystalline substance was obtained which decolorized solutions of bromine and potassium permanganate. Elementary analysis also supported an unsaturated product. Because the isopropylidene derivative of the D enantiomer of compound **7** was a known compound[2] whose properties differed considerably from those obtained here, it appeared most likely that elimination had occurred between positions 4′ and 5′ to give 9-(5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranosyl)adenine (**6**). This interpretation was supported by the nmr spectrum which showed a methyl resonance at τ 8.39 as a doublet which was assigned to the protons at C-6′. The chemical shift for the proton at C-5′ (τ 5.11) was identified by a decoupling experiment performed by irradiation at the resonance frequency of the C-6′ methyl group. It should perhaps be noted that the anomeric proton gave a singlet at τ 3.69 which would indicate a trans relationship between H-1′ and H-2′ and, therefore, a β-D configuration for the nucleoside, further evidence for the assigned anomeric

(4) L. M. Lerner and Y. Y. Cheng, *Carbohyd. Res.*, **14**, 297 (1970), and references cited therein.
(5) P. A. Levene and J. Compton, *J. Biol. Chem.*, **116**, 169 (1936).
2778 (1957).
(6) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).
(7) J. R. Parikh, M. E. Wolff, and A. Burger, *J. Amer. Chem. Soc.*, **79**, 2778 (1957).
(8) M. L. Wolfrom, A. B. Foster, P. McWain, W. von Bebenburg, and A. Thompson, *J. Org. Chem.*, **26**, 3095 (1961).
(9) E. J. Reist, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **80**, 5775 (1958).
(10) C. A. Dekker, *ibid.*, **87**, 4027 (1965).

configurations used in this and previous work.[4] It is also of interest to note that when the reaction of bromine with **6** was reinvestigated, it was found that the ultraviolet peak shifted from 261 to 275 mμ. This may mean that an N-3,4′ cyclonucleoside had formed, such as isolated by McCarthy, *et al.*,[11] for a similar reaction of 9-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)adenine (**8**) (Chart I).

CHART I



Although it has been shown that anions become more basic in aprotic dipolar solvents such as *N*,*N*-dimethylformamide,[12] the 35% yield in this elimination reaction was surprising. This is especially so when one considers that Baker and coworkers[9] converted methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-allofuranoside into methyl 6-deoxy-5-*O*-benzoyl-2,3-*O*-isopropylidene-α-L-talofuranoside in yields of 77–79% under similar conditions. Solutions of **4** in boiling *N*,*N*-dimethylformamide did not undergo reaction to **6**, as has been reported to happen in some cases where olefins have been prepared from sulfonate esters of secondary alcohols.[13] The yield of **6** obtained here compared favorably with the yield (40%) of olefinic sugar **9** which was obtained by reacting methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-allofuranoside with potassium *tert*-butoxide in boiling *tert*-butyl alcohol.[14] Treatment of **4** with a solution of potassium *tert*-butoxide in pyridine and *tert*-butyl alcohol at room temperature did not give a reaction and **4** was recovered unchanged. Under the same conditions, 5′-*O*-*p*-toluenesulfonyl-2′,3′-*O*-isopropylideneadenosine gave a 35% yield of **8** after 5 min.[11] Treatment of **4** with sodium methoxide in *N*,*N*-dimethylformamide at either room temperature or at 100° yielded a number of substances, among them a very small amount of **6** and what appeared to be **5** from tlc data. However, when **4** was heated at reflux with potassium *tert*-butoxide in a mixture of *tert*-butyl alcohol and *N*,*N*-dimethylformamide for 22 hr, the yield of **6** was 54% or better if the mother liquors were chromatographed on silicic acid columns. The isolation of unsaturated products from reactions of tosyl derivatives of alditols with sodium benzoate in boiling dimethylformamide have been reported previously[15] and papers describing the elimination of *p*-toluenesulfonic acid under similar conditions to form enol tosylates have been referred to in a previous article.[2]

When the methyl glycoside of **1** was allowed to react under basic conditions the product obtained was the same one which was obtained from methyl 6-deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-β-D-allofuranoside, namely **9**.[14] Since hydroboration of **9** gave the 6-deoxy-D-gulose derivative and not the 6-deoxy-L-mannose derivative, the conclusion was made that the elimination has occurred by an E2 mechanism and that the configuration of the methyl group in relation to the ring oxygen was trans. Hydroboration[14,16] of **6** resulted in darkened reaction mixtures and as many as six unidentified components as shown by tlc. Attempts to carry out a successful hydroboration were dropped and the structure of **6** as shown in Scheme I is assumed in analogy to **9**.

It has been found to be impossible to remove the isopropylidene group of **6** under all of the acidic conditions tried. Adenine was liberated immediately. It was now understood why only compound **7** was obtained in the earlier experiment. During the reaction which formed **6**, a small amount of the isopropylidene derivative of **7** was also formed by elimination between C-5′ and C-6′. Acid hydrolysis degraded **6** completely, but did not hydrolyze the C–N bond of **7**, which was freed of adenine on the ion-exchange column.[10] Similar results occurred in attempts to remove the isopropylidene group of **8**.[11]

Removal of the isopropylidene group of **6** would give the free nucleoside **10**, which would be an interesting analog of the unsaturated nucleoside antibiotic, decoyinine (**11**). Preparations of other nucleoside analogs of this antibiotic have been reported.[11,17] Further attempts to obtain **10** were now made and several approaches were considered. The first one was to replace the isopropylidene group of **6** with a group which was much more acid labile, such as a methoxymethylidene group.[18] To do this it was necessary to be able to selectively hydrolyze the isopropylidene group and as of this writing this task has not been accomplished satisfactorily. Next, the synthesis of 9-(6-deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)-adenine (**13**) was undertaken (Scheme II). The plan here was to remove the base-labile groups in one step with a strong base and get a concomitant elimination at C-4′ to form **10** or, if that was unsuccessful, to remove the acetyl groups with catalytic amounts of sodium methoxide or other base and then form the methoxymethylidene derivative. Compound **1** was subjected to acetolysis and a compound assumed to be the tri-*O*-acetate **12** was obtained. This was condensed with 6-benzamidochloromercuripurine, using titanium tetrachloride to generate the glycosyl chloride *in situ*,[19] and **13** was prepared *via* the picrate.[7,8] The anomeric con-

(11) J. R. McCarthy, R. K. Robins, and M. J. Robins, *J. Amer. Chem. Soc.*, **90**, 4993 (1968).

(12) A. J. Parker, *Quart. Rev., Chem. Soc.*, 163 (1962).

(13) H. R. Nace, *J. Amer. Chem. Soc.*, **81**, 5428 (1959); D. V. Banthorpe, "Elimination Reactions," Elsevier, New York, N. Y., 1963, pp 33 ff.

(14) H. Arzoumanian, E. M. Acton, and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 74 (1964).

(15) M. A. Bukhari, A. B. Foster, and J. M. Webber, *J. Chem. Soc.*, 2514 (1964); M. A. Bukhari, A. B. Foster, J. M. Webber, and J. Lehmann, *Carbohyd. Res.*, **1**, 485 (1966).

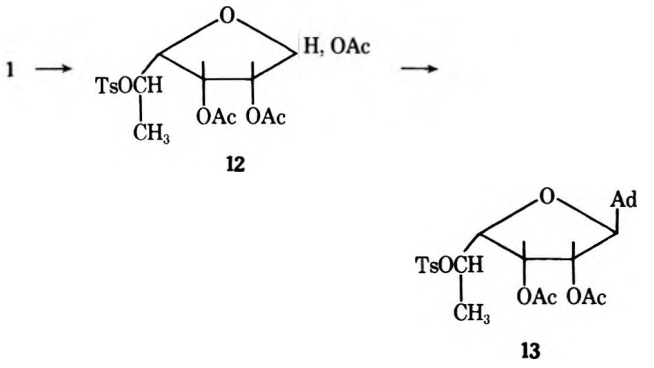
(16) M. L. Wolfrom, K. Matsuda, F. Komitsky, Jr., and T. E. Whiteley, *J. Org. Chem.*, **28**, 3551 (1963).

(17) J. P. H. Verheyden and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5684 (1966).

(18) B. E. Griffin, M. Jarman, C. B. Reese, and J. E. Sulston, *Tetrahedron*, **23**, 2301 (1967).

(19) B. R. Baker, R. E. Schaub, J. P. Joseph, and J. H. Williams, *J. Amer. Chem. Soc.*, **77**, 12 (1955); J. Prokop and D. H. Murray, *J. Pharm. Sci.*, **54**, 359 (1965).

SCHEME II



figuration of **13** was assigned as α by reference to the trans rule,[20] which predicts that the α anomer will predominate because of the directive effect of the acyloxy group at C-2. Treatment of **13** with potassium *tert*-butoxide in *N*,*N*-dimethylformamide or methanolic sodium methoxide caused the mixtures to darken and resulted in complex mixtures of products as shown by tlc. This characteristic was noted by McCarthy, *et al.*,[11] during similar reactions with 5′-tosyl derivatives of adenosine and seems to be a general feature of these types of compounds which either have base-labile blocking groups at C-2′ and C-3′ or no blocking groups whatsoever.

A number of unsuccessful attempts were made to deacylate **13** using conditions which have been used successfully to deacylate sugars without detosylating them.[21] Catalytic quantities of sodium methoxide in methanol had no effect on **13** even under boiling conditions. Methanolic ammonia gave a 50% recovery of crystalline **13** and five other components which chromatographed on tlc plates similarly to some of the products derived from the complex mixtures mentioned above. Sodium hydroxide in aqueous acetone gave results which were even less hopeful.

Further work is continuing in this laboratory leading to the preparation of **10**, an interesting but elusive compound.

Experimental Section[22]

6-Deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl Chloride (2).—6-Deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-L-mannofuranose[5] (8.2 g, 24 mmol) was dissolved in 14 ml of dichloromethane[23] and added dropwise to a stirring ice-cold mixture containing 4.6 ml of thionyl chloride in 11.5 ml of dry pyridine and 14 ml of dichloromethane. The reaction was allowed to proceed for 6 hr at 0° and then poured onto 100 g of ice. When the ice had melted, 50 ml of dichloromethane was added and the organic layer was separated. Two more extractions of the aqueous layer with 35-ml portions of dichloromethane were carried out, and the extracts were all combined and washed twice with 75-ml portions of ice-cold 1 *N* sodium hydroxide solution and twice with 100-ml portions of ice-cold water, and dried. The solution was evaporated to a syrup from which toluene was coevaporated two times to remove traces of pyridine. An orange syrup was obtained which gave an instantaneous positive alcoholic silver nitrate test: ir (film NaCl) 1174 cm^{-1} (sulfonate); nmr ($CDCl_3$) τ 2.25 (d, phenyl protons ortho to sulfonate), 2.75 (d, phenyl protons ortho to CH_3), 3.96 (s, H-1), 4.99 (m, unresolved H-2, H-3, H-4), 5.68 (m, H-5), 7.56 (s, CH_3 of tosyl group), 8.55 (d, C-6 CH_3), 8.75, 8.84 (both s, *gem*-dimethyl). This compound was used directly in reactions without further purification because it was rather unstable.

9-(6-Deoxy-2,3-*O*-isopropylidene-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine (4).—From a mixture of 5.5 g of 6-benzamidopurine, 6.9 g of mercuric cyanide, and 350 ml of nitromethane was distilled 50 ml of the latter to remove any traces of moisture. The mixture was cooled to below the boiling point and 12 g of anhydrous calcium sulfate was added, followed by the entire sample of **2** in 50 ml of dry nitromethane.[6] The mixture was heated at reflux for 4 hr and filtered while still warm, and the filter cake was washed with two 25-ml portions of warm nitromethane. The solvent was evaporated, and the residue was extracted with 300 ml of dichloromethane, filtered, washed three times with 150-ml portions of 30% potassium iodide and twice with 150-ml portions of water, and dried. Evaporation gave 8.4 g of a thick, orange syrup which was dissolved in 35 ml of absolute ethanol and treated with 50 ml of 10% ethanolic picric acid at reflux for 10 min, at which time crystals began to appear.[7] Crystallization was allowed to continue at room temperature to yield 4.31 g (26% from **1**) of yellow crystals in two crops: mp 190–196° dec. A 300-mg sample was recrystallized from methanol: mp 194–196°; $[\alpha]^{26}D$ −24° (*c* 1.13, acetone); ir (KBr) 1690 (protonated adenine ring), 1604 (phenyl and purine ring), 1544 (NO_2), 1375 sh, 1358 (*gem*-dimethyl and sulfonate), 1316 (NO_2), 1173 (sulfonate), and 1076 cm^{-1} (COC, CO).

Anal. Calcd for $C_{27}H_{28}N_8O_{13}S$: C, 46.02; H, 4.01; N, 15.90. Found: C, 45.65; H, 4.01; N, 15.79.

In other preparations of **3**, yields ranging up to 46% from **1** were obtained by this procedure.

A solution of 4.0 g of **3** in 175 ml of 80% aqueous acetone was stirred with Bio-Rad AG1-X8 (CO_3^{-2}) resin until the yellow color due to picrate ion was removed.[8] Some orange color due to a contaminant was removed by treatment with Darco G-60, affording a clear, colorless solution. Evaporation gave a hard white foam which was dried by evaporation of absolute ethanol. The foam weighed 1.4 g (52%): $[\alpha]^{26}D$ −15° (*c* 1.5, *N*,*N*-dimethylformamide); ir (film, NaCl) 3360 (NH) 1640, 1595 (phenyl and purine ring), 1378 sh, 1360 (*gem*-dimethyl and sulfonate), 1175 (sulfonate), 1074 cm^{-1} (broad CO). Tlc showed that the foam was not homogeneous, but was contaminated by trace amounts of two slower moving components: R_f of **4** in 1:1 ethyl acetate–methanol, 0.59.

Anal. Calcd for $C_{21}H_{25}N_5O_9S$: C, 53.04; H, 5.30; N, 14.73; S, 6.74. Found: C, 52.54; H, 5.52; N, 14.17; S, 6.07.

When addition of the ion-exchange resin and of the charcoal was more cautiously controlled, yields such as 71 and 97% were obtained, indicating that the product was being absorbed by these materials.

9-(6-Deoxy-2,3-*O*-isopropylidene-α-L-mannofuranosyl)adenine (5).—To a solution of 1 g of **4** in 50 ml of 80% aqueous methanol was added 25 g of 2.5% sodium amalgam in small portions, while stirring vigorously. After 24 hr, the solution was decanted, the mercury was washed a few times with methanol, and the washings were decanted. The washings were combined with the original solution, and carbon dioxide gas was bubbled through the solution for several hours. Following filtration, the solvents were removed by evaporation and the residue was partitioned between 30 ml each of water and chloroform. The aqueous layer was extracted two more times with 30-ml portions of chloroform, and the chloroform extracts were combined and dried. Evaporation and crystallization from ethyl acetate afforded 240 mg of **5**, mp 218–224°. Recrystallization from 30% aqueous methanol raised the melting point to 224–229°. There was no depression of melting point upon admixture of an authentic sample[4] of **5**, and the ir spectra and mobility on tlc plates were also identical.

9-(5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*erythro*-hex-4-enofuranosyl)adenine (6). Method A.—A mixture consisting of 7.2 g (15.1 mmol) of **4**, 10.9 g of sodium benzoate, and 640 ml of *N*,*N*-dimethylformamide was boiled under reflux for 24 hr and then evaporated to a dark brown residue.[9] This was partitioned between 250 ml each of chloroform and water and the chloroform layer was washed with 300 ml of saturated sodium bicarbonate and again with 300 ml of water. The solution was dried and the chloroform was removed by evaporation. A white solid formed when the residue was triturated with 30% aqueous methanol and most of the dark colored material was washed away with the fil-

(20) B. R. Baker, in Ciba Foundation Symposium, "Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p 120.

(21) R. S. Tipson, *Advan. Carbohyd. Chem.*, **8**, 107 (1953).

(22) General methods and instrumentation are described in the first paper of this series.[2] Tlc was carried out on silica gel HF (E. Merck A. G., Darmstadt) using plates of 0.25 mm thickness. Rad (adenine) = 1.00.

(23) Dried over molecular sieve 3A.

trate. The solid weighed 1.57 g (35%), mp 193–195°. Two recrystallizations from methanol gave the analytical sample: mp 209–210.5°, with fine needles forming during heating; $[\alpha]^{24}D$ +87° (c 1.4, $CHCl_3$); uv max (CH_3OH) 261 mμ; nmr (DMSO-d_6) τ 1.82, 1.88 (both s, 1 proton each, H-2, H-8), 3.69 (s, 1, H-1'), 4.28 (s, 1, H-3'), 4.70 (s, 1, H-2'), 5.11 (m, 1, H-5'), 8.39 (d, 3, C-6' CH_3), 8.56, 8.65 (both s, 6, *gem*-dimethyl); tlc in 9:1 ethyl acetate–methanol, R_f 0.41; paper chromatography on Whatman No. 1 paper, Rad 2.58. This compound rapidly decolorized solutions of bromine in carbon tetrachloride and potassium permanganate in aqueous ethanol.

Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.47; H, 5.65; N, 23.09. Found: C, 55.29; H, 5.58; N, 23.06.

Additional **6** can sometimes be obtained from the brown filtrates by chromatography on silicic acid[24] with 9:1 ethyl acetate–methanol. This chromatographic system worked well for the isolation of **6** in those cases where it would not crystallize easily from aqueous methanol.

Method B.—To a solution of 9 g (18.9 mmol) of **4** in 225 ml of *N*,*N*-dimethylformamide under a nitrogen atmosphere was added dropwise 225 ml of 1 *N* potassium *tert*-butoxide in *tert*-butyl alcohol and the mixture was heated at reflux for 22 hr. The dark brown residue obtained after evaporation of the solvents was partitioned between 150 ml each of chloroform and water. The water layer was extracted several more times with chloroform, and the extracts were combined, dried, and evaporated to dryness. Crystallization from methanol afforded 3.15 g (54%) of **6**. One recrystallization gave analytically pure material, mp 208.5–209.5°. This material was identical in every way to the crystals obtained from method A.

Anal. Found: C, 55.56; H, 5.76; N, 23.12.

9-(5,6-Dideoxy-α-L-*lyxo*-hex-5-enofuranosyl)adenine (7).—Compound **4** (4.5 g) was treated as described in method A for the preparation of **6**. The crude product was treated directly with 90% formic acid for 19 hr. The residue obtained after evaporation of the acid was dissolved in 30% aqueous methanol and chromatographed on a column of Bio-Rad AG1-X2 (OH, 200–400 mesh) using the same solvent system. Two uv-absorbing peaks were obtained, one of which was identified as **7** after crystallization from aqueous ethanol: yield 34 mg; mp 246–247° dec; $[\alpha]^{27}D$ −52.1° (c 0.305, 1 *N* HCl). The ir spectrum of **7** was identical with that of the D enantiomer prepared earlier.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 49.88; H, 5.04; N, 26.24.

9-(6-Deoxy-2,3-di-*O*-acetyl-5-*O*-*p*-toluenesulfonyl-α-L-mannofuranosyl)adenine (13).—A reaction mixture containing 13 g (38 mmol) of **1**, 22.4 ml of acetic anhydride, 224 ml of glacial acetic acid, and 12.5 ml of concentrated sulfuric acid was made up by a previously described procedure[3] and kept at room temperature for 48 hr. The mixture was poured on 500 g of ice, stirred until the ice melted, and extracted with chloroform (three 100-ml portions). The chloroform solution was washed with saturated aqueous sodium bicarbonate and sodium chloride (300 ml), and again with sodium chloride solution (250 ml). The organic layer was dried and evaporated, and traces of acetic acid were removed by evaporation of toluene, leaving 10 g (59%) of an oil (**12**).

The preparation of the nucleoside was carried out by previously described procedures. The oil was added to a reaction mixture consisting of 13.5 g of 6-benzamidochloromercuripurine, 13.5 g of Celite-545, 3.1 ml of titanium tetrachloride, and 1050 ml of 1,2-dichloroethane.[19] A hard syrup (11.1 g) was obtained which was dissolved in 100 ml of ethanol and treated at reflux with 56 ml of 10% ethanolic picric acid for 30 min.[7] Crystallization of the picrate of **13** ensued in the boiling solution at this point and was continued for several hours at room temperature, then in the refrigerator overnight. Recrystallization from acetone–ethanol gave 7.45 g (44%) of yellow crystals, mp 157–160°.

A solution containing 7.05 g of the picrate in 500 ml of 80% aqueous acetone was stirred for 3 hr with Bio-Rad AG1-X8 (CO_3^{-2}) resin.[8] The clear, colorless solution was filtered to remove the resin and evaporated, whereupon crystallization occurred. Recrystallization from acetone afforded 2.22 g of **13**: mp 179–181° to a viscous liquid which decomposed at about 200°; $[\alpha]^{26}D$ +36° (c 1.7, $CHCl_3$); ir (KBr) 3380 (NH), 1745 (C=O of acetate), 1678, 1608, 1572 (purine ring), 1170 (sulfonate) 1094, 1075 cm^{-1} (CO).

Anal. Calcd for $C_{22}H_{25}N_5O_8S$: C, 50.86; H, 4.85; N, 13.48. Found: C, 51.19; H, 4.82; N, 13.49.

Registry No.—**2**, 32658-92-7; **3**, 32658-93-8; **4**, 32658-94-9; **5**, 29847-42-5; **6**, 32658-96-1; **7**, 32658-97-2; **13**, 32658-98-3.

(24) Mallinckrodt, 100 mesh.

Ring Expansion of Hydroxyoxetanes to Dihydrofurans

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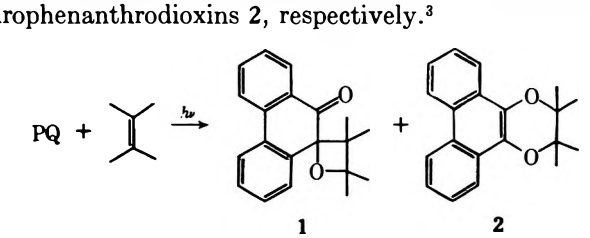
Reduction of the ketooxetanes **1** to the secondary alcohols **3** followed by treatment with acid led to rearrangement to the diols **4**, which, on dehydration, yielded the dihydrophenanthrofurans **5**. This reaction sequence and lanthanide-induced shift data were applied in elucidating the stereochemistry of **1**. The dehydration **4** → **5** proceeds either with retention or with inversion of the configuration depending on the nature of substituents.

α-Ketooxetanes can be prepared by the photoaddition of *o*-quinones or α diketones to olefins.[2] Most of these reactions have been carried out with phenanthrenequinone (PQ) which, in competing 1,2- and 1,4-cycloadditions, yields the ketooxetanes **1** and the dihydrophenanthrodioxins **2**, respectively.[3]



1 **2**

Oxetanes in general are known to undergo a number of acid catalyzed reactions, which may be used for different syntheses (for a review *cf.* ref 4). Rearrangement of oxetanes is, however, quite an unusual reaction.[4]

We have found that reduction of derivatives of **1** with $NaBH_4$ to the hydroxyoxetanes **3** and subsequent acid treatment led to rearrangement to the 1,4-diols **4**, which were readily dehydrated to the dihydrophenanthrofurans **5**.

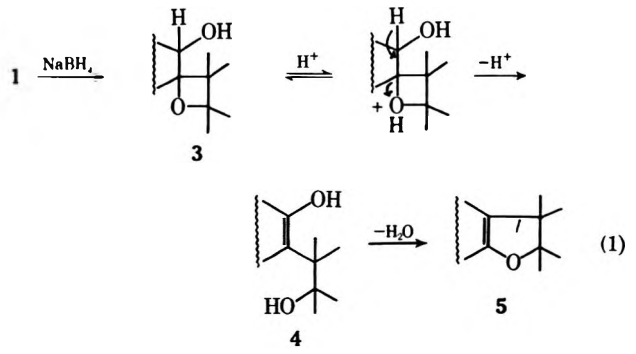
In this way, the compounds **5a–g** could be prepared from the corresponding oxetanes (**1a–g**). The struc-

(1) Research Laboratories, Eastman Kodak Company, Rochester, N. Y. 14650.

(2) S. Farid, D. Hess, and C. H. Krauch, *Chem. Ber.*, **100**, 3266 (1967).

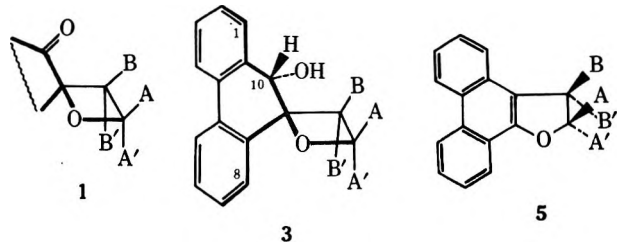
(3) S. Farid and D. Hess, *ibid.*, **102**, 3747 (1969).

(4) S. Searles, Jr. in "The Chemistry of Heterocyclic Compounds," Vol. 19, Part 2, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, Chapter 9.

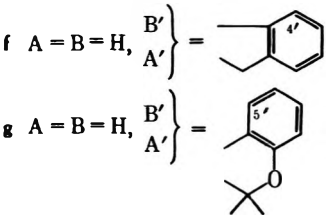


(1)

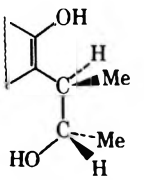
tural elucidation was based on spectroscopic data (see Experimental Section).



	A	A′	B	B′
a	H	Me	Me	H
b	H	Me	H	Me
c	H	H	Me	Me
d	H	Me	Me	Me
e	Me	Me	Me	Me (5e not prepared)



Since the dehydration is also an acid-catalyzed reaction, **3** could be directly transformed to the furans **5** without isolation of the diols **4**. Diol **4a** as derived from oxetane **1a** was isolated and its structure established by spectroscopic means (see Experimental Section).



4a

The present reaction is, to our knowledge, the first oxetane ring-expanding rearrangement. The aromatization of the phenanthrene system in the rearrangement **3** → **4** is probably an important driving force for this reaction. Similar behavior is to be expected for related systems, *e.g.*, of the corresponding naphthalene derivatives. The reduced ketooxetanes derived from α diketones may, however, be more difficult to rearrange.

Stereochemistry of the Ketooxetanes 1.—The above reaction sequence has been applied in elucidating the stereochemistry of the ketooxetanes **1a**, **b**, and **d**. The photoaddition of PQ to either *cis*- or *trans*-2-butene yields two (**1a**, mp 99–101°, and **1b**, mp 123–126°) of the four possible oxetanes.[5] Reduction and acid treatment of **1a** and **1b** result in stereospecific formation of the furans **5a** and **5b**, respectively. According to the chemical shifts and coupling constants,[6] **5a** is assigned the trans and **5b** the cis structure. Hence one of the oxetanes **1a** or **1b** should have a cis, and the other a trans configuration.

The signals of the two methyl groups at the β-carbon atom in **1c–e** appear at τ 9.00 ± 0.07 and 9.25 ± 0.04. In the reduced derivatives **3c–e**, the corresponding signals are shifted slightly to lower ($\Delta\tau$ −0.04 ± 0.04) and to higher ($\Delta\tau$ +0.19 ± 0.04) field, respectively. Inspection of Dreiding models shows that the methyl group trans to the C=O or CHOH group (position B′) is in stronger shielding field of the neighboring benzene ring than the group at position B. Moreover, the slight change in the configuration of the six-membered ring on reduction of the keto group brings the B′ methyl protons more in the positive shielding envelope of the second benzene ring. Accordingly the lower field signals are assigned to the methyl group at position B, those at higher field to the methyl group at position B′. The methyl group at the β-carbon atom in **1a** shows its signals at τ 9.17, which is shifted to lower field ($\Delta\tau$ −0.06) in **3a**. The signals of the corresponding group in **1b** appear at τ 9.40, which is shifted to higher field ($\Delta\tau$ +0.25) on reduction to **3b**. This indicates that the methyl groups at the β-carbon atom in **1a** and **1b** are located cis and trans to the C=O group, respectively.

The assignment of the trans structure to **1a** and the cis to **1b** followed from the chemical shifts of the protons on the oxetane ring. In **1a** (**3a**) these protons are shifted to higher field [τ 5.20 (5.25) and 7.28 (7.55)] than in **1b** (**3b**) [τ 4.72 (4.95) and 6.88 (6.69)] as a result of their being located cis to the methyl groups.[7]

A difference of 0.4 ppm in the chemical shift of the two methylene protons A and A′ is observed in the nmr spectrum of **3c** (τ 5.82 and 5.43), as well as in that of the corresponding compound in which the methyl groups are replaced by Cl atoms. Since similar τ values are obtained for the α proton in **1a** and **1d** (τ 5.25 and 5.18, respectively) both compounds should have the same stereochemistry at the α-carbon atom. Otherwise a τ value larger by about 0.4 ppm would have been observed for this proton in **1d** since a trans methyl group has only a small effect (0–0.1 ppm to lower field) on the chemical shift of a vicinal proton.[7]

The signals of the α and β protons in **1b**, **1f**, and **1g** undergo similar upfield (+0.2 ± 0.03 ppm) and downfield (−0.17 ± 0.02 ppm) shifts, respectively, on reduction to the corresponding alcohol. This points to similar stereochemistry of the oxetane ring in these compounds. Strong support for this view is obtained from the chemical shifts of the H-1 and H-8 protons in derivatives of **1** and **3**. These values were determined by

(5) S. Farid and K.-H. Scholz, *Chem. Commun.*, 412 (1968).

(6) **5a**: τ 5.27 (A), 6.48 (B′), 8.51 (A′), 8.51 (B) ($J_{AB'}$ = 4.2, $J_{AA'}$ = 6.4, $J_{BB'}$ = 7.0 Hz). **5b**: τ 4.88 (A), 6.26 (B), 8.36 (A′), 8.72 (B′) (J_{AB} = 8.1, $J_{AA'}$ = 6.8, $J_{BB'}$ = 7.2 Hz). These chemical shifts and coupling constants are in very good agreement with data for *trans*- and *cis*-2,3-dimethyl-2,3-dihydrobenzofurans, respectively [D. P. Brust, D. S. Tarbell, S. M. Hecht, E. C. Hayward, and L. D. Colebrook, *J. Org. Chem.*, **31**, 2192 (1966)].

(7) As found in an nmr study of several cyclobutane derivatives: J. Leitich, unpublished data, 1968; *cf.* also H. Weitkamp and F. Korte, *Tetrahedron, Suppl.*, **7**, 75 (1966).

using spin–spin decoupling, indor, and induced shift techniques. Both the H-1 and H-8 signals in **1a–d** appear at τ 2.06–2.18. In **1f** the H-1 proton signals appear at a slightly lower field (τ 1.93), whereas the H-8 signals are, in comparison, strongly shifted to higher field (τ 3.03). Also in the reduced derivatives the H-8 signals in **3a** and **3c** appear at τ 2.27 and 2.29, respectively, whereas the corresponding signals in **3f** appear at higher field (τ 3.05). This indicates that the H-8 proton in **1f** (**3f**) "lies" on the top of the benzene ring of the indene moiety; *i.e.*, the latter is trans to the C=O (CHOH) group.

The stereochemistry at the carbinol carbon in **3a**, **3c**, and **3f** was deduced from lanthanide-induced shift data. The shifts of the proton signals due to complex formation with tris(dipivalomethanato)europium(III) [Eu(DPM)$_3$][8] are given in Table I. The signals of the α-

TABLE I

Eu(DPM)$_3$-INDUCED SHIFTS[a] IN THE NMR SPECTRA OF **3a**, **3c**, AND **3f**

Proton		1	2	3	4	5	6	7
Induced shift	**3a**	3.6	1.9	1.9	3.1	2.2	0.5	−1.3
	3c	3.5	1.9	1.9	3.4	2.9	1.4	0.2
Proton		8	10	OH	A	A′	B	B′
Induced shift	**3a**	16.8	18.0	12.1	27.9	(9.5)	(9.8)	19.2
	3c	22.3	15.2	13.3	25.4	27.3	(10.3)	(11.9)
Proton		1	4	5	6	7	8	10
Induced shift	**3f**	2.6	2.5	1.9	0.9	0.4	17.1	12.5
Proton		OH	A	B	4′	5′	—CH$_2$—	
Induced shift	**3f**	9.6	20.4	11.1	6.1	1.9	10.0[b]	4.2[c]

[a] Determined from the slopes of the plots of shifts (in parts per million) *vs.* molar ratios of Eu(DPM)$_3$:**3**; concentration of **3** *ca.* 0.2 molar in CCl_4. Positive values indicate shifts to lower field and negative values to higher field. The induced shifts for methyl groups appear in parentheses. The shift of the OH signal is not taken in computation of the location of the lanthanide ion because of uncertainty in predicting the predominant position of this rotating hydrogen atom. [b] Trans to the proton at position A. [c] Cis to the proton at position A.

hydrogen atoms undergo larger shifts than that of the alcoholic α hydrogen and the latter is shifted more than the OH signal. This indicates that the ethereal oxygen and not the alcoholic oxygen associates with the lanthanide ion since, on complex formation with hydroxyl oxygens, the shift of the OH signal is three to five times that of the α hydrogen.[8]

We found[9] that the equilibrium constant for the complex formation between Eu(DPM)$_3$ and trimethylene oxide exceeds that for cyclohexanol only by a factor of *ca.* 2. We also found,[9] however, that steric hindrance suppresses the complex formation. The lack of significant complex formation with the hydroxyl oxygen indicates, therefore, that this group is sterically hindered, which is the case with the isomer, in which the OH is cis to the oxetane β-carbon atom (see formula). One would reach the same conclusion on the basis of the concept of steric approach control in hydride reduction of carbonyl compounds, which implies that the approach of the reagent to a sterically hindered carbonyl group will be from the least hindered side.[10]

A computer program[11] was used to determine the location of the Eu^{3+} ion in the complex with **3a**, **3c**, and **3f**, which maximizes the correlation between the induced shift and the geometric factor $[3(\cos^2\theta - 1)r^{-3}]$ of pseudocontact shift. These calculations were executed for planar and differently puckered oxetane conformers. The best agreement between measured and predicted shifts was obtained for the oxetane ring, which is puckered by about 40° in **3a** (Figure 1), by about 20° in **3c** (Figure 2), and planar ring for **3f** (Figure 3). It is interesting that this puckered conformer of **3a** has both methyl groups in equatorial positions, which is optimum for the most stable conformer. For both **3a** and **3c** such distortion of the oxetane ring leads to less sterically hindered conformers.

Kinetics and Mechanisms.—The kinetics of the conversions **3** → **4** → **5** were studied by uv spectroscopy. Compounds **4** and **5** show the first absorption band (^1L_b) in the range 26–30 × 10^3 cm^{-1}, with a vibrational structure ($\Delta\nu \approx 1400$ cm^{-1}) similar to that of the dihydrophenanthrodioxins **2** (*cf.* ref 12). The O–O′ transition of this band in the spectrum of **5** (at 26.9 ± 0.3 × 10^3 cm^{-1}, $\epsilon \approx 2100$ in benzene) is shifted (*ca.* 500 cm^{-1}) to a lower wavenumber than that of **4**. Because of this difference in the spectra of **4** and **5** the rate of formation of these compounds could be measured.

Depending on the compound and the reaction conditions the ratio of k_1/k_2 varies considerably.[13] At 40°

$$3 + H^+ \xrightarrow{k_1} 4$$

$$4 + H^+ \xrightarrow{k_2} 5$$

with 10^{-3} *M* hydrogen chloride in benzene, **3a** was transformed almost quantitatively to **4a** ($k_1 \approx 1$ l. mol^{-1} sec^{-1}). Compound **5a** was not formed in appreciable amounts under these conditions ($k_1 \gg k_2$).[14] On the other hand, **3b** reacted detectably only at much higher acid concentrations. For example, at 40° with 4 × 10^{-2} *M* hydrogen chloride in benzene, k_1 has the value ~ 2 × 10^{-4} l. mol^{-1} sec^{-1}. In this reaction the characteristic uv maxima of the diol could be detected only in the early phases of the reaction ($k_1 \ll k_2$).[14] In the reaction of **3a** with 10^{-1} *M* CF_3COOH in benzene, both **4a** and **5a** were detected in comparable amounts over a relatively long reaction period ($k_1 \sim k_2$).

For the hydrolysis of trimethylene oxide, Pritchard, *et al.*,[15] have shown that a preliminary equilibrium proton transfer giving an oxonium ion precedes an SN1 sub-

(8) C. C. Hinckley, M. R. Klotz, and F. Patil, *J. Amer. Chem. Soc.*, **93**, 2417 (1971); J. K. M. Sanders and D. H. Williams, *ibid.*, **93**, 641 (1971); P. V. Demarco, T. K. Elzey, R. B. Lewis, and E. Wenkert, *ibid.*, **92**, 5734 (1970).

(9) S. Farid and C. Schnuell, unpublished results.

(10) *Cf.* S.-I. Yamada and K. Koga in "Selective Organic Transformations," Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970.

(11) S. Farid, A. Ateya, and M. Maggio, *Chem. Commun.*, 1285 (1971).

(12) C. H. Krauch, S. Farid, and G. O. Schenck, *Chem. Ber.*, **98**, 3102 (1965).

(13) The observed reaction constant k_1 is given by $k_1 = K \cdot k$, where K is the equilibrium constant for the formation of the conjugate acid of **4** and k the constant of the rate-determining elimination reaction

$$H^+ + 4 \overset{K}{\rightleftharpoons} (4 - H^+) \overset{k}{\rightarrow} 5$$

The same applies for k_2, where the rate-determining step is a nucleophilic displacement.

(14) The kinetics of the reaction **3** → **4** can be easily studied if $k_1 \gg k_2$ or $k_1 \ll k_2$ (in the later case $d[4]/dt \approx 0$). The rate of disappearance of **3** can be derived from plots of the absorption at the O–O′ transition of **4** or **5** *vs.* time, respectively.

(15) F. A. Long, J. G. Pritchard, and F. E. Stafford, *J. Amer. Chem. Soc.*, **79**, 2362 (1957); J. G. Pritchard and F. A. Long, *ibid.*, **80**, 4162 (1958).

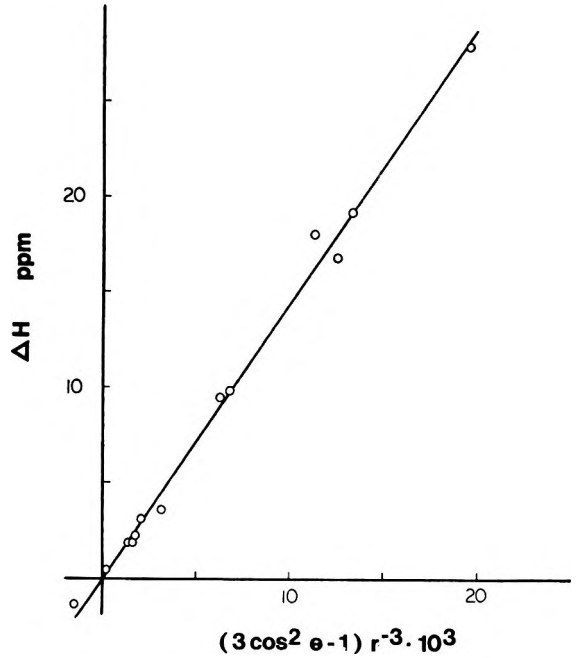


Figure 1.—Plot of the Eu(DPM)$_3$-induced shift in **3a** *vs.* the pseudocontact geometric factor for the computer-determined location of the lanthanide ion (Eu–O distance, 2.8 Å).

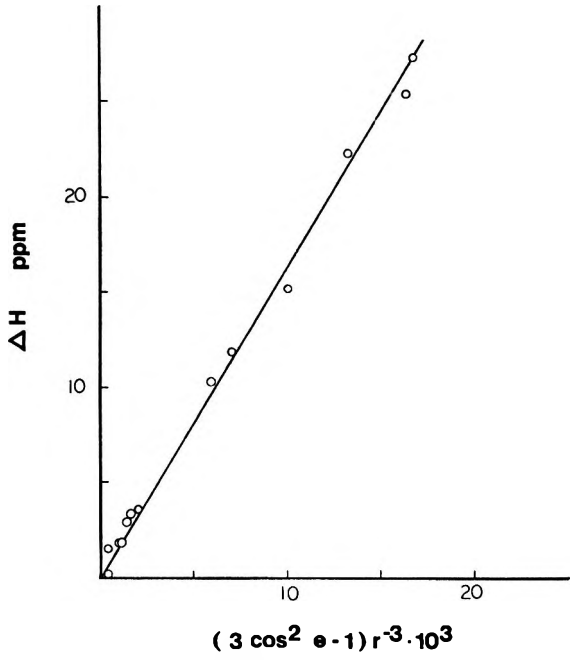


Figure 2.—Plot of the Eu(DPM)$_3$-induced shift in **3b** *vs.* the pseudocontact geometric factor for the computer-determined location of the lanthanide ion (Eu–O distance, 3.1 Å).

stitution. It is reasonable to assume also that in the rearrangement **3** → **4** a fast equilibrium between **3** and its conjugate acid (eq 1) precedes the kinetically controlling E1 or E2 elimination step. This reaction would be expected to proceed with retention of configuration regardless of the reaction order of the elimination. We obtained **5a** from **3a** and **5b** from **3b** on carrying out the reaction in either water-free benzene with hydrogen chloride or CF_3COOH, in aqueous dioxane with hydrochloric acid or in 90% acetic acid (**3b** did not react under the latter conditions). Since **5a** and **5b** have the same configuration as the starting oxetanes **3a** and **3b**, the dehydration to the furans in these cases

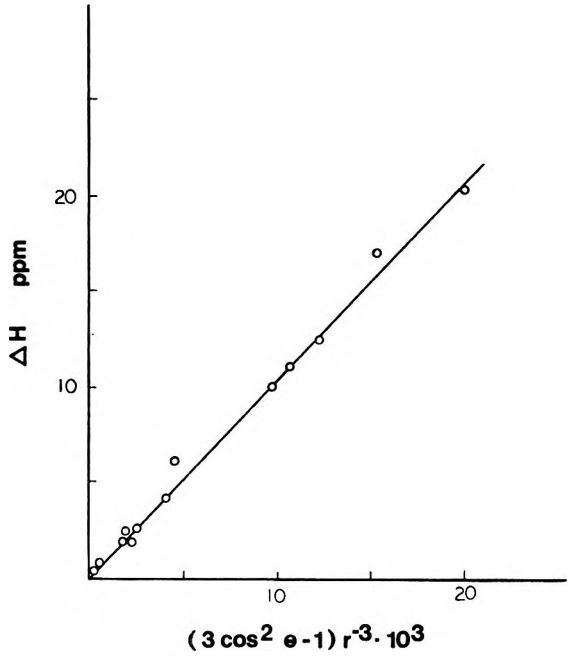
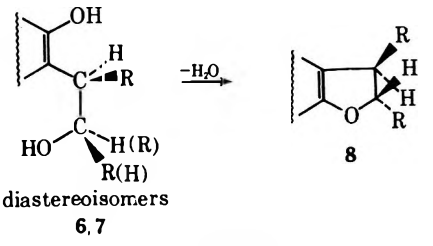


Figure 3.—Plot of the Eu(DPM)$_3$-induced shift in **3f** *vs.* the pseudocontact geometric factor for the computer-determined location of the lanthanide ion (Eu–O distance, 2.9 Å).

should have occurred *without* inversion.[16] On the other hand, both diastereoisomers[17] of the di-*tert*-butyl-substituted diols **6** and **7** yield on dehydration the same trans furan derivative[18] **8**. Thus, in one of these reactions inversion should have occurred. This dehydration clearly proceeds according to another mechanism (SN2 with inversion or SN1) owing to steric factors.



diastereoisomers
6, **7**

8

R = *tert*-butyl

The kinetics of the dehydration of **4a** with CF_3COOH (7.1×10^{-2} *M*) in benzene were studied also by uv spectroscopy. Reaction constants of 4.6, 5.8, 7.6, and 8.9×10^{-3} l. mol^{-1} sec^{-1} were measured at 29.6, 34.8, 39.5, and 43.8°, respectively. This corresponds to an activation energy and an entropy of activation of 9.3 ± 0.3 kcal mol^{-1} and −38 ± 3 cal mol^{-1} °C^{-1}, respectively.

The dihydrofuran **5h** could also be prepared from the corresponding hydroxyoxetane **3h** having an acetal structure. This, however, followed another reaction route in which the other C–O bond of the oxetane ring is cleaved. On mild acid treatment, **3h** gave the tetra-

(16) The exact nature of this stereochemically unexpected reaction needs further investigation.

(17) These compounds are synthesized *via* photoaddition of PQ to 1,2-di-*tert*-butylethylene, which will be described in a separate publication.

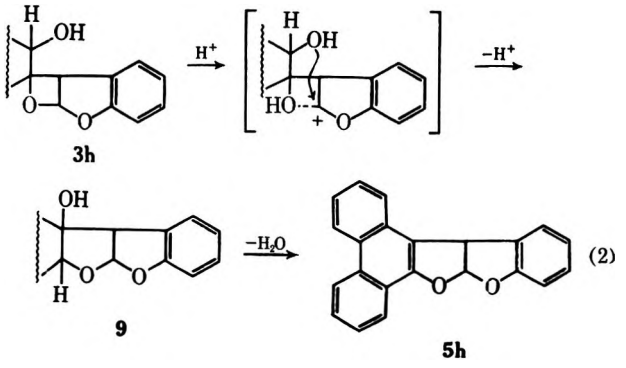
(18) As indicated by a distinctly smaller coupling constant of 1.8 Hz between the C-2 and C-3 protons in **8** compared with the normal value of 4.2 Hz in **5a**, the five-membered ring in **8** is apparently so distorted, owing to steric interference of the two *tert*-butyl groups, that the dihedral angle Φ between the H–C–C–H planes is considerably less than 120°.[19]

(19) H. Conroy, *Advan. Org. Chem.*, **2**, 265 (1960).

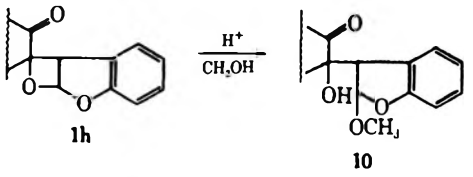
TABLE II

Compd	Recryst from	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
3a	Ethanol	192–194	$C_{18}H_{16}O_2$	81.17	6.81	80.92	6.77
3b	Petroleum ether	168–173	$C_{18}H_{16}O_2$	81.17	6.81	80.97	6.75
3c	Ethanol	135–136	$C_{18}H_{16}O_2$	81.17	6.81	81.22	6.80
3d	Benzene	177–179	$C_{19}H_{20}O_2$	81.40	7.19	81.40	7.08
3e	Nmr spectroscopically detected, not isolated						
3f	Petroleum ether	182–185	$C_{22}H_{18}O_2$	84.64	5.56	84.48	5.60
3g	Ethanol	201–204	$C_{25}H_{22}O_3$	81.06	5.99	80.94	6.00

hydrohydroxyfuran **9**, a reaction which can be explained in terms of an intramolecular nucleophilic displacement (*cf.* eq 2); **5h** was obtained on dehydration of **9** with P_2O_5.



Treatment with strong acid (0.2 *M* CF_3COOH, in benzene) cleaved **3h** (as indicated by uv) to 9,10-dihydroxyphenanthrene, which was oxidized readily with atmospheric oxygen to PQ. Similarly, the ketooxetane **1h** reopened to PQ and benzofuran on reacting with H_2SO_4 in aqueous dioxane.[12] When the reaction was carried out in methanol/HCl, however, ketol **10** was obtained. This intermolecular displacement points to a C–O bond cleavage analogous to that in eq 2.



Experimental Section

The nmr spectra were taken on Varian A-60A and A-56/60 spectrometers using TMS as internal standard. Infrared spectra were recorded in KBr or in CCl_4 on a grating spectrophotometer MH-2 SEM Brückl, Munich. The uv spectra were determined on a modified Bausch and Lomb 505 spectrophotometer. The uv measurements for the kinetic studies were carried out on a Beckman DK2 spectrophotometer using 1-cm water-jacketed cells (accuracy ±0.1°). Mass spectra were obtained with an Atlas CH-4 mass spectrometer (70 eV). Melting points were determined on a Kofler hot stage and are uncorrected. The petroleum ether used has a boiling range of 50 to 70°. Florisil (60–100 mesh, Fluka) was used for column chromatography and silica gel H (Merck) for preparative layer chromatography.

Reduction of 1[20] to 3.—To 100 mg of **1** in 5 ml of dioxane, a solution of *ca.* 30 mg of $NaBH_4$ and 5 mg of NaOH in 5 ml of 80% methanol was added dropwise. The mixture was stirred for 30 min. After distillation of the solvents at reduced pressure, the residue was diluted with water and twice extracted with ether to give **3** (in colorless crystalline form) in 80–90% yield. Analytical samples were obtained by recrystallization as given in Table II. All derivatives of **3** showed in uv (dioxane) a shoulder at *ca.* 33.2 × 10^3 cm^{-1} ($\epsilon \approx 3500$) and a maximum at *ca.* 36.8 × 10^3 cm^{-1} ($\epsilon \approx 12{,}000$); in ir (KBr) ν_{OH} ranging between 3330 and 3390 cm^{-1} (broad, intermolecular hydrogen bonding). In the nmr spectra ($CDCl_3$) of **3a–g** the CH–OH signal was observed between τ 4.78 and 5.03 (as singlet after shaking the solution with D_2O). The signals of the methyl groups at the α-carbon atom of the oxetane ring appeared at τ 8.53 (**3a**), 8.64 (**3b**), 8.72 (**3d**), 8.47 and 8.57 (**3e**); of those at the β-carbon atom at 9.11 (**3a**), 9.65 (**3b**), 8.93, 9.35 (**3c**), 9.02, 9.51 (**3d**), 8.98 and 9.52 (**3e**). The CH–CH_3 coupling constants were $J_{AA'}$ = 6.3 (**3a**), 6.8 (**3b**), 6.5 (**3d**) Hz; $J_{BB'}$ = 7.5 (**3a**), 7.9 (**3b**) Hz. The CH–CH coupling constants were $J_{AB'}$ = 7.9 (**3a**) and J_{AB} = 8.6 (**3b**) Hz. The H–C–H coupling constant, $|J_{AA'}|$, in **3c** was 5.0 Hz. Other nmr data are given in the text. Nmr ($CDCl_3$) data: of **3f**, τ 3.96 (broad d, J = 7.0 Hz, 1, H-4′ of the indene moiety), 4.37 (m, 1, –OCH<), 5.66 (d, J = 6.0 Hz, 1, –CH<), 6.65 (m, 2, $>CH_2$); **3g**, τ 4.19 (broad d, J = 7.5 Hz, 1, H-5′), 5.05 (d, J = 7.8 Hz, 1, –OCH<), 5.82 (d, J = 7.8 Hz, 1, –CH<), 8.35 and 9.07 [two s, each 3, $>C(CH_3)_2$].

10-(3-Hydroxy-2-butyl)-9-phenanthrol (4a).—A solution of 270 mg of **3a** in 20 ml of 60% acetic acid was heated for 0.5 hr at 50–60°, neutralized with $NaHCO_3$, and extracted with ether. After distillation of the ether, 10 ml of benzene was added to the residue; 45 mg of colorless crystals of **4a** remained insoluble. Compound **5a** (105 mg) was obtained by preparative layer chromatography of the mother liquor. In another experiment, 50 mg of **3a** was treated for 2 hr at 40° with 20 ml of 10^{-3} *M* hydrogen chloride in benzene. The solution was concentrated at reduced pressure to provide on cooling 38 mg of **4a**: mp 235–238° (from benzene); ir (KBr) 3340 (hydroxyl), 1595, 753, 722 cm^{-1} (aromatic); nmr (acetone-d_6) τ 5.47 (d of q, J = 3.7 and 6.4 Hz, 1, >CH–OH), 6.04 (d of q, J = 3.7 and 7.4 Hz, 1, >CH–), 8.50 (d, J = 7.4 Hz, 3, $>CHCH_3$), 8.84 [d, J = 6.4 Hz, 3, $-CH(OH)CH_3$]; mass spectrum *m/e* (rel intensity) 266 (69) (M^+), 248 (38) ($M - H_2O^+$), 233 (40) ($M - H_2O - CH_3^+$), 221 (100) ($M - CH(CH_3) - OH^+$), 202 (20), 193 (19) [$M - CH(CH_3) - CH(CH_3) - OH^+$], 178 (31), 165 (21).

Anal. Calcd for $C_{18}H_{18}O_2$ (266.3): C, 81.17; H, 6.81; active H(2), 0.75. Found: C, 81.00; H, 7.07; active H, 0.68.

Acetylation of Diol 4a.—A mixture of 35 mg of **4a**, 5 ml of acetic anhydride, and 0.5 ml of pyridine was refluxed for 2 hr. Decomposition with ice, neutralization with $NaHCO_3$, and extraction with ether provided 30 mg of the diacetate of **4a**: mp 100–102°; ir (CCl_4) $\nu_{C=O}$ 1735 cm^{-1} (aliphatic acetate),[22] 1772 cm^{-1} (vinyl acetate);[22] nmr ($CDCl_3$) τ 4.36 (d of q, J = 9.8 and 6.3 Hz, 1, >CH–OAc), 6.07 (d of q, J = 9.8 and 7.7 Hz, 1, >CH–), 7.47 (s, 3, phenanthryl $OCOCH_3$), 8.39 (s, 3, aliphatic $OCOCH_3$),[23] 8.51 (d, J = 7.7 Hz, 3, $>CHCH_3$), 8.55 [d, J = 6.3 Hz, 3, $-CH(OAc)CH_3$]; mass spectrum *m/e* (rel intensity) 350 (26) (M^+), 308 (42) (M – ketene$^+$) pointing to the vinyl acetate,[24] 248 (100) (308 – acetic acid$^+$) pointing to the aliphatic acetate,[24] 233 (49), 221 (28).

Anal. Calcd for $C_{22}H_{22}O_4$ (350.4): C, 75.41; H, 6.33. Found: C, 75.62; H, 6.28.

Methyl-Substituted 2,3-Dihydrophenanthro[9,10-*b*]furans (5a–d).—A solution of 100 mg of **3a–d** in 5 ml of dioxane was treated with 5 ml of 10% hydrochloric acid and heated at 70–80° for 3 hr. The solution was neutralized with $NaHCO_3$, concentrated under reduced pressure, and extracted with ether. The

(20) The formation of **1a–e** is briefly mentioned in ref 5 and ref 21; the experimental details will be described in a separate publication. Compounds **1f** and **1g** are described in ref 12.

(21) S. Farid, *Chem. Commun.*, 1268 (1967).

(22) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1959, pp 179–182.

(23) This unusual high-field shift is interpreted in terms of the acetyl group being located predominantly above the phenanthrene moiety.

(24) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 468–471.

TABLE III

Compd	Substituents	Mp, °C	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
5a	*trans*-2,3-Dimethyl	73–76	$C_{18}H_{16}O$	87.06	6.50	86.89	6.57
5b	*cis*-2,3-Dimethyl	78–82	$C_{18}H_{16}O$	87.06	6.50	86.81	6.43
5c	3,3-Dimethyl	123–125	$C_{18}H_{16}O$	87.06	6.50	87.13	6.68
5d	2,3,3-Trimethyl	147–149	$C_{19}H_{18}O$	86.98	6.91	86.85	6.86

residue after distillation of ether was purified by layer chromatography (silica gel H, developed with benzene, R_f ~0.7, detected by its violet fluorescence, extracted with ether), yield 60–70%. Analytical samples were obtained by sublimation (distillation) and recrystallization from methanol. In the ir (KBr) the enol ether C=C stretching vibration at *ca.* 1640 cm^{-1} was much weaker than the corresponding band[12] in **2**. The nmr data ($CDCl_3$) of **5a** and **5b** are given in footnote 6; **5c**, τ 5.48 (s, 2, $-OCH_2-$), 8.32 [s, 6, $>C(CH_3)_2$]; **5d**, τ 5.46 (q, J = 6.7 Hz, 1, $-OCH<$), 8.45 (d, J = 6.7 Hz, 3, $-OCHCH_3$), 8.41 and 8.69 [two s, each 3, $C(CH_3)_2$]. The signals of protons at the carbon atom directly attached to the phenanthrene moiety were broadened by 0.4–0.6 Hz owing to long-range coupling with aromatic protons. Melting points and analytical data are given in Table III.

Compound **5a** was also formed on heating 30 mg of **3a** with 30 ml of 90% acetic acid for 10 hr as indicated by nmr of the residue remaining after distillation of the solvents.

Compound **3a** (50 mg) was treated with 20 ml of 0.5 *M* hydrogen chloride in absolute benzene for 2 hr at room temperature. On evaporation of the the solution under reduced pressure **5a** was obtained as a colorless oil in almost quantitative yield (identification by nmr, ir, and uv). Repeating the last reaction with 3×10^{-2} *M* CF_3COOH instead of hydrogen chloride and recrystallizing the residue from benzene yielded 9 mg of **4a** (identified by melting point and nmr). The mother liquor contained mainly **5a** and traces of **4a** (as shown by nmr); no other compounds could be detected.

Similar treatment of **3b** with 10^{-1} *M* CF_3COOH or 5×10^{-2} *M* hydrogen chloride in benzene for 4 hr at 30–35° afforded **5b** (as shown by nmr). In another experiment, 2 drops of CF_3COOH were added to 20 mg of **3b** in 1 ml of $CDCl_3$ in an nmr tube; after a few minutes the spectrum indicated complete transformation to **5b**.

Dehydration of 4a to 5a.—Diol **4a** (100 mg) was heated at 70–80° with 8% hydrochloric acid (10 ml) in dioxane (10 ml) for 3 hr. Working up as described for the corresponding experiments mentioned above yielded 78 mg of **5a** (uv, nmr). Refluxing a benzene solution of **4a** (30 mg) with ~200 mg of P_2O_5 for 1 hr, washing with water, and purifying by layer chromatography provided 17 mg of **5a** (nmr, ir, and uv).

9a,14b-Dihydro-10*H*-indeno[2,1-*b*]phenanthro[9,10-*d*]furan (5f).—A solution of 250 mg of **3f** in 10 ml of dioxane was heated 3 hr at 70° with 10 ml of 10% hydrochloric acid. After a few minutes, colorless needles of **5f** began to precipitate (150 mg). Another 70 mg of **5f** was obtained by concentrating the solution, mp 238–239° (from ethanol). A sublimed sample gave the same melting point; nmr ($CDCl_3$) τ 4.15 (m, 1, $-OCH<$), 4.66 (d, J = 7.8 Hz, 1, $>CH-$). The mass spectrum showed a parent peak at m/e 308.

Anal. Calcd for $C_{23}H_{16}O$: C, 89.58; H, 5.23. Found: C, 89.40; H, 5.28.

9a,15b-Dihydro-10,10-dimethyl-10*H*-[1]benzopyrano[3,4-*b*]-phenanthro[9,10-*d*]furan (5g).—Compound **3g** (140 mg) was treated with hydrochloric acid as described for **5f** to provide 120 mg of **5g**: mp 247° (sublimed sample); nmr ($CDCl_3$) τ 5.07 (s, 2, $-OCH_aCH_b<$), 8.17 and 8.55 [two s, each 3, $>C(CH_3)_2$] [J_{ab} = 7.5 Hz (measured from spectrum in C_6D_6)]; mass spectrum parent peak at m/e 352.

Anal. Calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 84.90; H, 5.77.

2,3-Di-*tert*-butyl-2,3-dihydrophenanthro[9,10-*b*]furan (8).—A solution containing 50 mg of either **6** (mp 193–195°) or **7** (mp 153–156°) in 10 ml of benzene was refluxed for 3 hr with ~200 mg of P_2O_5. The solution was washed with water and evaporated, and the residue was purified by layer chromatography, yielding 20–30 mg of **8** and a few milligrams of the starting compounds. Recrystallization from ethanol afforded colorless crystals of **8**: mp 129–130°; nmr ($CDCl_3$) τ 5.43 (d, J = 1.8 Hz, 1, $-OCH<$), 6.58 (d, J = 1.8 Hz, 1, $>CH-$), 9.01 and 9.12 [two s, each 9, two $C(CH_3)_3$]; mass spectrum parent peak at m/e 332.

Anal. Calcd for $C_{24}H_{28}O$: C, 86.70; H, 8.49. Found: C, 86.39; H, 8.41.

8b,9a,14b,14c-Tetrahydro-14c-hydroxybenzofuro[2,3-*b*]phenanthro[9,10-*d*]furan (9).—A solution of 650 mg of **3h**[12] in 10 ml of dioxane was heated at 50° with 10 ml of 50% acetic acid. After 1 hr the solution was neutralized, concentrated under reduced pressure, and extracted with ether to give 450 mg of **9** (in crystalline form): mp 212–214° (acetone–petroleum ether); ν_{OH} (KBr) 3510 cm^{-1}; uv (dioxane) ν_{max} at 36.7×10^3 cm^{-1} (ϵ 20,600); nmr ($CDCl_3$) τ 3.97 (d, J = 6.0 Hz, 1, $-OCHO-$), 5.15 (s, 1, $>CHO-$), 5.53 (d, J = 6.0 Hz, 1, $>CH-$); mass spectrum parent peak at m/e 328.

Anal. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.34; H, 4.89.

9a,14b-Dihydrobenzofuro[2,3-*b*]phenanthro[9,10-*d*]furan (5h).—A solution of **9** (220 mg) in benzene (15 ml) was refluxed for 4 hr with ~0.5 g of P_2O_5. After filtration, washing with water, and distillation of the solvent, the residue was fractionally sublimed at 200° (0.1 Torr) to provide colorless crystals of **5h** (~10% yield): mp 249–250° (the melting point did not change after recrystallization from acetone); nmr ($CDCl_3$) τ 4.48 (d, J = 7.4 Hz, $>CH-$) [the signals of the $-OCHO-$ proton fall together with the aromatic signals (τ <3)]; mass spectrum parent peak at m/e 310.

Anal. Calcd for $C_{22}H_{14}O_2$: C, 85.14; H, 4.55. Found: C, 85.05; H, 4.65.

10-(2,3-Dihydro-2-methoxy-3-benzofuryl)-10-hydroxy-9(10*H*)-phenanthrone (10).—Concentrated hydrochloric acid (0.2 ml) was added to 100 mg of **1h** in 10 ml of methanol. The solution was warmed to 30–40° for 30 min. After concentration of the solution at reduced pressure and cooling, colorless crystals of **10** (75 mg) precipitated out: mp 128–132° (recrystallized from methanol); ir (KBr) ν_{CH} 3480 cm^{-1}, $\nu_{C=O}$ 1680 cm^{-1}; uv (dioxane) ν_{max} 30.5 (ϵ 3100), 35.6 (9000), 41.0 $\times 10^3$ cm^{-1} (26,000); nmr ($CDCl_3$) τ 4.63 (d, J = 1.7 Hz, 1, $-OCHO-$), 5.86 (s, 1, $-OH$), 6.52 (m, long range coupling with the aromatic protons[12] in addition to the vicinal coupling, 1, $>CH-$), 6.67 (s, 3, $-OCH_3$); mass spectrum m/e 358 (M^+), main peaks at m/e 326 (M − methanol$^+$), 209 (phenanthrene semiquinone$^+$), 210 (phenanthrenehydroquinone$^+$), 149 (M − 209$^+$).

Anal. Calcd for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 77.29; H, 5.02.

Registry No.—**3a**, 32528-65-7; **3b**, 32528-66-8; **3c**, 32528-67-9; **3d**, 32528-68-0; **3e**, 32528-69-1; **3f**, 32528-70-4; **3g**, 32528-71-5; **4a**, 32528-72-6; **4a** diacetate, 32528-73-7; **5a**, 32528-74-8; **5b**, 32528-75-9; **5c**, 32528-76-0; **5d**, 32528-77-1; **5f**, 32528-78-2; **5g**, 32528-79-3; **5h**, 32528-80-6; **8**, 32528-81-7; **9**, 32528-82-8; **10**, 32528-83-9; Eu(DPM)$_3$, 15522-71-1.

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Friedel–Crafts Reaction of 3,4,4-Trimethybutyrolactone and Benzene

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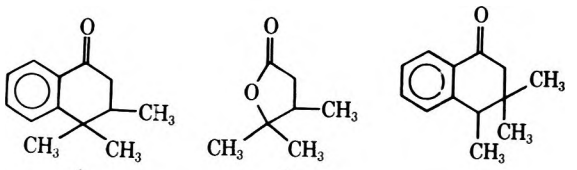
The Friedel–Crafts reaction of 3,4,4-trimethylbutyrolactone (2) and benzene in the presence of greater than 2 equiv of aluminum chloride has been found to give three ketones, 3,4,4-trimethyl-1-tetralone (1), 3,3,4-trimethyl-1-tetralone (3), and 3,4-dimethyl-1-phenyl-1-pentanone (4). With 2 equiv of aluminum chloride, 1 is the only neutral product, and, with less than 2 equiv, 4-phenyl-3,4-dimethylpentanoic acid (5) is obtained. The use of benzene-d_6 in these reactions leads to incorporation of deuterium in the aliphatic portion of the molecule in the ketones but not in the acid. A mechanism is proposed which suggests that, in the presence of 1 equiv of aluminum chloride, 2 is converted to a tertiary carbonium ion which with excess Lewis acid is transformed into an acyl carbonium ion and thence to 3,4-dimethyl-1-phenyl-3-penten-1-one (10). 3,4-Dimethyl-1-phenyl-2-penten-1-one was prepared and with 3 equiv of aluminum chloride gives 1 and 4. A detailed mechanism is suggested for these reactions.

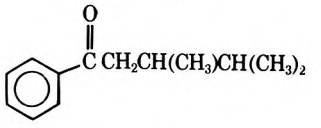
Some time ago, in an effort to prepare 3,4,4-trimethyl-1-tetralone (1), we reported the reaction of 3,4,4-trimethylbutyrolactone (2) and benzene with excess aluminum chloride.[2] Although reactions of this type had been reported by others and seemed to proceed smoothly to give a single product,[3] we obtained a mixture consisting of 53% 1, 41% 3,3,4-trimethyl-1-tetralone (3), and 6% of a third compound of unknown structure.[2] On the basis of analytical and spectral data, this compound appeared to be isomeric with 1 and 3, but it was none of the several obvious products which could be obtained from a carbonium ion intermediate derived from 2. Since there were only very small



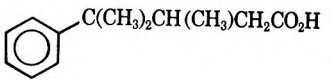
1

2

3



4



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amounts of this compound obtainable and the instrumental tools available to us at the time were very limited, the approach to the elucidation of the structure was the synthesis of various compounds which appeared to be logical products of the reaction.[2,4]

In an effort to gain further insight into the nature of this compound, it was subjected to mass spectrometry;[5] however, rather than the expected parent ion at *m/e* 188, this compound showed a peak at *m/e* 190. A first-order analysis of the mass spectrum clearly indicated that it was 3,4-dimethyl-1-phenylopentan-1-one (4). The mass spectral data (see Table I) may be interpreted as follows: the base peak at *m/e* 105 corresponds to an acylium ion ($C_6H_5C{\equiv}O^+$), while the peak at *m/e* 120 is the result of a McLafferty rearrangement. The peak at *m/e* 147 is the result of the loss of the isopropyl group, while the one at *m/e* 77 arises from a phenyl ion. The nmr data for this compound were also in agreement with the assigned structure (see Experimental Section) which was confirmed by the synthesis of 4 from 3,4-dimethylpentanoic acid[6] and benzene.

Table I

Mass Spectral Data[a]

Compd	m⁺ (rel abundance)	*m/e*	*m/e*	*m/e*	*m/e*
1	188 (100)	173 (97)	145 (78)	131 (61)	
3	188 (97)	145 (47)	132 (100)	104 (92)	
4	190 (40)	147 (88)	120 (98)	105 (100)	77 (98)

[a] Principal peaks only.

Although reductions under relatively mild Friedel–Crafts conditions have been reported by Fuson[7] and under more vigorous conditions by Dippy,[8] very little is known concerning the course of these reactions. In an effort to gain some insight into the mechanism of the reduction, as well as the course of the alkylation–acylation reaction of 2 with benzene, the Friedel–Crafts reaction was carried out using benzene-d_6. The same mixture of ketones was obtained; however, all three compounds exhibited very high and specific incorporation of deuterium, as disclosed by their nmr spectra. In the case of 1, the C-3 methyl doublet at 0.99 ppm was now a singlet and the three-proton multiplet at 2.46 ppm had become an AB quartet with a coupling constant (17 Hz) indicative of nonequivalent geminal protons. Thus, there was exclusive and nearly 100% deuterium incorporation at C-3. In 3, the methyl doublet at 1.26 ppm had become a singlet and the signal due to the benzylic proton had disappeared, indicating deuterium incorporation at this position. The nmr spectrum of deuterated 4 showed only a broadened

(1) Abstracted from the M.S. Thesis of J. J. Starnes, Clemson University, May 1971.

(2) J. W. Huffman and T. W. Bethea, *J. Org. Chem.*, **30**, 2956 (1965).

(3) (a) R. T. Arnold, J. S. Buckley, and J. Richter, *J. Amer. Chem. Soc.*, **69**, 2322 (1947); (b) W. L. Mosby, *ibid.*, **74**, 2546 (1952); (c) W. E. Truce and C. E. Olson, *ibid.*, **74**, 4721 (1952).

(4) In addition to the compounds described in ref 2, two other ketones, 3- and 4-isopropyl-1-tetralone, have been synthesized by unexceptional methods.[1]

(5) The authors would like to thank the Research Triangle Institute for Mass Spectrometry, Research Triangle Park, N. C., for carrying out this determination.

(6) R. C. Haston and A. H. Agett, *J. Org. Chem.*, **6**, 132 (1941). Our synthesis of this compound is somewhat different from that reported by these workers and is described in detail in the Experimental Section.

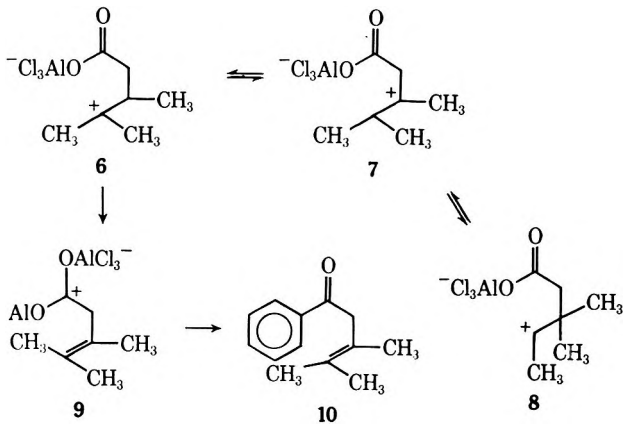
(7) (a) R. C. Fuson, L. L. Alexander, and A. L. Jacoby, *J. Amer. Chem. Soc.*, **57**, 2208 (1935); (b) R. C. Fuson and L. L. Alexander, *ibid.*, **58**, 1745 (1936).

(8) (a) J. F. J. Dippy and A. L. L. Paulluel, *J. Chem. Soc.*, 1415 (1951); (b) J. F. J. Dippy and J. T. Young, *ibid.*, 3919 (1955).

methyl singlet at 0.89 ppm and an AB quartet (J = 15 Hz) at 2.80 ppm, indicating the incorporation of two deuterium atoms into the alkyl side chain at C-3 and C-4.[9]

In view of the fact that **1** is stable to further reaction with excess (3.18 mol) aluminum chloride in benzene and the apparently generally accepted mechanism for the reaction of lactones under Friedel–Crafts conditions,[2,3c] these results were most surprising. The Truce mechanism suggests alkylation as a first step to give a γ-arylbutyric acid, in this case **5**, as the initial product, with cyclization to the tetralone as a subsequent step.[3c] If alkylation to **5** were occurring first, then it becomes very difficult to reconcile the formation of **4**. Also, the very high incorporation of deuterium into **1** and the formation of **3** would necessitate the formation of an equilibrating mixture of carbonium ions (**6**, **7**, and **8**) which would have to undergo deuterium exchange with the solvent.

This mechanism is unsatisfactory for two reasons. First, no trace of the indanone derived from **7** could be detected; and second, the tertiary carbonium ion (**6**) should be sufficiently more stable than either **7** or **8** that the bulk of the product should arise from this intermediate.

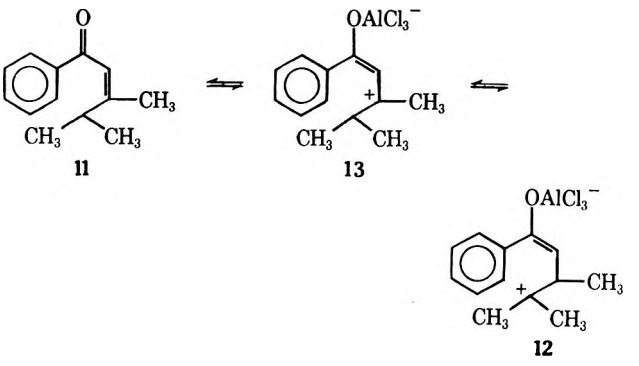


Since it has been previously noted that the reaction of **2** with benzene gave **5** in reasonable yield with 1 equiv of aluminum chloride,[2] this reaction was repeated using benzene-d_6. *The acid in this manner was free of isomers and had no deuterium in the alkyl side chain.* These results indicate that, with 1 equiv of aluminum chloride, carbonium ion **6** is formed, and, without rearrangement, alkylates the substrate. Further, it is apparent that, since no deuterium is incorporated into **5**, the ketones formed with excess aluminum chloride must arise by way of a different mechanism.

Since the molar ratio of aluminum chloride to lactone appears to profoundly affect the course of this reaction, it was repeated using 2.0 and 2.6 equiv of aluminum chloride. With 2.0 equiv there was obtained only 3,4,4-trimethyl-1-tetralone (**1**) and, when the reaction was carried out in benzene-d_6, deuterium was incorporated at C-3 as described above. With 2.6 equiv of aluminum chloride ketones **3** and **4** were also formed, but in smaller amounts than when 3 or more equiv were used.

(9) In all these compounds, there was, of course, complete deuteration of the aromatic ring.

A consideration of the reactions of lactones with superacids[10] indicates that, in the presence of more than 1 equiv of aluminum chloride, carbonium ion **6** is probably converted to the acyl carbonium ion derived from 3,4-dimethyl-3-pentenoic acid (**9**). This carbonium ion can then react with benzene to give an unsaturated ketone (**10**) which, under the influence of acid, either hydrogen chloride formed *in situ*, or excess aluminum chloride would cyclize to the tetralones or undergo reduction to **4**.



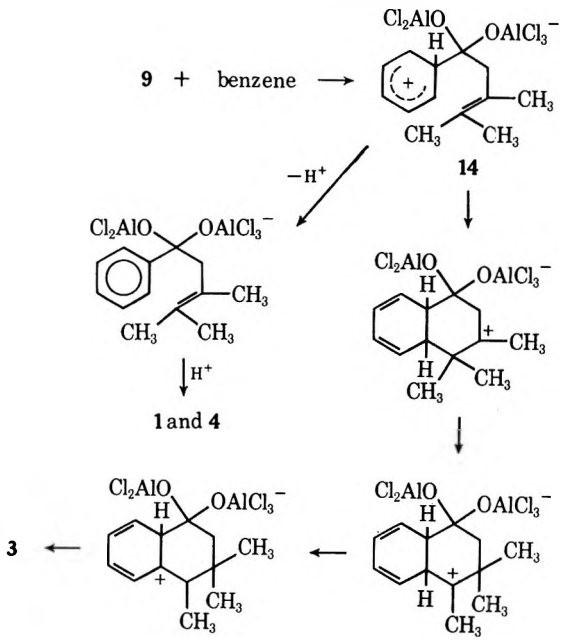
In order to check this hypothesis, 3,4-dimethyl-1-phenyl-2-penten-1-one (**11**) was synthesized by the reaction of the appropriate acid chloride and benzene. This ketone is considerably more accessible than **10** and on acid treatment would be expected to be converted to a similar carbonium ion (**12**). This expectation was borne out when **11** was treated with 3.2 equiv of aluminum chloride to give a mixture of 6% reduction product (**4**) and 94% **1**. However, when the reaction was carried out in benzene-d_6, little, if any, deuterium incorporation was observed. Surprisingly, the rearranged tetralone (**3**) was not obtained in these reactions. Insufficient **4** was obtained from the experiments in benzene-d_6 to permit its isolation and characterization. Although the failure to obtain deuterium incorporation in the cyclization of **11** was unexpected, it is easily explained if the intramolecular hydride shift from **13** to **12** and the cyclization of **12** are fast compared to exchange with solvent, which would lead to deuteration.

The reactions of **2** with benzene and excess aluminum chloride may all be interpreted in terms of the mechanism outlined in Scheme I. This mechanism accounts well for all the observed results, and in particular the failure to obtain **3** in the cyclization of **11**. In the presence of excess aluminum chloride, intermediate **14** may be stabilized, thus permitting significant amounts of ketone **3** to be formed by way of the intermediates shown. The exact mechanism of the reduction of **11** to **4** is not clear. Although the derived hydrogens are obtained from benzene, biphenyl is not a product of this reaction.

Whether this type of multiple reaction path is operative in the Friedel–Crafts reaction of simple lactones is not known, but it is quite certain that in this case, at least, the Truce mechanism[3c] is excluded. In the course of this work, the mass spectra of both tetralones (**1** and **3**) were determined, and these are included in Table I.

(10) G. A. Olah and A. T. Ku, *J. Org. Chem.*, **35**, 3916 (1970).

SCHEME I



Experimental Section[11]

Reaction of 3,4,4-Trimethylbutyrolactone and Benzene.—This reaction was carried out, and the mixture of ketones was isolated by the method reported earlier.[2] Separation of the mixtures of isomeric ketones was accomplished by preparative glc to give **3,4,4-trimethyl-1-tetralone** (1) which shows nmr signals at 0.99 (d, J = 7 Hz, CH_3CH), 1.22 (s, 3 H, CH_3), 1.37 (s, 3 H), 2.46 (m, 3 H, CH_2CH), 7.36 (m, 3 H, ArH), 7.92 ppm (m, 1 H, ArH); **3,3,4-trimethyl-1-tetralone** (3), nmr 1.01 (s, 6 H, CH_3), 1.26 (d, J = 7 Hz, 3 H, CH_3CH), 2.74 (m, 3 H, CH_2 and CH), 7.40 (m, 3 H, ArH), 7.92 ppm (m, 1 H, ArH); and **3,4-dimethyl-1-phenylpentan-1-one** (4), nmr 0.92 (overlapping d, J = 7 Hz, 9 H, CH_3CH), 1.81 (m, 2 H, CHCH), 2.82 (m, 2 H, CH_2), 7.45 (m, 3 H, ArH), 7.93 ppm (m, 2 H, ArH).

When the reaction was carried out in benzene-d_6 and the compounds were isolated as described above, the deuterium-decoupled nmr spectra of the ketones are, for **3,4,4-trimethyl-1-tetralone**, 1.04 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 2.65 ppm (AB, J = 7 Hz, CH_2); **3,3,4-trimethyl-1-tetralone**, 0.99 (s, 6 H, CH_3), 1.26 (s, 3 H, CH_3), 2.48 (AB, J = 17 Hz, CH_2); and **3,4-dimethyl-1-phenylpentan-1-one**, 0.89 (br s, 9 H, CH_3CD), 2.80 (AB, J = 15 Hz, CH_2).

The use of limited quantities of aluminum chloride gave as reported previously **3,4-dimethyl-4-phenylpentanoic acid** (5): mp 64–67° (lit. mp 74–75°);[2] nmr 0.90 (d, J = 6 Hz, 3 H, CH_3CH), 1.28 (s, 6 H, CH_3), 2.16 (m, 3 H, CH_2CH), 7.28 ppm (br s, 5 H, ArH). When the alkylation was carried out in benzene-d_6 the nmr was identical with the exception of the loss of the signal at 7.28 ppm. The methyl ester of the once recrystallized acid was homogenous to glc.

The results of several reactions of this type are summarized in Table II.

Ethyl 3,4-Dimethyl-2-pentenoate.—To a stirred slurry of 4.8 g of 50% sodium hydride in 190 ml of 1,2-dimethoxyethane cooled in an ice bath and under a nitrogen atmosphere was added dropwise 22.4 g of triethyl phosphonoacetate. The mixture was stirred for 1 hr and 8.6 g of methyl isopropyl ketone were then added dropwise. The reaction mixture was heated at 60° for 24 hr, cooled to room temperature, diluted with water, and extracted with ether. The ethereal extracts were dried and the solvent was evaporated. Distillation afforded 9.8 g (63%) of unsaturated ester: bp 185–187° (lit.[12] 189–191°); nmr 1.2 (m, 9 H, CH_3CH and CH_3CH_2), 2.13 (d, J = 1 Hz, 3 H, CH_3), 2.15 (m, 1 H, CH), 4.12 (q, 2 H, CH_3CH_2), 5.16 ppm (br s, 1 H, vinyl CH); ir 3.42, 5.82, 6.08 μ.

TABLE II

PRODUCTS FROM THE REACTION OF 3,4,4-TRIMETHYLBUTYROLACTONE AND BENZENE

Run	Solvent[b]	2, mmol	$AlCl_3$, mmol	5, %[a]	1, %[a]	3, %[a]	4, %[a]
1	Benzene	120	410	0	41	32	5
2	Benzene	15.6	31.5	0	60	0	0
3	Benzene	15.6	41.3	0	57	13	1
4	Benzene-d_6	20.3	69.3	0	43	34	5
5	Benzene-d_6	4.20	8.30	0	49	0	0
6	Benzene	5.90	7.60	57[c]	0	0	0
7	Benzene-d_6	1.56	1.88	87	0	0	0
8[d]	Benzene	120	410	0	41	32	5
9[d]	Benzene	150	120	60	18	0	0
10[e]	Benzene	0	8.22	0	100	0	0

[a] Reported in per cent based on lactone. [b] All reactions were carried out at 15° for 1 hr and then heated at reflux for 2 hr. [c] After two recrystallizations. [d] Reference 2. [e] Attempted isomerization of 2.18 mmol of 1. Carried out at reflux for 24 hr.

3,4-Dimethyl-2-pentenoic Acid.—To 5.0 g of ethyl 3,4-dimethyl-2-pentenoate were added 50 ml of 20% potassium hydroxide and 50 ml of ethanol. The mixture was heated at reflux for 12 hr and the acid was isolated in the usual manner and distilled to give 2.6 g (63%): bp 73–76° (0.5 mm) [lit.[13] 83–94° (1.5 mm)]; nmr 1.09 (d, J = 7 Hz, 6 H, CH_3CH), 2.17 (s, 3 H, CH_3), 3.4 (m, 1 H, CH), 5.75 ppm (s, 1 H, vinyl CH).

3,4-Dimethylpentanoic Acid.—This compound was prepared by hydrolysis of ethyl 3,4-dimethylpentanoate,[14] which was in turn obtained by reduction of the unsaturated ester described above. From 9.70 g of pentenoate 4.70 g (60%) of saturated acid, bp 209–210° (lit.[6] 210–214°), were obtained: nmr 0.85 (overlapping d's, 9 H, CH_3CH), 1.55 (m, 2 H, CHCH), 2.22 ppm (m, 2 H, CH_2).

3,4-Dimethyl-1-phenylpentan-1-one (4).—To 3.0 g of 3,4-dimethylpentanoic acid were added 13.0 g of thionyl chloride and the mixture was heated on the steam bath for 2 hr. The excess thionyl chloride was removed, leaving a residue of 3.2 g of acid chloride, which was added to a chilled, stirred slurry of 5.0 g of anhydrous aluminum chloride in 100 ml of dry benzene. The slurry was stirred in an ice bath for 1 hr and heated under reflux for 2 hr. The solution was cooled to room temperature and poured into a slurry of ice and hydrochloric acid. The aqueous layer was separated and extracted with ether. The organic fractions were combined, washed with 5% sodium hydroxide and water, and dried. The solvent was removed under reduced pressure and the resulting oil was distilled, giving 3.1 g (68%) of ketone, bp 85° (0.25 mm). The infrared and nmr spectra were identical with those of the compound obtained from the Friedel–Crafts reaction of 3,4,4-trimethylbutyrolactone and benzene.

3,4-Dimethyl-1-phenyl-2-penten-1-one (11).—To a solution of 4.0 g of 3,4-dimethyl-2-pentenoic acid in 50 ml of benzene was added 7.5 ml of oxalyl chloride, during which time a vigorous reaction took place. The solution was stirred at room temperature for 2 hr and the excess oxalyl chloride and benzene were distilled off. The product was dissolved in 25 ml of benzene and the benzene was again removed, leaving 4.5 g of crude acid chloride. This material was added to a stirred slurry of 4.7 g of aluminum chloride in 100 ml of benzene cooled in an ice bath. The reaction mixture was stirred at ice bath temperature for 0.5 hr and at room temperature for 24 hr and then heated to 60° for 25 min. The solution was cooled to room temperature and poured into a slurry of ice and concentrated hydrochloric acid. The aqueous layer was drawn off and extracted with ether. The organic extracts were combined, washed with 5% sodium hydroxide and water, and dried. The solvent was removed at reduced

(11) All melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were taken as potassium bromide disks or liquid films on sodium chloride plates using a Perkin-Elmer Model 137 spectrophotometer and are reported in microns. Nuclear magnetic resonance spectra were obtained in deuteriochloroform using a Varian Associates A-60 nuclear magnetic resonance spectrometer. All spectra are reported in parts per million relative to internal tetramethylsilane (δ). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Gas–liquid chromatography was carried out on an F and M Model 810 analytical gas chromatograph using helium as the carrier gas at a flow rate of 35 ml/min through a 10 ft × 0.125 in. copper column of 10% QF1 on 'HP' Chromosorb W (80–100 mesh).

(12) R. Fittig and O. Kraft, *Justus Liebigs Ann. Chem.*, **208**, 71 (1881).

(13) L. I. Smith, W. L. Kohlhase, and R. J. Brotherton, *J. Amer. Chem. Soc.*, **78**, 2533 (1956).

(14) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **111**, 308 (1935).

pressure, yielding 4.02 g of crude product, which was dissolved in hexane and chromatographed on Merck alumina. Elution with hexane gave 1.20 g (20%) of pentenone: bp 99–101° (0.32 mm); nmr 1.21 (d, J = 6 Hz, CH_3CH), 2.10 (br s, 3 H, CH_3), 2.15 (m, 1 H, CH), 6.49 (br s, 1 H, vinyl CH), 7.13 (m, 3 H, ArH), 7.62 ppm (m, 2 H, ArH); ir 3.35, 5.95, 6.25 μ. This material could not be obtained completely homogenous to glc and was characterized by mass spectrometry, molecular ion at m/e 188.

Cyclization of 3,4-Dimethyl-1-phenyl-2-penten-1-one. A.—A solution of 0.10 g (0.53 mmol) of 3,4-dimethyl-1-phenyl-2-penten-1-one in 1.0 ml of dry benzene was added to a chilled slurry of 0.227 g (1.7 mmol) of aluminum chloride in 4.0 ml of dry benzene. The reaction mixture was stirred at ice bath temperature for 1 hr and then heated at reflux for 2 hr. Isolation of the product in the manner previously described gave 0.095 g (95%) of a viscous oil which was shown by glc to consist of 3,4-dimethyl-1-phenylpentan-1-one (4) and 3,3,4-trimethyl-1-tetralone (1) in a ratio of 6:94, respectively.

B.—A solution of 0.4 g (2.1 mmol) of 3,4-dimethyl-1-phenyl-2-penten-1-one in 5.0 ml of benzene-d_6 was added to a chilled, stirred slurry of 0.64 g of aluminum chloride in 15 ml of benzene-d_6. The reaction was carried out and the product was isolated as described above to give 0.36 g (90%) of viscous oil. The crude product was dissolved in benzene and chromatographed on alumina. Ether eluted the product, which was shown to be homogenous by vapor phase chromatography and the nuclear magnetic resonance and infrared spectra of which were identical with those of 3,4,4-trimethyl-1-tetralone obtained from the Friedel–Crafts reaction of 3,4,4-trimethylbutyrolactone and benzene.

Registry No.—**1**, 2981-99-9; **2**, 2981-96-6; **3**, 2982-01-6; **4**, 32557-33-8; **5**, 2977-36-8; **11**, 32557-35-0; benzene, 71-43-2; ethyl 3,4-dimethyl-2-pentenoate, 6570-79-2; 3,4-dimethyl-2-pentenoic acid, 32557-37-2; 3,4-dimethylpentanoic acid, 3302-06-5.

Interaction of Carbanions with Azobenzene and Related Compounds[1a,b]

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Reaction of alkali salts of active hydrogen compounds with azobenzene follow three general pathways: (1) addition to afford substituted hydrazobenzenes; (2) oxidation–reduction to often give dimer of the active hydrogen compound; and (3) addition–elimination to afford anils. In contrast to earlier work, the current study has ascertained that the most general pathway for such reactions is addition. Thus, the synthesis of 21 new hydrazobenzenes, prepared by three different methods, is reported. The addition reactions, apparently kinetically controlled in ammonia, proceed *via* intermediate monoanions of the hydrazobenzenes as evidenced by a trapping experiment with benzoyl chloride. Redox reactions have currently been observed only in two rather special cases: 9,10-dipotassioacenaphthene with azobenzene, and lithiodiphenylmethane with a highly conjugated azo compound. Interaction of either the monoalkali or geminal dialkali salts of phenylacetonitrile with azobenzene has given an interesting cyanoenamine, presumably *via* a novel "base-catalyzed" deamination. Similar deaminations have been observed with other systems, including some hydrazobenzenes, to afford anils. Certain of the latter conversions are rationalized by considering the thermodynamic and kinetic acidities of the hydrazobenzenes.

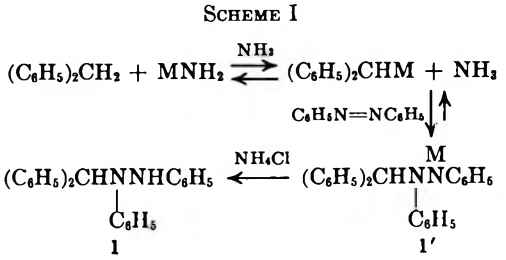
Previously, it has been shown that carbanions usually transfer an electron to the azo linkage of aromatic azo compounds in solutions of ether[2a] or dimethyl sulfoxide,[2b] resulting in reduction of the nitrogen–nitrogen double bond and, sometimes, in isolation of the oxidative dimer of the carbanion.[2a] Only rarely, though, have such reactions resulted in ionic addition of carbanions across the azo linkage to give substituted hydrazo compounds. Thus, the highly reactive phenylpotassium,[2a] phenylcalcium iodide,[2a] and phenyllithium[3] have been observed to so add to azobenzene to afford 1,1,3-triphenylhydrazine in low yields.

Our initial interest in azobenzene and related compounds stemmed from their potential use as oxidants in the dimerization of carbanions in liquid ammonia.[4] Instead of the expected oxidation–reduction reactions, though, these interactions have been found to constitute a presumably general synthesis of arylated hydrazines. This paper describes the three methods developed to effect such syntheses and illustrates not only interesting solvent and temperature effects, but also discusses novel base-catalyzed deaminations of certain of the hydrazine products.

Results and Discussion

Initial efforts were directed toward interacting the monoalkali salts of diphenylmethane with azobenzene in liquid ammonia. Surprisingly, aside from some recovered starting materials, only hydrazine **1**, the product arising from addition across the azo linkage, was isolated in variable yields (Scheme I); the expected dimeric product, 1,1,2,2-tetraphenylethane, was absent. The highest yields of **1** were realized by employing sodium or potassium cations for relatively short reaction periods (5–10 min) and by inversely neutralizing the reaction mixtures[5] (method A). For

SCHEME I



1 1′

(1) (a) Supported by the Petroleum Research Fund, administered by the American Chemical Society, on Grant 3710-A. (b) A preliminary report has been published; see E. M. Kaiser and G. J. Bartling, *Tetrahedron Lett.*, 4357 (1969). (c) Shell Fellow, 1971.

(2) (a) H. Gilman and J. C. Bailie, *J. Org. Chem.*, **2**, 84 (1937), and references cited therein; (b) G. A. Russell, R. Konaka, E. T. Strom, W. C. Danen, K.-Y. Chang, and G. Kaupp, *J. Amer. Chem. Soc.*, **90**, 4646 (1968), and references cited therein.

(3) P. F. Holt and B. P. Hughes, *J. Chem. Soc.*, 764 (1954).

(4) E. M. Kaiser, *J. Amer. Chem. Soc.*, **89**, 3659 (1967).

(5) Inverse neutralization involves the pouring of a reaction mixture into ammonia containing excess ammonium chloride.

TABLE I
PREPARATION OF $RNNHC_6H_5$
C_6H_5

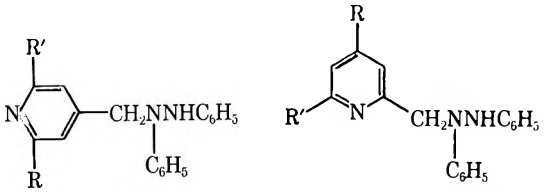
Active hydrogen compound, RH	Product	Mp, °C	Yields,[a] % A	B	C	Ir, cm⁻¹	Calcd, % C	H	N	Found % C	H	N
Diphenylmethane	1	115–119[b]	77	49	92	3290 (NH)	85.66	6.34	7.99	85.47	6.41	7.89
4-Piccline	2	124–126[c]	31	51	97	3240 (NH)	78.50	6.23	15.26	78.70	6.40	15.45
2,4-Lutidine	3	116–117[c]	5–10		82	3230 (NH)	78.85	6.63	14.52	79.06	6.58	14.46
2,4,6-Collidine	4	168–170[b]	28		77	3210 (NH)	79.16	6.99	13.85	79.25	7.08	13.78
2-Piccline	5	112–113[c]	0	29	69	3250 (NH)	78.50	6.24	15.26	78.51	6.05	15.11
2,4-Lutidine	6	142–144[b]		47[d]		3270 (NH)	78.85	6.63	14.52	79.00	6.70	14.38
2,6-Lutidine	7	119–121[b]			83	3270 (NH)	78.85	6.63	14.52	79.07	6.45	14.47
2,4,6-Collidine	8	104–105[c]		63[d]		3320 (NH)	79.16	6.99	13.85	79.16	7.04	13.80
2-Methylpyrazine	9	90–91[e]	39			3280 (NH)	73.87	5.84	20.28	74.00	5.68	20.43
2-Methylquinoline	10	137–140[c]	50			3230 (NH)	81.19	5.90	12.91	81.10	5.90	12.88
p-Tolunitrile	11	119–121[b]		19	73	3320 (NH) 2230 (CN)	80.23	5.73	14.04	80.15	5.67	13.89
3-Phenylphthalide	12	171–172[b]	30			3270 (NH)	79.56	5.14	7.14	79.41	5.12	7.21
2-Phenylacetamide	13	94–97[f]	29[g]			3500 (OH)[h] 3330 and 3175 (NH)	73.17[h]	7.22[h]	11.11[h]	73.05	7.09	10.93
2-Phenylacetanilide	14	134–137[e]	49[g]			3300, 3370 (NH)	79.33	5.90	10.68	79.16	5.99	10.75

[a] Method A, 1 equiv each of potassium amide (or sodium amide), RH, and azobenzene in liquid ammonia; method B, 1 equiv each of lithium diisopropylamide, RH, and azobenzene; method C, 2 equiv each of lithium diisopropylamide and RH, 1 equiv of azobenzene. [b] Recrystallized from ethanol. [c] Recrystallized from cyclohexane. [d] 1 equiv of *n*-butyllithium was used as the base. [e] Recrystallized from aqueous ethanol. [f] Recrystallized from 2-propanol. [g] 2 equiv of sodium amide were employed. [h] This compound was obtained as a monosolvate (2-propanol).

example, sodiodiphenylmethane and azobenzene gave **1** in yields of 77 and 67% upon inverse neutralization after reaction periods of 5 and 15 min, respectively. Similarly, potassiodiphenylmethane afforded **1** in yields of 70 and 28% after 20-min reaction periods upon inverse and direct neutralization, respectively; direct neutralization of a similar 2-hr reaction using the potassium cation gave **1** in only 15% yield.

The above results are similar to the previously reported condensations of certain carbanions with aldehydes and ketones in ammonia and may be ascribed to the competition of a kinetically controlled addition reaction *vs.* a thermodynamically controlled reversion reaction.[6] In the current study, this would mean that the formation of **1′** is kinetically controlled and that, after some time, the active hydrogen compound, diphenylmethane, is reversibly regenerated along with alkali metal amide (Scheme I). The alkali metal amide then adds to or complexes with the azobenzene in a thermodynamically controlled process to possibly afford $C_6H_5N(M)$–$N(NH_2)C_6H_5$. Although attempts to isolate or trap this latter adduct were unsuccessful in addition reactions where reversion had occurred or in blank experiments involving potassium amide and azobenzene, both systems exhibited a unique purple color not seen in any other current reaction. More importantly, hydrazine **1** was found to be unstable to catalytic amounts of potassium amide in ammonia, since such treatment caused it to reverse to diphenylmethane and azobenzene. This result suggests that neutral diphenylmethane and neutral azobenzene are more thermodynamically stable than neutral hydrazine **1**.[6] In this reversion reaction, small amounts of **1′** would be formed which reverse to azobenzene and potassiodiphenylmethane; the latter salt would be protonated by un-ionized **1** to give diphenylmethane and **1′**. The process then would be repeated until all of **1** has been exhausted. A similar situation is thought to prevail when the normal addition reactions of carbanions with azobenzene are directly neutralized.

In addition to alkali salts of diphenylmethane, a wide variety of other carbanions were condensed with azobenzene in liquid ammonia (method A) as well as by means of an additional base–solvent system, lithium diisopropylamide in THF–hexane (method B). Moreover, the use of a twofold excess of carbanion over azo compound (method C), prepared by this latter base, proved even more successful. The results are listed in Table I. This table shows that diphenylmethane was condensed by each of the three methods to afford hydrazine **1** in fair to excellent yields. Similarly, the 4- and 2-picolyl anions were reacted to give hydrazines **2** and **5**, respectively. Likewise, 2,4-lutidine and 2,4,6-collidine, converted to their 4-lithio derivatives by lithium diisopropylamide, were condensed with azobenzene to give adducts **3** and **4**, respectively. Finally, 2,4-lutidine, 2,6-lutidine, and 2,4,6-collidine, converted to their 2-lithio salts by *n*-butyllithium, were similarly condensed to afford hydrazines



2, R = R′ = H
3, R = CH_3; R′ = H
4, R = R′ = CH_3

5, R = R′ = H
6, R = CH_3; R′ = H
7, R = H; R′ = CH_3
8, R = R′ = CH_3

(6) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3873 (1966).

TABLE II

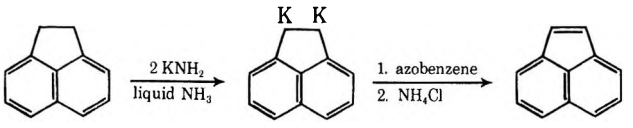
PREPARATION OF RN—NH—(X, X, Y)—Y

Active hydrogen compound, RH	Product	Method[a]	X	Y	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Diphenylmethane	16	A	Cl	H	152–154[b]	20	71.59	4.81	6.68	71.57	4.87	6.41
4-Picoline	17	B	Cl	H	155–156[c]	53	62.79	4.40	12.21	63.00	4.31	12.19
2-Picoline	18	B	Cl	H	95–96[d]	36	62.79	4.40	12.21	62.90	4.34	12.22
2-Methylquinoline	19	B	Cl	H	109–110[c]	7	67.00	4.35	10.66	67.25	4.47	10.76
p-Tolunitrile	20	C	Cl	H	128–130[e]	68	65.22	4.11	11.41	65.28	4.22	11.28
Phenylacetanilide	21	C	Cl	H	168–169[b]	6[f]	67.53	4.59	9.09	67.80	4.58	9.08
4-Picoline	22	B	H	Cl	135–136[g]	44	62.79	4.40	12.21	62.71	4.41	12.21

[a] See footnote *a*, Table I. [b] Recrystallized from 2-propanol. [c] Recrystallized from cyclohexane. [d] Recrystallized from 30–60° petroleum ether. [e] Recrystallized from benzene–ethyl acetate. [f] 2 equiv of lithium diisopropylamide were employed. [g] Recrystallized from benzene.

6, **7**, and **8**, respectively.[7] In all of the above reactions, method C was clearly superior to the other methods and is recommended as the one of choice for synthetic purposes. The superiority of method C is probably due to favorable shifts in equilibria toward intermediates like **1′** (Scheme II).

Certain other active hydrogen compounds were also condensed with azobenzene to give hydrazines. Thus, 2-methylpyrazine and 2-methylquinoline gave compounds **9** and **10**, respectively. Likewise, *p*-tolunitrile and 3-phenylphthalide gave **11** and **12**, while phenylacetamide and phenylacetanilide, which were converted to their 1,3-disodio salts,[8] gave adducts **13** and **14**, respectively. Interestingly, interaction of 9,10-dipotassioacenaphthene, prepared by treatment of acenaphthene with 2 equiv of potassium amide, and azobenzene afforded acenaphthylene (**15**) and hydrazobenzene (eq 1). In the current study, the latter reaction constitutes the only example of an oxidation–reduction reaction effected by azobenzene.

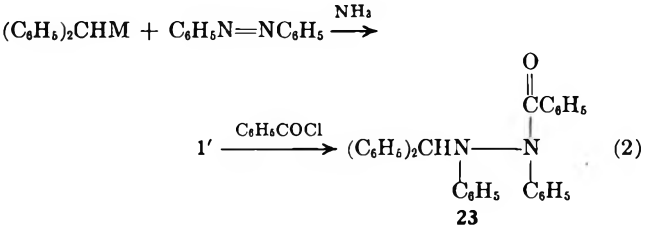


15 (1)

Incidentally, methods B and C were successful only when the addition of the azobenzene to the solutions of the carbanions were effected at low temperatures. For example, hydrazine **1** was obtained in only 18% yield when the condensation was carried out at 25° (method B), but the yield increased to 40% when the temperature was maintained at −78°. Models indicate that **1** is not entirely free of rotational restrictions. Thus, it is attractive to explain the above temperature effects in terms of steric compression in intermediates like **1′**; such compression should be felt less at lower temperatures than at higher ones.

Next, several condensations of carbanions with chlorinated azobenzenes were realized, mostly by employing methods B and C. The results, listed in Table II, are similar to those realized above on the parent azo compound. Thus, 2,2′-dichloroazobenzene was condensed with diphenylmethane, 4-picoline, and 2-picoline to give hydrazines **16**, **17**, and **18**, respectively. This azo compound was also condensed with 2-methylquinoline, *p*-tolunitrile, and phenylacetanilide to give **19**, **20**, and **21**, respectively. Finally, 4,4′-dichloroazobenzene was condensed with 4-picoline to give **22**. Although the yields in these reactions were, at best, only fair, the material balances were excellent, unreacted starting materials being quantitatively recovered. These results would suggest that the anions in the current study are not displacing the halides in the molecules. Such nucleophilic aromatic substitutions have been reported on certain azobenzenes containing an *o*-methoxy group.[9] It should be mentioned that attempted condensations of certain carbanions with 4,4′-dimethylazobenzene failed, presumably because of the limited solubility of this compound; even if this compound were soluble, though, the substituent effects of the methyl groups would be expected to decrease the reactivity of the azo linkage toward addition reactions.

The above condensations of carbanions with azobenzene probably proceed *via* a nucleophilic addition type of mechanism similar to that observed with carbonyl compounds. This was demonstrated by trapping the proposed intermediate **1′** in the reaction of potassiodiphenylmethane with azobenzene by means of benzoyl chloride. Thus, in addition to obtaining some of **1**, benzoyl derivative **23** was obtained in low yield (eq 2).



(2)

23

One condensation of an active hydrogen compound with azobenzene deserves special mention. Thus, reaction of sodio- or lithiophenylacetonitrile, prepared by means of the corresponding alkali amides in ammonia, or of dilithiophenylacetonitrile, prepared by *n*-

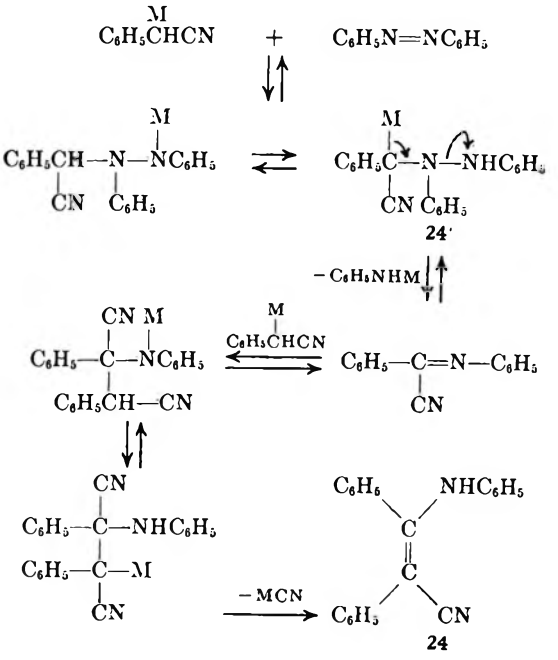
(7) A manuscript is currently in preparation dealing with the different site of metalation of polymethylpyridines as a function of the base.

(8) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3696 (1961).

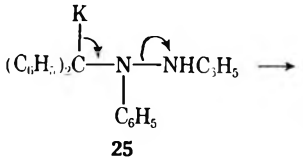
(9) For example, see S. Bozzini, A. Risaliti, and A. Stener, *Tetrahedron*, **26**, 3927 (1970).

butyllithium in THF–hexane,[10] all surprisingly afforded cyanoenamine **24** in low yield (Scheme II). Product **24**, pictured as arising from the elimination of the alkali metal derivative of aniline from **24′** to give benzoyl cyanide anil, was not expected since deminations are usually promoted by acid catalysts. A similar reaction has been reported in the addition of potassiophenylacetonitrile to nitrosobenzene in *tert*-butyl alcohol[11] where the leaving group is potassium oxide (or hydroxide).

SCHEME II



The novel base-catalyzed deamination reaction proposed in Scheme II was also observed in certain other cases. For example, treatment of hydrazine **1** with 1 molecular equiv of potassium amide in liquid ammonia cleanly afforded benzophenone anil (**26**). This anil can be pictured as arising *via* ionization of the benzhydrylic proton of **1** to give **25** followed by loss of *N*-potassioaniline (eq 3).

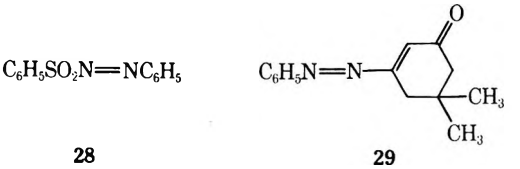


25

$$(C_6H_5)_2C{=}NC_6H_5 \quad + \quad C_6H_5NHK \qquad (3)$$
26 **27**

That treatment of hydrazine **1** with potassium amide afforded **26** (presumably *via* **25**) is particularly interesting when compared with the base-catalyzed reversion of **1** to diphenylmethane and azobenzene described above. It thus appears that **1** may interact with base either at the nitrogen hydrogen to give **1** which can eliminate potassiodiphenylmethane, or at the benzhydrylic hydrogen to give **25** which can eliminate *N*-potassioaniline. It is attractive to explain such differences in products in terms of kinetic *vs.* thermodynamic acidities. Based on rapid exchange reactions with deuterium oxide, the N–H, but not the benzhydrylic protium, readily and completely exchanges as evidenced by nmr spectroscopy. Therefore, we suggest that, kinetically, the N–H is more acidic than the benzhydrylic proton of **1** and rapidly, but reversibly, is ionized. We further suggest that, thermodynamically, the benzhydrylic proton is more acidic than the N–H since the resulting carbanion (**25**) is more highly resonance stabilized than is the nitrogen anion (**1′**). Once **25** is formed, though, it apparently eliminates *N*-potassioaniline (**27**) immediately, since all attempts to trap **25** have failed and only anil **26** has been obtained.

Finally, certain condensations of lithiodiphenylmethane were attempted on two azo compounds other than those directly related to azobenzene. Thus, interaction of this carbanion with azo sulfone **28** at 25° afforded anil **26** in 21% yield along with an equivalent amount of benzenesulfonamide. The mechanism of this conversion is presumably similar to that shown in eq 3. Surprisingly, though, reaction of lithiodiphenylmethane with the novel azo compound **29** failed to give either addition or elimination product. Instead, oxidation–reduction occurred, since 1,1,2,2-tetraphenylethane was obtained in 72% yield.



28 **29**

All of the hydrazines described above appear to be new. Their structures were supported by infrared spectroscopy and by correct elemental analyses (Tables I and II) and, in some cases, by nmr spectroscopy.

The currently described condensations of azobenzene and its derivatives with various organometallic reagents should be capable of extension to afford a wide variety of highly substituted hydrazines. Moreover, products of addition, elimination, and oxidation–reduction can be expected from these reactions, with the reaction path obviously dependent on specific structural characteristics of the azo compound. Methods by which these characteristics may be correlated with reaction paths to allow prediction of the products are at present unknown. Even more interesting is the broader area of condensations of carbanions with "novel" electrophiles of which azobenzene may be considered to be the first example.

Experimental Section[12]

Preparation of Substituted Hydrazobenzenes.—Tables I and II list the specifics for each of the hydrazines prepared in this study. Examples illustrating the preparation of *N*-diphenylmethylhydrazobenzene by means of each of the methods follow.

Method A.—To a stirred solution of 0.05 mol of potassium amide (or sodium amide) in 350 ml of anhydrous liquid ammonia[13] was added a solution of 8.4 g (0.05 mol) of diphenylmethane in 50 ml of anhydrous ethyl ether. After 30 min, the resulting solution was treated with a solution of 9.1 g (0.05 mol) of azobenzene in 30 ml of ether added during 5 min. The now blue-

(10) E. M. Kaiser and C. R. Hauser, *J. Amer. Chem. Soc.*, **88**, 2348 (1966).

(11) H. G. Aurich, *Chem. Ber.*, **98**, 3917 (1965).

(12) Infrared spectra were measured on a Perkin-Elmer Model 237B grating infrared spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(13) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 122 (1954).

green mixture was stirred for an additional 5 min and then poured with stirring into 300 ml of ammonia containing 20 g of ammonium chloride. After allowing the solvents to evaporate, the solid residue was extracted with benzene. Upon concentration, a red oil was obtained which solidified upon standing.[14] The crude solid was purified as indicated in Table I.

Method B.—To a solution of 5.0 g (0.05 mol) of diisopropylamine in 200 ml of anhydrous THF was added, *via* a hypodermic syringe, 32 ml (0.05 mol) of 1.6 *M* *n*-butyllithium in hexane.[15] After stirring for 15 min, the yellow solution was treated with 8.4 g (0.05 mol) of diphenylmethane in 50 ml of THF and the mixture was stirred for 1 hr. Upon cooling to −78° by means of a Dry Ice–acetone bath, the mixture was then treated during 5 min by the dropwise addition of a solution of 9.1 g (0.05 mol) of azobenzene in 50 ml of THF. After stirring for 5 min, the mixture was poured into 400 ml of water containing excess ammonium chloride. The organic phase was separated, the aqueous phase was extracted with benzene, and the extracts were combined. Removal of the solvent by distillation yielded crude solid product which was purified as indicated in Table I.

Method C.—This method is identical with method B except for the use of 0.5 equiv (4.5 g, 0.025 mol) of azobenzene. The yields thus reported in Tables I and II are based on azobenzene.

Conversion of Acenaphthene to Acenaphthylene.—Solid acenaphthene (7.7 g, 0.05 mol) was added in portions to a solution of 0.1 mol of potassium amide in 350 ml of liquid ammonia.[13] After 30 min, the dark green mixture was treated with a solution of 9.1 g (0.05 mol) of azobenzene in 50 ml of ether and the mixture was stirred for 4 hr. At the end of this time, the mixture was directly neutralized by the addition of ammonium chloride and worked up as in method A above to give a red oil which was chromatographed on alumina with benzene, then methanol, to give 11.3 g of material. The latter was treated with a solution of 11.0 g (0.05 mol) of picric acid in 30 ml of boiling ethanol to afford 10.1 g (53%) of acenaphthylene picrate, mp and mmp 201–203° (lit.[16] mp 201–202°).

Preparation of 1-Anilino-2-cyano-1,2-diphenylethylene (24).—To 0.05 mol of sodium amide in 300 ml of liquid ammonia was added a solution of 5.8 g (0.05 mol) of phenylacetonitrile in 50 ml of ether. After stirring briefly, the mixture was treated with a solution of 9.1 g (0.05 mol) of azobenzene in 50 ml of ether added during 10 min. The mixture was stirred for 5 min, then neutralized and worked up as above. The resulting red oil (16.6 g) was chromatographed on alumina using benzene and ethyl acetate as eluents to give 3.7 g of yellow solid. Recrystallization of the solid from alcohol gave 0.9 g (6.0%) of fine yellow needles: mp 203–204° (lit.[11] mp 202–203.5°); ir (Nujol) 3250 (NH), 2200 (CN), 1240, 1030, and 750 cm^{-1}.

Anal. Calcd for $C_{21}H_{16}N_2$: C, 85.11; H, 5.44; N, 9.45. Found: C, 85.31; H, 5.48; N, 9.30.

Similar results were obtained by employing lithium amide in ammonia or with 2 equiv of *n*-butyllithium in THF–hexane.

Preparation of *N*-Diphenylmethyl-*N'*-benzoylhydrazobenzene (25).—To a solution of 0.05 mol of lithiodiphenylmethane in THF at −78° was added during 5 min a solution of 0.025 mol of azobenzene in THF as in method C above. The resulting mixture was treated immediately with a solution of 7.0 g (0.05 mol) of benzoyl chloride in THF added during 5 min. After stirring for 1 hr at −78°, the dark blue mixture was poured into 600 ml of water containing excess ammonium chloride. The organic layer was separated and the aqueous layer was extracted several times with benzene. Removal of the solvent gave 17.8 g of a thick orange oil which was crystallized from acetone to give 2.6 g (23%) of product **25**: mp 194° dec; ir (Nujol) 1650 (C=O), 1590, 1280, 1235, and 1155 cm^{-1} (aromatic).

Anal. Calcd for $C_{32}N_{26}N_2O$: C, 84.55; H, 5.77; N, 6.16. Found: C, 84.77; H, 5.66; N, 5.90.

Reaction of *N*-Diphenylmethylhydrazobenzene (1) with Stoichiometric Amounts of Potassium Amide in Liquid Ammonia.—To 0.029 mol of potassium amide in 350 ml of ammonia was added a solution of 10.0 g (0.029 mol) of hydrazine **1** in 30 ml of THF. After 1 hr, the blue-green mixture was inversely neutralized and worked up as usual to give 9.9 g of a red oil. Crystallization of the oil from alcohol gave 0.6 g (6.2%) of 1,1,2,-2-tetraphenylethane, mp 208–210° (lit.[17] mp 209°); the ir of this compound was identical with that of an authentic sample. Concentration of the alcohol solution afforded 5.2 g (70%) of benzophenone anil (**26**): mp 113–115° (lit.[18] mp 113–114°); ir (Nujol) 1615 (C=N), 1590, 1225, 1140, and 955 cm^{-1} (aromatic).

Anal. Calcd for $C_{19}H_{15}N$: C, 88.67; H, 5.89; N, 5.44. Found: C, 89.10; H, 5.50; N, 5.36.

Reaction of *N*-Diphenylmethylhydrazobenzene with Catalytic Amounts of Potassium Amide in Liquid Ammonia.—This reaction was carried out exactly as described above, except for the use of only a catalytic amount (0.005 mol) of potassium amide. The work-up of the mixture afforded an orange oil which was chromatographed on alumina. Elution with ligroin followed by ligroin–benzene mixtures allowed isolation of 5.1 g of an orange oil which consisted of starting materials as analyzed by tlc and nmr. The middle fractions were combined to yield 0.3 g of 1,1,2,2-tetraphenylethane (3.1%), and concentration of the filtrate gave 0.4 g (5.4%) of benzophenone anil (**26**), mp 111–113°.

Reaction of Potassiodiphenylmethide with Phenylphenylsulfonyl Diimide (28).—To 0.025 mol of potassiodiphenylmethane in 350 ml of liquid ammonia, prepared as above, was added dropwise a solution of 6.1 g (0.025 mol) of **28** in ether. After stirring for 3 hr, the reaction mixture was inversely neutralized and worked up as above to give 1.3 g (21%) of benzophenone anil, mp 112–114°.

Interaction of Lithiodiphenylmethane with 5,5-Dimethyl-3-oxo-1-phenylazo-1-cyclohexene (29).—Lithiodiphenylmethane (0.05 mol) in 180 ml of THF, prepared by method B, was treated at 0° with a solution of 5.7 g (0.025 mol) of **29**[19] in 30 ml of THF added during 5 min. The resulting mixture was stirred for 30 min at 0°, then neutralized and worked up as above to afford, upon treatment with boiling alcohol, 6.0 g (72%) of 1,1,2,2-tetraphenylethane, mp 207–209°; the infrared spectrum was identical with that of an authentic sample.

Registry No.—**1**, 32812-31-0; **2**, 32812-32-1; **3**, 32812-33-2; **4**, 32812-34-3; **5**, 32812-35-4; **6**, 32812-36-5; **7**, 32812-37-6; **8**, 32812-38-7; **9**, 32812-39-8; **10**, 32812-40-1; **11**, 32812-41-2; **12**, 32812-42-3; **13**, 32812-43-4; **14**, 32812-44-5; **16**, 32812-45-6; **17**, 32812-46-7; **18**, 32812-47-8; **19**, 32812-48-9; **20**, 32812-49-0; **21**, 32812-50-3; **22**, 32812-51-4; **24**, 4686-15-1; **25**, 32819-57-1; **26**, 574-45-8; azobenzene, 103-33-3.

(14) In certain cases, the crude reaction mixtures were chromatographed on alumina and the products were eluted with benzene–ethyl acetate; unreacted azobenzene was always the first compound to be eluted.

(15) Obtained from the Foote Mineral Co., Exton, Pa.

(16) M. C. Kloetzel and H. E. Mertel, *J. Amer. Chem. Soc.*, **72**, 4786 (1950).

(17) A. Zagoumenny, *Ann. Chim. (Paris)*, **184**, 177 (1876).

(18) C. M. Rosser and J. J. Ritter, *J. Amer. Chem. Soc.*, **59**, 2179 (1937).

(19) A. J. Fatiadi, *J. Org. Chem.*, **35**, 831 (1970).

High Pressure Studies. IX. Activation Volumes and Solvent Internal Pressure[1,2]

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The effects of externally applied pressure on reaction rate constants for some free-radical reactions are compared with the solvent dependence of rate constants for these reactions at atmospheric pressure. In particular, there appears to be no correlation of the rate data with "internal pressure" of the solvents. A clarification of the relationship between internal pressure $(\partial E/\partial V)_T$ and cohesive energy density $(\Delta E_{vap}/V_T)$ is presented. The latter is commonly referred to as "internal pressure" but it differs markedly from $(\partial E/\partial V)_T$ for many common liquids.

Activation volumes for chemical reactions in solution are traditionally derived from the dependence of their rate constants on *externally* applied pressure (eq 1).[3,4] However, it has been suggested that values of

$$\Delta V^* = -RT(\partial \ln k/\partial P)_T \quad (1)$$

ΔV^* might be obtained using a solvent property referred to as "internal pressure."[5,6]

During the course of our studies on solution phase reactions at elevated pressure, we have determined activation volumes for a variety of free-radical reactions.[4] For some of these, kinetic data are also available at atmospheric pressure in different solvents. We felt that a comparison of both sets of these data presented the possibility of examining whether internal and external pressure effects were correlated.

Results and Discussion

Activation volumes determined by external pressure variation for decomposition of a variety of free-radical initiators are given in Table I.[4,7] In all cases, the values of ΔV^* are positive, indicating that the decomposition rate constants decreased with increasing pressure. Such results are expected, since homolytic scission is characterized by a volume expansion, and also because cage return of radicals is pressure accelerated.[1,4]

If, as suggested by others,[5,6] values of ΔV^* can also be obtained using the solvent property internal pressure, these homolytic scission rate constants should decrease with increasing internal pressure at atmospheric pressure. Available data[8] are presented in Table II and it is immediately obvious that the predicted behavior is not observed. The data show either no correlation with "internal pressure" or an increase.[9]

TABLE I
EXTERNAL PRESSURE DEPENDENCE OF INITIATOR DECOMPOSITION RATES

Initiator	Conditions	ΔV^*, cc/mol	Ref
Azocumene	Cumene, 55°	5	*a*
	Chlorobenzene, 55°	4	*a*
tert-Butyl phenylperacetate	Cumene, 80°	1	*b, c*
	Chlorobenzene, 80°	1	*b, c*
Di-*tert*-butyl hyponitrite	*n*-Octane, 55°	4	*d*
tert-Butyl peroxide	CCl_4, 120°	13	*e*
	Benzene, 120°	13	*e*
	Cyclohexene, 120°	7	*e*
	Toluene, 120°	5	*e*
Ketenimine[f]	Chlorobenzene	5	*a*
	tert-Butylbenzene	6	*a*

[a] Taken from the Ph.D. Dissertation of Michael Amrich, University of California, Riverside, Calif., Dec 1971. [b] References 4b and 4e. [c] These values of ΔV^* increase with increasing pressure to 3–4 cc/mol at 6000 atm. [d] Reference 4c. [e] Reference 7. [f] From azocyanocyclohexane; ketenimine = *N*-(1-cyanocyclohexyl)pentamethyleneketenimine; see, *e.g.*, H. P. Waits and G. S. Hammond, *J. Amer. Chem. Soc.*, 86, 1911 (1964).

In contrast to these negative correlations, we have noted that the effect of external pressure on the diffusion–combination ratios for *tert*-butoxy radicals[4c] does qualitatively parallel the variation of this ratio with solvent internal pressure[10] (Table III). The correspondence is not very good, however. Between the external pressures of 1 and 500 atm in *n*-octane at 45°, the value of $\Delta V_d^* - \Delta V_c^*$ is about 30 cc/mol, and it decreases with increasing pressure.[4c] The values of $\Delta V_d^* - \Delta V_c^*$ calculated from the solvent dependence data (Table III) are substantially larger and unrealistic.

One possible reason for the lack of correlation of these results may reside in the choice of values for "internal pressure." We have given two sets of values in Tables II and III, which have been taken from an extensive tabulation presented by Allen, Gee, and Wilson.[11] The first column gives values purported to correspond to $(\partial E/\partial V)_T$ for the various liquids. If so, these are correctly called *internal pressures.*[12] The

(1) Part VIII: R. C. Neuman, Jr., and G. D. Holmes, *J. Amer. Chem. Soc.*, **93**, 4242 (1971).

(2) Support by the National Science Foundation (GP-23968) is gratefully acknowledged.

(3) For reviews see (a) W. J. le Noble, *Progr. Phys. Org. Chem.*, **5**, 207 (1967); (b) E. Whalley, *Advan. Phys. Org. Chem.*, **2**, 93 (1964); (c) S. D. Hamann in "High Pressure Physics and Chemistry," Vol. II, R. S. Bradley, Ed., Academic Press, New York, N. Y., 1963, Chapter 8.

(4) See also (a) R. C. Neuman, Jr., and J. V. Behar, *J. Org. Chem.*, **36**, 657 (1971); (b) R. C. Neuman, Jr., and J. V. Behar, *ibid.*, **36**, 654 (1971); (c) R. C. Neuman, Jr., and R. J. Bussey, *J. Amer. Chem. Soc.*, **92**, 2440 (1970); (d) R. C. Neuman, Jr., *Intra-Sci. Chem. Rep.*, **3**, 269 (1969); (e) R. C. Neuman, Jr., and J. V. Behar, *ibid.*, **91**, 6024 (1969).

(5) For a review of some of these proposals see W. J. le Noble, *Progr. Phys. Org. Chem.*, **5**, 230 (1967).

(6) For a recent suggestion see R. J. Ouellette and S. H. Williams, *J. Amer. Chem. Soc.*, **93**, 466 (1971).

(7) C. Walling and G. Metzger, *ibid.*, **81**, 5365 (1959).

(8) (a) S. F. Nelsen and P. D. Bartlett, *ibid.*, **88**, 137 (1966); (b) R. C. Petersen, J. H. Markgraf, and S. D. Ross, *ibid.*, **83**, 3819 (1961); (c) H. Kiefer and T. G. Traylor, *Tetrahedron Lett.*, 6163 (1966); (d) E. S. Huyser and R. M. Van Scoy, *J. Org. Chem.*, **33**, 3524 (1968); (e) C. Walling and H. P. Waits, *J. Phys. Chem.*, **71**, 2361 (1967).

(9) (a) Two values of "internal pressure" are reported for most solvents. The quantity $(\partial E/\partial V)_T$ is *internal pressure* while $\Delta E_{vap}/V_T$ is *cohesive energy density.* Their relationship will be discussed later in the text. (b) Rate data in other solvents are available, but internal pressure values are lacking. (c) External pressure data are not available for diphenylazoethane, but it should have an activation volume comparable to that for azocumene.

(10) H. Kiefer and T. Traylor, *J. Amer. Chem. Soc.*, **89**, 6667 (1967).

(11) G. Allen, G. Gee, and G. J. Wilson, *Polymer*, **1**, 456 (1960).

(12) (a) W. Westwater, H. W. Frantz, and J. H. Hildebrand, *Phys. Rev.*, **31**, 135 (1928); (b) J. H. Hildebrand, *ibid.*, **34**, 649 (1929); (c) J. H. Hildebrand, *ibid.*, **34**, 984 (1929); (d) J. H. Hildebrand and J. M. Carter, *J. Amer. Chem. Soc.*, **54**, 3592 (1932); (e) see also J. H. Hildebrand and R. L. Scott, "The Solubility of Nonelectrolytes," 3rd ed, Reinhold, New York, N. Y., 1950, Chapter 5; (f) for a recent review see A. F. M. Barton, *J. Chem. Educ.*, **48**, 156 (1971).

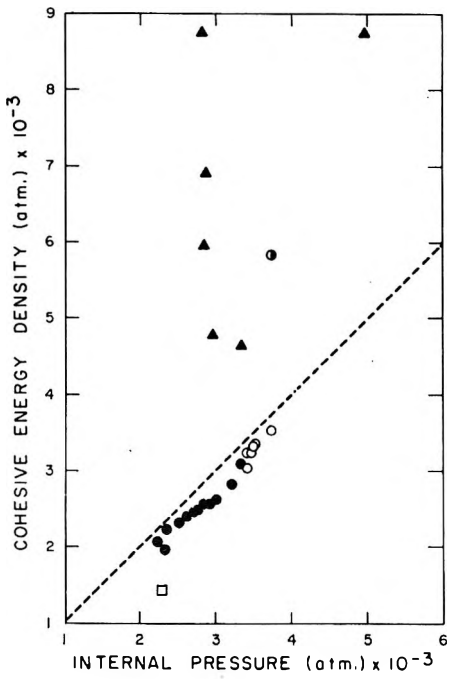

Figure 1.—Relationship between cohesive energy density ($\Delta E_{vap}/V_T$) and internal pressure $(\partial E/\partial V)_T$ for simple alkanes (●), aromatic hydrocarbons (○), alcohols (▲), acetonitrile (◑), and perfluoromethylcyclohexane (□). The dashed line has a slope of one.

second set correspond to $\Delta E_{vap}/V_T$ where ΔE_{vap} is the energy of vaporization of a mole of the liquid occupying a volume V at the temperature T; these are called *cohesive energy densities*.[12]

Internal pressures of liquids may be determined according to eq 2, by measuring $(\partial P/\partial T)_V$ at different

$$(\partial E/\partial V)_T = T(\partial P/\partial T)_V - P \qquad (2)$$

temperatures, but few such data are available. By and large, most authors attempting correlations with "internal pressure" *appear* to have utilized values of *cohesive energy densities*, perhaps assuming that these were reasonable approximations to $(\partial E/\partial V)_T$.[13] However, early work showed that these quantities differed rather substantially for certain liquids[14] and the apparent lack of correlation between them can be seen from the data plotted in Figure 1.[11]

In considering potential correlations between "internal pressure" and rate constants (Tables II and III) the temperature dependence of both $(\partial E/\partial V)_T$ and $\Delta E_{vap}/V_T$ has usually been ignored. In our comparison, the "internal pressures" correspond to 20°, while the rate constants were obtained at a variety of temperatures. It is known that $(\partial E/\partial V)_T$ is quite sensitive to temperature and this can be seen from work of Scott with CCl_4.[15] He found that $(\partial E/\partial V)_T$ decreased from 3346 atm at 25° to *ca.* 2044 atm at 70°.

In summary, there appears to be no obvious correlation at this time between the effects of externally applied pressure and internal solvent pressure on free-radical decomposition rates. However, the utility of this latter parameter may not yet have been fully realized due to the lack of proper comparisons with kinetic data.

(13) For example see (a) A. P. Stefani, *J. Amer. Chem. Soc.*, **90**, 1694 (1968); (b) J. Halpern, G. W. Brody, and C. A. Winkler, *Can. J. Res.*, **28b**, 140 (1950); (c) reference 6.

(14) See (a) ref 12e, p 97; (b) J. H. Hildebrand and R. L. Scott, "Regular Solutions," Prentice-Hall, Englewood Cliffs, N. J., 1962, pp 77–79.

(15) H. Benninga and R. L. Scott, *J. Chem. Phys.*, **23**, 1911 (1955).

TABLE II
KINETIC DATA FOR DECOMPOSITION OF INITIATORS IN VARIOUS SOLVENTS COMPARED TO THEIR INTERNAL PRESSURES

Solvent	"Internal Pressure"[a] $(\partial E/\partial V)_T$, atm	"Internal Pressure"[a] $\Delta E_{vap}/V_T$, atm	$k \times 10^5$, sec^{-1}		Ref
Azocumene Decomposition (55°)					
Dodecane	2870	2564		(14.7)[b]	*c*
CCl_4	3402	3080	8.13		*d*
Cumene	3427	3039	8.10		*d*
Toluene	3501	3328	8.90	(18.0)[b]	*c*
Chlorobenzene		3730	8.50		*d*
Diphenylazoethane Decomposition (97.30°)					
Dodecane	2870	2564	3.18		*e*
Diphenylmethane		3700	4.00		*e*
***tert*-Butyl Phenylperacetate Decomposition (79.6°)**					
Cumene	3427	3039	6.78		*f*
Chlorobenzene		3730	10.20		*f*
Di-*tert*-butyl Hyponitrite Decomposition (65°)					
Isooctane	2325	1970	40.0		*g*
n-Butyl ether	(3000)		45.0		*g*
tert-Butyl alcohol	3344	4666	46.8		*g*
***tert*-Butyl Peroxide Decomposition (120°)**					
Cyclohexane	3212	2812	0.63		*h*
tert-Butyl alcohol	3344	4666	1.41		*h*
CCl_4	3402	3080		0.90	*i*
Toluene	3501	3328		1.34	*i*
Benzene	3737	3518	1.10	1.39	*h*, *i*
Acetonitrile	3737	5822	2.21		*h*
Tetrahydrofuran		3847	0.97		*h*
Nitrobenzene		4466	1.31		*h*
Ketenimine Decomposition (100°)[j]					
n-Octane	2626	2391	1.63		*d*
tert-Butylbenzene		3000	2.38		*d*
Chlorobenzene		3730	3.85		*d*

[a] $(\partial E/\partial V)_T$ is *internal pressure* while $\Delta E_{vap}/V_T$ is *cohesive energy density*; these were taken from ref 11. [b] 60.2°. [c] Reference 8a. [d] Taken from the Ph.D. Dissertation of Michael Amrich, University of California, Riverside, Calif., Dec 1971. [e] Reference 8b. [f] References 4b and 4e. [g] Reference 8c. [h] Reference 8d. [i] Reference 8e. [j] See footnote *f* of Table I.

TABLE III
COMPARISON OF THE DIFFUSION–COMBINATION RATIOS FOR GEMINATE *tert*-BUTOXY RADICALS WITH INTERNAL PRESSURE OF SOLVENTS

Solvent	"Internal Pressure"[a] $(\partial E/\partial V)_T$, atm	"Internal Pressure"[a] $\Delta E_{vap}/V_T$, atm	k_d/k_c[b]	$\Delta\Delta V^*$,[c] cc/mol	Ref
n-Pentane	2241	2073	26.1		*d*
Isooctane	2325	1970	9.3	322	*d*
n-Hexane	2358	2221	15.1	120	*d*
n-Heptane	2527	2316	10.9	79	*d*
n-Octane	2626	2391	10.0	64	*d*, *e*
n-Nonane	2725	2457	7.7	66	*d*, *e*

[a] See footnote *a* of Table II. [b] 45°. [c] $\Delta V_d^* - \Delta V_c^*$; calculated using pentane as the reference system and $(\partial E/\partial V)_T$ values for "pressure." [d] Reference 10. [e] Reference 4c.

Registry No.—Azocumene, 33029-36-6; diphenylazoethane, 33029-37-7; *tert*-butyl phenylperacetate, 3377-89-7; di-*tert*-butyl hyponitrite, 14976-546; *tert*-butyl peroxide, 110-05-4; ketenimine, 32970-00-6; *tert*-butoxy, 3141-58-0.

Acknowledgment.—Helpful discussions with Professor Hartland Schmidt are gratefully acknowledged.

Notes

^{14}N-^{1}H Coupling in Some *N*-Alkylnitrilium Salts[1]

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While investigating[3] the reaction of *N*-alkylnitrilium salts[4] with sodium and dimethylammonium azide, proton magnetic resonance spectra of the nitrilium salts were studied. Although Goodrich and Treichel[5] reported pmr data for the *N*-methylacetonitrilium ion, no interpretation of the complex spectrum was given. Olah and Kiovsky[6] have studied a number of *N*-alkylnitrilium ions in sulfur dioxide using ^{15}N, ^{13}C, and ^{1}H nuclear magnetic resonance.

The first resolvable ^{14}N-^{1}H interaction was observed in several isonitriles.[7] Splitting in isonitriles has been attributed to an unusually small electric field gradient and spin-lattice relaxation times of ^{14}N.[7,8] The low electric field gradient is thought to result from axial symmetry of electron density near the nitrogen atom.[7] Although nitriles resemble isonitriles in being linear groups, nitriles have the lower electronic symmetry because of the nonbonding electrons on nitrogen. The observation of a singlet at δ 1.99 for CH_3CN rather than a 1:1:1 triplet is consistent with this theory. One would anticipate an approach toward electronic symmetry conditions in isonitriles when the lone-pair electrons on nitrogen are involved in bonding. Indeed, this is so in the case of some *N*-alkylnitrilium salts. In an effort to test the validity of the theory further, the pmr spectrum of $CH_3CN^+BF_3^-$ in CD_3CN was taken. The spectrum showed one singlet at δ 2.08 indicating no ^{14}N-^{1}H coupling or exchange with the solvent. The pmr spectrum of protonated acetonitrile in FSO_3H–SbF_5–SO_2 solution has been reported[6] as a sharp doublet at δ −3.25, relative to TMS, corresponding to the methyl group split by the NH proton. The NH^+ absorption is not observable at −90°. These results possibly suggest that, even though the electronic symmetry requirements may have been satisfied, improper relaxation times for ^{14}N cause decoupling through quadrupole relaxation.

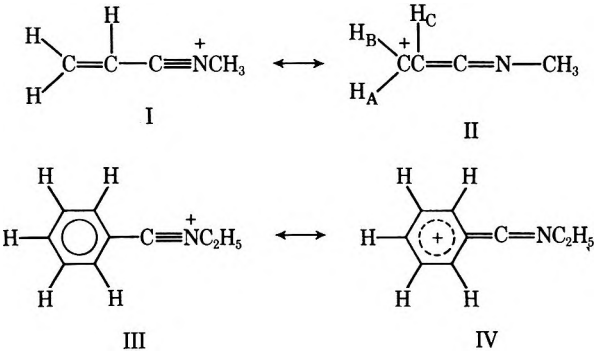
The pmr spectra of six *N*-alkylnitrilium ions in CD_3CN are summarized in Table I and representative spectra are given in Figures 1–3. The complex pmr spectra (*e.g.*, Figure 1) were due to long-range coupling of *N*- and *C*-alkyl protons through the C≡N bond in addition to coupling of the alkyl groups to the ^{14}N nucleus.[6] There was no change in the pmr spectrum of *N*-ethylacetonitrilium fluoroborate in CD_3CN at −40, 25, and 80°. Experiments were performed in which the alkyl groups were effectively decoupled from nitrogen by irradiation. Coupling between alkyl groups was minimized by substitution of ^{1}H by ^{2}H. The spectra of *N*-methyl- and *N*-ethylaceonitrilium ions after ir-

TABLE I

PMR DATA OF NITRILIUM IONS[a] IN CD_3CN

	δRC				δNR	
Compd (BF_4^-)	CH_3	CH	CH_2	C_6H_5	CH_3	CH_2
$CH_3CN^+CH_3$	2.78 m				3.71 m	
$CD_3CN^+CH_3$					3.71 t (J = 3)	
$CH_3CN^+C_2H_5$	2.78 m		4.03 m		1.46 m	
$C_2H_5CN^+C_2H_5$	1.40 m		3.10 m		1.40 m	4.01 m
H_2C=CHCN		5.77 q	6.08 m			
H_2C=$CHCN^+CH_3$		6.45 m	7.17 m		3.89 br	
C_6H_5CN				7.32 m		
$C_6H_5CN^+C_2H_5$				7.80 m	1.65 t (J = 7)	4.42 q (J = 7)

[a] Values are in ppm from TMS. J values are in Hz. Abbreviations used are br, broad; m, multiplet; t, triplet; q, quartet.



(1) Taken from the dissertation of L. A. Lee in partial fulfillment of the requirement for the Ph.D. degree, Howard University, 1970.

(2) Author to whom correspondence should be addressed at Polaroid Corp., Cambridge, Mass. 02139.

(3) L. A. Lee, R. Evans, and J. W. Wheeler, *J. Org. Chem.*, **37**, 343 (1972).

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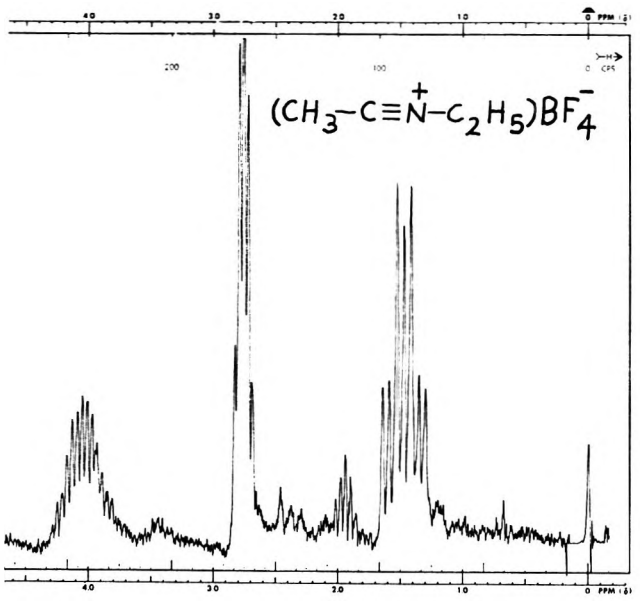

Figure 1.—Pmr spectrum of *N*-ethylacetonitrilium fluoroborate in CD_3CN.

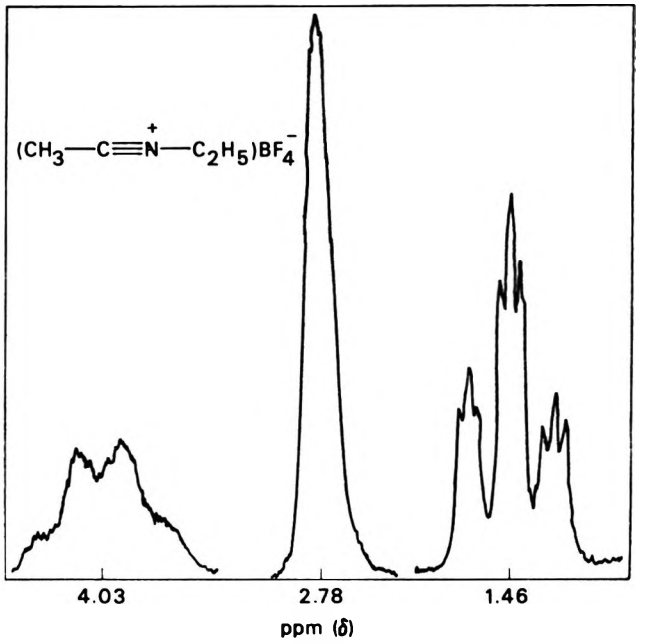

Figure 3.—Pmr spectrum of *N*-ethylacetonitrilium ion, with irradiation of ^{14}N, in CD_3CN.

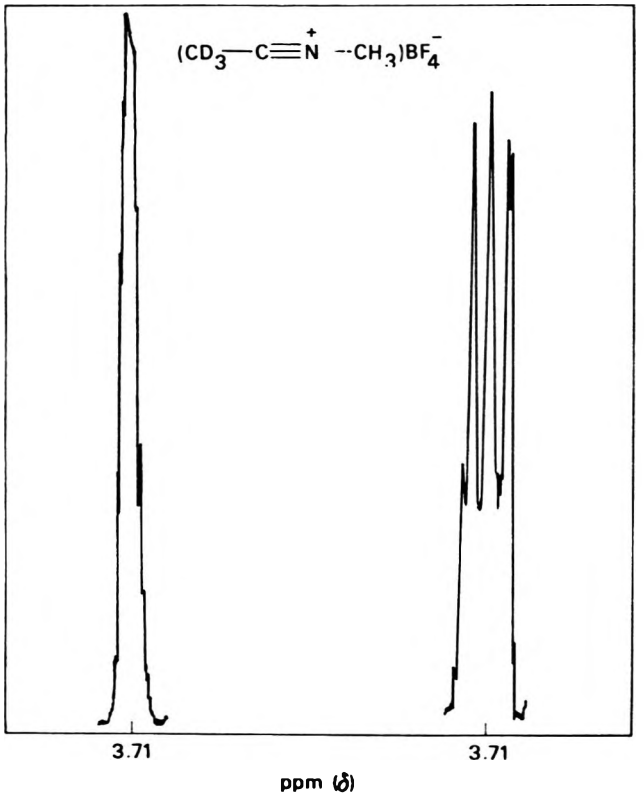

Figure 2.—Pmr spectra of *N*-methylacetonitrilium-d_3 ion, with irradiation of ^{14}N on left, in CD_3CN.

radiation and substitution of deuterium are shown in Figures 2 and 3.

The pmr spectra of *N*-ethylbenzonitrilium and *N*-methylacrylonitrilium fluoroborate show only slight long-range ^1H–^1H and/or ^1H–^{14}N coupling. These results suggest the importance of other resonance structures of the nitrilium salts such as II and IV. The pmr spectrum of *N*-methylacrylonitrilium fluoroborate shows that the H_A and H_B protons are deshielded more than the H_C proton by 1.09 ppm relative to H_A and H_B protons in acrylonitrile. The phenyl protons in *N*-ethylbenzonitrilium fluoroborate are deshielded by 0.48 ppm relative to the phenyl protons in benzonitrile.

Similar results have been reported[6] for *N*-methylbenzonitrilium fluoroborate and protonated acrylonitrile in SO_2 and FSO_3H–SbF_5–SO_2, respectively.

Experimental Section

N-**Alkylnitrilium Fluoroborates.**—All nitrilium salts used in this study were prepared according to the procedure of Meerwein and coworkers.[4]

Boron Trifluoride–Acetonitrile Complex.—The addition compound was prepared by the method of Coerver and Curran[9] which requires passing BF_3 into an ice-cooled flask containing acetonitrile until the whole mass solidifies, mp 119–120°.

Pmr Spectra.—Proton magnetic resonance spectra of freshly prepared solutions of nitrilium salts in CD_3CN were taken on a Varian Associates A-60 or HR-60 spectrometer. Positions are reported in parts per million from tetramethylsilane (δ). Nitrogen decoupling experiments were performed with the aid of an nmr Specialties Model SD-60B heteronuclear spin–spin decoupler.

Registry No.—$CH_3CN^+CH_3BF_4^-$, 21353-63-9; $CD_3CN^+CH_3BF_4^-$, 32830-03-8; $CH_3CN^+C_2H_5BF_4^-$, 462-35-1; $C_2H_5CN^+C_2H_5BF_4^-$, 333-94-8; $H_2C{=}CHCN$, 107-13-1; $H_2C{=}CHCN^+CH_3BF_4^-$, 32830-06-1; C_6H_5CN, 100-47-0; $C_6H_5CN^+C_2H_5BF_4^-$, 459-39-2.

Acknowledgment.—We wish to thank Dr. E. D. Becker, Jr., and Mr. Robert Bradley of the National Institutes of Health for the ^{14}N–H decoupling measurements, Professor Elton Price for helpful discussions, and Mr. R. D. Barefoot, Naval Ordnance Station, Indian Head, Md., for some of the pmr measurements. This work was supported by the Foundational Research Program of the Naval Air Systems Command.

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Barriers to Rotation about the Nitrogen–Oxygen Single Bond in Substituted Hydroxylamines[1]

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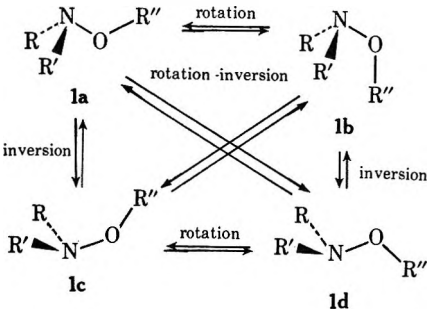
Substituted hydroxylamines have occupied a central position in Dnmr studies of barriers to nitrogen inversion and barriers to rotation about nitrogen–heteroatom bonds.[2] One of the earliest reports of slow nitrogen inversion described chemical shift nonequivalence in a cyclic hydroxylamine, an oxaziridine.[3a] The oxaziridine system also furnished the first example of an optically active compound whose optical stability was due to slow inversion of a nitrogen pyramid.[3b] Recently, substantial barriers to nitrogen inversion have been observed in other cyclic hydroxylamines, where the nitrogen and oxygen atoms form part of a four[4]- or five[5]-membered ring. Chemical shift nonequivalence and barriers to conformational interchange have also been studied in tetrahydrooxazines,[5a,b] although, as Lambert has pointed out, it is difficult to distinguish nitrogen inversion from ring reversal in six-membered ring systems.[2d]

Chemical shift nonequivalence and coalescence of signals from diastereotopic nuclei have also been observed in acyclic trialkyl hydroxylamines and, in fact, these initial reports attributed these phenomena to slow nitrogen inversion.[6,7] Subsequently, it was pointed out that the observed phenomena might have originated from slow rotation about the N–O single bond instead of slow nitrogen inversion.[8,9] If the ground state conformation of hydroxylamines and their derivatives is represented by **1a** or **1b** (Scheme I) coalescence of diastereotopic benzyl methylene protons or isopropyl methyl groups must be associated with a degenerate racemization: **1a** ⇄ **1d**, or **1b** ⇄ **1c**. As illustrated in Scheme I, both rotation and inversion are required for topomerization, and the question at issue is the specification of the rate-determining step as either inversion or rotation.[10] A third possibility

SCHEME I

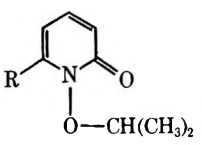


which may be considered is that torsion and inversion occur synchronously rather than sequentially and that the transition state for the topomerization involves both flattening of the nitrogen pyramid and torsion about the N–O bond.

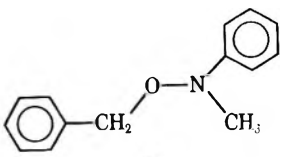
This paper describes conformational interchanges associated with N–O torsional barriers in compounds in which nitrogen must be planar, or inverting rapidly, and, consequently, for which slow nitrogen inversion may be excluded as a possible rate determining step in the topomerization.

Results

Conjugation of the nitrogen lone pair with a carbonyl group or a phenyl ring is known to lower nitrogen inversion barriers very considerably. The replacement of an *N*-alkyl group in aziridines by phenyl lowers the nitrogen inversion barrier by 8 kcal/mol,[11] while the barrier in *N*-acylaziridines is apparently too small to be measured (less than 5 kcal/mol). Substituted hydroxylamines **2a**, **2b**, and **3** containing both structural features were examined. All three compounds showed line broadening as torsion about



2a, R = H
b, R = Cl



3

the N–O bond became slow on the nmr time scale. Alkoxypyridone **2b** exhibited line broadening at a much higher temperature than did **2a**. The transition state for topomerization in **2b** probably involves steric crowding of the isopropyl group with either the oxygen or chlorine atom. The rate constant for torsion at the coalescence temperature was obtained by complete line shape analysis and afforded the free energy of activation ($\Delta\nu$ = 23 Hz, T_c = −73.5°, $\Delta G^{\ddagger}$ = 10.0 kcal/mol). Although we were unable to measure the low temperature limit spectra for **2a** and **3**, we were able to obtain ranges for their free energies of activation using complete line shape analysis. The spectra were measured at temperatures at which line broaden-

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(2) Several excellent reviews in this area have appeared recently: (a) J.-M. Lehn, *Fortschr. Chem. Forsch.*, **15**, 311 (1970); (b) A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, **9**, 400 (1970); (c) H. Kessler, *ibid.*, **9** 219 (1970). (d) J. Lambert in "Topics in Stereochemistry," Vol. VI, E. L. Eliel and N. L. Allinger, Ed., Wiley, New York, N. Y., 1971; (e) S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc. B*, 136 (1971).

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(9) M. Raban and G. W. J. Kenney, Jr., *Tetrahedron Lett.*, 1295 (1969).

(10) Although the interconversion **1a** ⇄ **1b**, or **1c** ⇄ **1d** could be effected by "planar inversion" at divalent oxygen, this process very probably requires a great deal more energy and need not be considered in systems where torsion is a possible alternative: A. J. Gordon and J. P. Gallagher, *Tetrahedron Lett.*, 2541 (1970).

(11) F. A. L. Anet and J. M. Osyany, *J. Amer. Chem. Soc.*, **89**, 352 (1967).

ing was substantial and were matched with theoretical spectra. A range of values was used for the chemical shift difference, $\Delta\nu$, and each value of $\Delta\nu$ afforded a different value for the first-order rate constant and subsequently for the free energy of activation. Thus we obtained in each case a range for k and for $\Delta G^{\ddagger}$, corresponding to a range for $\Delta\nu$: **2a**, $\Delta\nu$ = 15–50 Hz, k = 45–340 sec^{-1}, T = −86°, $\Delta G^{\ddagger}$ = 8.6–9.4 kcal/mol; **3**,[12] $\Delta\nu$ = 25–50 Hz, k = 90–320 sec^{-1}, T = −93°, $\Delta G^{\ddagger}$ = 8.3–8.7 kcal/mol. A "best estimate" for the rate constant and free energy of activation for **2a** was obtained by assuming a comparable value of $\Delta\nu$ to that measured for **2b**. The values (**2a**, k = 51 sec^{-1}, $\Delta G^{\ddagger}$ = 9.3 kcal/mol) fall in the ranges quoted above. Although the free energies could not be measured precisely, the ranges obtained are fairly narrow and are sufficient for further discussion.

Discussion

Slow rotation about bonds between heteroatoms bearing nonbonding valence electrons is a fairly well documented phenomenon, and torsional barriers have been measured by Dnmr spectroscopy[2c] for P–N,[13] S–N,[14] N–N,[15] and S–S[16] bonds. Our results confirm that substantial barriers to rotation about N–O single bonds do exist as well and that we may suppose that comparable barriers exist in other compounds containing N–O single bonds. In this respect they support, in a qualitative sense at least, the *ab initio* calculations on hydroxylamine by Pedersen and Morokuma which indicated a torsional barrier of 9.9 kcal/mol.[17]

There has been considerable disagreement concerning the rate-determining step in the topomerization of acyclic trialkylhydroxylamines. Some workers have argued that the rate-determining step is slow nitrogen inversion.[18,19] Others have suggested that slow rotation about the N–O single bond can account as well or better for the experimental observations of chemical shift nonequivalence and coalescence of signals from diastereotopic groups.[8,9,20] One approach to this problem has been to examine compounds in which either of these processes can be excluded.

In cyclic trialkylhydroxylamines the torsional process can be excluded when both heteroatoms are part of a three-, four-, and five-membered ring. Experiments in this area have indicated that nitrogen inversion is indeed slowed by the presence of the oxygen atom. In evaluating experiments on cyclic compounds as predictors for similar trends in acyclic compounds it is of crucial importance to determine whether retardation of the inversion rate derives from the electronegativity of the oxygen atom or the presence of nonbonding valence electrons. If electronegativity alone is important, we would expect comparable rate retardation in cyclic and acyclic compounds, since the inductive potency of oxygen should be only a weak function of torsion angle. If, on the other hand, interactions between vicinal electron pairs are dominant, we may expect to find that the magnitude of the rate retardation is a strong function of dihedral angle. Unlike the cyclic examples, the acyclic molecules are free to adopt a geometry of minimum interaction. Our results for **2** and **3** indicate that the ground state for these hydroxylamines, like their sulfur analogs, the sulfenamides, must be chiral. Given the planarity of the pyridone ring in **2**, we may conclude that the NOC plane approximately bisects the bond angle formed by the other two ligands at nitrogen.[5c] The geometry in the cyclic compounds approximates that in the transition state for torsion about the N–O bond. If repulsive interactions do indeed contribute substantially to torsional barriers, as has been suggested, it is necessary that the magnitude of the interaction be greater in a geometry approximating that in the transition state for torsion than it is when the molecule is free to achieve a geometry of minimum interaction.

The strongest evidence that electronegativity is important has been the finding, in both experimental investigations and studies using molecular orbital calculations, that the electropositive elements silicon, germanium, and tin lower barriers to pyramidal inversion.[2,21] On the other hand, experimental investigations have indicated that the barriers to nitrogen inversion in acyclic hydrazines are substantially lower than in cyclic analogs. This apparent dependence of the barrier increase due to heteroatom substitution at nitrogen does not seem to be consistent with the sole importance of electronegativity. It is more difficult to make such a comparison in the hydroxylamine series. However, the barriers to nitrogen inversion in acyclic trialkylhydroxylamines can be no higher than 12–13 kcal/mol, *i.e.*, lower than those in cyclic analogs. If we take *N*-benzyl-*N*,*O*-dimethylhydroxylamine and *N*-methylisoxazolidine as comparable acyclic and cyclic compounds the difference amounts to 3.3 kcal/mol.[5a,7] This comparison suggests a significant dihedral angle requirement and a contribution to the inversion rate diminution from the interaction between electron pairs on neighboring heteroatoms. When all of the evidence is taken together it seems most likely that both electronegativity and lone pair interactions contribute to increases in inversion barriers, although it does not seem possible, at this time, to make a definitive conclusion about the relative importance of these two factors.

The present study, as well as a previous investigation of *N*,*O*-diacylhydroxylamines,[18] deal with compounds in which conjugation lowers nitrogen inversion barriers enough that the barriers observed must be torsional. Further the *N*-alkoxy pyridone system is one in which there can be no confusion between tor-

(12) A value of 12–14 Hz was assumed for the geminal coupling constant between the benzylic protons.

(13) (a) A. H. Cowley, M. J. S. Dewar, W. R. Jackson, and W. B. Jennings, *J. Amer. Chem. Soc.*, **92**, 1085 (1970); **92**, 5206 (1970); (b) H. Goldwhite and D. G. Rowsell, *Chem. Commun.*, 713 (1969).

(14) (a) M. Raban and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **93**, 2692 (1971); (b) part XIII;[18a] (c) J.-M. Lehn and J. Wagner, *Chem. Commun.*, 1298 (1968); (d) M. Raban, G. W. J. Kenney, Jr., and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **91**, 6677 (1969).

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(18) J. R. Fletcher and I. O. Sutherland, *Chem. Commun.*, 687 (1970).

(19) D. L. Griffith, B. L. Olson, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 1648 (1971).

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(21) R. D. Baechler and K. Mislow, *J. Amer. Chem. Soc.*, **93**, 773 (1971); A. Rauk, J. D. Andose, W. G. Frick, R. Tang, and K. Mislow, *ibid.*, **93**, 6507 (1971).

sion about an amide linkage and torsion about the N–O bond.

On the one hand, the observation of barriers to rotation in **2** and **3** makes the suggestion that torsional barriers may account for the observed nonequivalence in other hydroxylamine derivatives seem reasonable. On the other hand, it may be argued[18] that the magnitude of the barriers observed for **2** and **3** suggests that the somewhat higher barriers observed for trialkylhydroxylamines derive from another hindered conformational interchange, namely nitrogen inversion. However, we note that torsional barriers as well as inversion barriers seem to be subject to substituent effects. In particular the torsional barriers in *N*,*N*-(dialkyl)trichloromethanesulfenamides are lowered by about 3 kcal/mol when the two alkyl groups are replaced by the diacyl succinimide ring.[14d] If the replacement of the *N*-alkyl groups by the pyridone ring were to result in a comparable lowering of the N–O torsional barrier we would expect the torsional barriers in trialkylhydroxylamines to be about 11–12 kcal/mol, which is very close to the barriers observed. Because of these, as yet poorly understood, substituent effects on torsional barriers we do not believe that comparisons of this sort offer convincing evidence concerning the nature of the rate-determining step in topomerization of trialkylhydroxylamines in the absence of confirming evidence.

We do not believe that it is possible, at this time, to definitively assign the barriers to topomerization in trialkylhydroxylamines to either slow inversion or slow rotation. The evidence accumulated thus far seems to indicate that both inversion and rotation barriers are substantial in compounds containing N–O single bonds. Given the probability that substituents and solvents can affect the shape of the conformational energy surface it seems possible that subtle changes in structure and medium should be capable of shifting from a torsional transition state for topomerization to an inversional one or vice versa.

Experimental Section

Elemental analyses were performed by Midwest Microlab, Inc. Nmr spectra were measured on a Varian A-60A spectrometer, in toluene-d_8 solution. Temperatures were calibrated using methanol spectra as described in the Varian manual. Melting points were measured on a Thomas–Hoover melting point apparatus. *N*-Benzyloxy-*N*-methylaniline (**3**) was prepared as described in the literature.[22] Both *N*-isopropoxy-2(1*H*)-pyridones were prepared in a manner similar to that described by Paquette.[23]

***N*-Isopropoxy-2(1*H*)-pyridone (2a).**—Pyridone **2a** was synthesized from 2-ethoxypyridine *N*-oxide[24] by treatment of the latter with excess 2-bromopropane and heating under reflux for 4 days. The mixture was distilled under reduced pressure and a fraction boiling at 69–72° (0.2 mm) was collected (80%). This material was shown by its nmr spectrum to be a 5:2 mixture of **2a** and *N*-ethoxy-2(1*H*)-pyridone which resulted from rearrangement of the starting material. Chromatography of 0.30 g of distillate on 25 g of silica gel (3:1 hexane–acetone eluent) afforded 0.20 g of pure **2a**.

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.28; H, 7.52; N, 8.98.

2-Chloro-6-ethoxypyridine *N*-Oxide (4).—2-Chloro-6-ethoxypyridine *N*-oxide (**4**) was synthesized from commercial 2-chloro-6-ethoxypyridine by hydrogen peroxide–trifluoroacetic acid oxidation, using a procedure described for the oxidation of substituted pyridines.[25] The crude oxide was purified by chromatography on alumina (chloroform eluent), and then crystallized from a benzene–hexane mixture, mp 93.5–95°.

Anal. Calcd for $C_7H_8ClNO_2$: C, 48.43; H, 4.65; Cl, 20.42; N, 8.07. Found: C, 48.21; H, 4.72; Cl, 20.26; N, 8.03.

***N*-Isopropoxy-6-chloro-2(1*H*)-pyridone (2b).**—Oxide **4**, (0.5 g) was dissolved in 10 ml of 2-bromopropane, and the mixture was refluxed for 24 hr. The excess alkyl bromide was removed under vacuum, and chromatography of the remaining dark oil on 25 g of silica gel (3:1 hexane–acetone eluent) afforded 0.10 g of **2b**.

Anal. Calcd for $C_8H_{10}ClNO_2$: C, 51.21; H, 5.37; N, 7.47. Found: C, 51.45; H, 5.60; N, 7.49.

Registry No.—**2a**, 32846-47-2; **2b**, 32846-48-3; **4**, 32846-49-4.

Acknowledgment.—We are grateful to Dr. Dorothy Hwang for preparing the *N*-benzyloxy-*N*-methylaniline used in this study. We thank Professors K. Mislow and W. Walter for communicating pertinent results to us prior to publication.

(22) U. Schollkopf, W. Ludwig, M. Patsch, and W. Franken, *Justus Liebigs Ann. Chem.*, **703**, 77 (1967).

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A Comparison of the Electronic Effects of Substituents Bonded to Annular Nitrogen and Carbon Atoms

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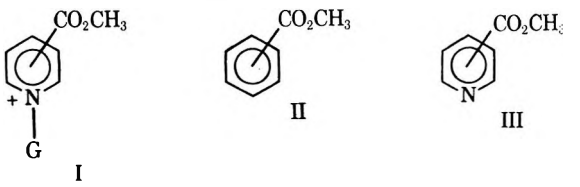
Received June 24, 1971

Much is known about the electronic effects exerted by meta and para substituents bonded to carbon.[2] By comparison, very little is known about the electronic effects exerted by the same groups bonded to an annular nitrogen atom.[3]

We have determined the rates of hydroxide ion catalyzed hydrolysis of esters I where the N substituents, CH_3O, CH_3, and O^-, are meta and para to the reactive center.[4] Comparison of our results with those for esters II[5] provides an insight into the ability of a positively charged annular nitrogen atom to transmit resonance and inductive effects.



I II III

Kinetic studies were carried out using a pH-Stat. In the case of the para *N*-methyl ester, the hydroxide ion concentration was varied by a factor of 8 and the second-order rate constant, k_2, was found to be given

(1) On leave from LaTrobe University, Melbourne, Australia.

(2) C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

(3) H. H. Jaffé and H. L. Jones, *Advan. Heterocycl. Chem.*, **3**, 209 (1964).

(4) Results for hydrolysis in 70% ethanol–water of I (G = O^-) and III have been reported by P. R. Falkner and D. Harrison: *J. Chem. Soc.*, 1171 (1960). Hydrolysis is considerably faster in water.

(5) Results for oxide ion esters II can be predicted using substituent constants reported by J. Hine, *J. Amer. Chem. Soc.*, **82**, 4877 (1960).

TABLE I

CONDITIONS AND RESULTS OF THE HYDROXIDE ION CATALYZED HYDROLYSIS OF META AND PARA N-SUBSTITUTED ESTERS IN WATER AT 25.0° AND 0.5 *M* IONIC STRENGTH[a]

G	Registry no.	pH	k_2, M^{-1} min^{-1}	k_{rel}	k_p/k_m
p-O$^-$	3783-38-8	9.7–10.1	5.8×10^2	1.0	0.67
m-O$^-$	15905-18-7	9.7–10.0	8.6×10^2	1.5	
p-CH_3	7630-02-6	7.5–8.4	3.2×10^4	55.0	9.1
m-CH_3	4685-10-3	9.1–9.3	3.5×10^3	6.0	
p-CH_3O	32812-78-5	8.0–8.4	4.2×10^4	72.0	4.5
m-CH_3O	32785-04-9	8.7–9.0	9.4×10^3	16.0	
b	2459-09-8	10.4–10.5	2.2×10^2	0.38	4.5
c	93-60-7	10.9–11.0	4.9×10^1	0.084	

[a] pOH = 14.30 − pH. [b] Methyl 4-pyridinecarboxylate. [c] Methyl 3-pyridinecarboxylate.

by $k/[OH^-]$, where k is the observed pseudo-first-order constant. This means that the hydrolysis of the ester is catalyzed only by hydroxide ion under the conditions employed.[6] The k_2 values given in Table I represent the average of two experiments at the indicated pH; the average deviation is <10%. Nmr experiments employing a phosphate buffer solution of the para *N*-methoxy ester showed that only ester hydrolysis takes place; no side products were detected.[7]

In order to obtain a measure of the activating effect of the positive charge in I, the hydrolysis of meta and para methyl pyridinecarboxylates (III) also was studied (Table I).[4] Comparison with the results for the *N*-methyl esters indicates that the positive charge increases reactivity by a factor of about 100. The para ester is more reactive than the meta ester in both types of compounds, suggesting activation of the para positions by a resonance effect.

The results for I indicate that there is a 72-fold spread in reactivity with the para *N*-oxide ester being the least and the para *N*-methoxy compound being the most reactive. The nature of the electronic effects of the N substituents is revealed by a comparison of the positional rate constants. It is assumed that the electronic effects of the substituents are superimposed on the effects of the annular nitrogen atom and the positive charge. Relative to the *N*-methyl compound, the methoxy group activates while the oxide substituent deactivates meta positions in both I and II, indicating the presence of inductive effects. A methoxy group is activating relative to a methyl group in para positions of I but the opposite order is found in II. This result clearly indicates that the resonance effect of the methoxy group is less important in the heterocyclic series. A similar conclusion has been advanced concerning the importance of resonance effects in *N*-alkoxypyridinium ions on the basis of ground state infrared studies.[8] That resonance effects do operate in I is seen by the para/meta ratio which decreases in the order CH_3, CH_3O, and O^-. A reduced resonance effect for an uncharged group on a positively charged annular nitrogen atom is readily understandable. Electron delocalization by such a process places a positive charge on the group and this is inhibited electrostatically by the adjacent positive charge on the nitrogen atom.

It is clear that the electronic effects of substituents on a positively charged annular nitrogen atom can be quite different from those on an annular carbon atom.

(6) M. L. Bender, *Chem. Rev.*, **60**, 53 (1960).
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Experimental Section

Compounds.—*N*-methyl esters were prepared from the esters and methyl iodide in methanol and were recrystallized from ethanol: 1-methyl-3-carboxymethylpyridinium iodide, mp 130° (lit.[9] mp 129.5–130.2°); 1-methyl-4-carboxymethylpyridinium iodide, mp 180–181° (lit.[10] mp 179°). *N*-oxide esters were prepared by N oxidation of the esters using H_2O_2–CH_3CO_2H: 3-carboxymethylpyridine 1-oxide, mp 101–102° (lit.[10] mp 101–102°); 4-carboxymethylpyridine 1-oxide, mp 115–117° (lit.[10] mp 118–119°). *N*-methoxy esters were prepared from the *N*-oxide esters using dimethyl sulfate by minor variations of a method used to prepare similar compounds.[7] These compounds were isolated as perchlorate salts. Ether aided precipitation of the perchlorate salts, though initial precipitation was induced only at −70° in the case of 1-methoxy-4-carboxymethylpyridinium perchlorate, mp 71–72° (ethanol). *Anal.* Calcd for $C_8H_{10}ClNO_7$: C, 35.9; H, 3.7; O, 41.9. Found: C, 35.8; H, 3.8; O, 41.6. 1-Methoxy-3-carboxymethylpyridinium perchlorate had mp 88–89° (ethanol). *Anal.* Found: C, 36.1; H, 3.8; O, 41.7.

Rates of Ester Hydrolysis.—Reactions were followed using a Radiometer TTT-1c titrator operating in the pH-Stat mode. Reaction mixtures consisted of ester and 0.5 *M* KCl. Complete reaction represented the addition of ~0.45 ml of 0.1 *M* KOH to 25 ml (initial) of the reaction mixture. Constant temperature (25.0°) was maintained by circulation of water about the titration cell. Pseudo-first-order rate plots were obtained by the Guggenheim method;[11] they were linear over 2–3 half-lives.

Acknowledgment.—This work was supported in part by the National Science Foundation (GP 25500).

(9) H. L. Bradlow and C. A. VanderWerf, *J. Org. Chem.*, **16**, 1143 (1951).
(10) "Dictionary of Organic Compounds," 4th ed, Oxford University Press, New York, N. Y., 1965.
(11) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961.

Organic Mass Spectrometry. I. Retro-1,3-dipolar Cycloaddition Reaction Induced by Electron Impact

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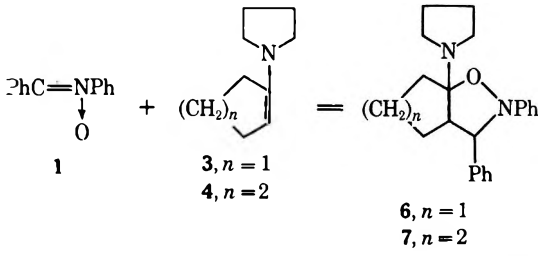
The mechanistic interrelation between the two important electrocyclic reactions, Diels–Alder and the 1,3-dipolar cycloaddition, is of current interest.[1] Although it is well established that both reactions are

(1) A. Firestone, *J. Org. Chem.*, **33**, 2285 (1968); R. Huisgen, *ibid.*, **33**, 2291 (1968).

thermally and photochemically reversible[2] and that the Diels–Alder reaction can also be reversed by electron impact,[3] little has been reported on the possible retro-1,3-dipolar cycloaddition induced by electron impact. Here we report an example of such a reaction.

We determined the mass spectra of the isoxazolidines **6** and **7**,[4] the dipolar cycloadducts between α,*N*-diphenylnitrone (**1**) and 1-pyrrolidino-1-cyclopenene (**3**) or 1-pyrrolidino-1-cyclohexene (**4**).



1 **3**, $n = 1$; **4**, $n = 2$ **6**, $n = 1$; **7**, $n = 2$

If the thermal retro-1,3-dipolar cycloaddition takes place prior to ionization, the mass spectra of **6** and **7** should be superimposable on those of **1**[5] and **3** or **4**.[6] Indeed the mass spectrum of the 1:1 mixture of **1** and **3**, determined under the same operating condition, was explainable in terms of the additivity principle.

The peaks in the spectra of **6** and **7** were summarized in Table I. The pattern is substantially different from that of the mixture. Thus, there are strong peaks at *m/e* 334 or 348 (M^+) and at *m/e* 227 or 241 (M^+ − PhNO). The base peak is the respective enamine molecular ion (*m/e* 137 or 151) while the nitrone molecular ion peak is rather weak. Moreover, the ratio of the relative abundance of *m/e* 197 and of *m/e* 91 is 0.05 and 0.07 for **6** and **7**, respectively, while the same ratio was 0.38 for **1** itself.[5] This strongly indicates that the thermal retrocycloaddition prior to electron impact is highly unlikely.

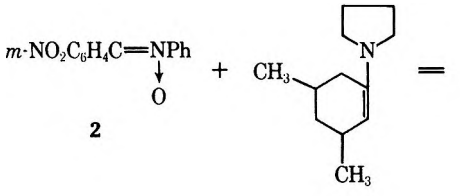
TABLE I
MASS SPECTRA OF NITRONE–ENAMINE CYCLOADDUCTS (IONIZATION VOLTAGE 70 eV)

Compd, ion	*m/e*[a] 6	7	8
M^+	334 (6)	348 (8)	411 (10)
$M^+ - C_4H_8N$	264 (1)	278 (1)	351 (1)
M^+ − nitroso-benzene	227 (9)	241 (3)	314 (3)
Nitrone$^+$	197 (2)	197 (2)	242 (4)
Schiff base$^+$	181 (6)	181 (5)	226 (7)
Enamine$^+$	137 (100)	151 (100)	179 (100)[b]
Enamine$^+$ − H	136 (53)	150 (39)	178 (49)
$C_6H_5N^+$	91 (39)	91 (28)	91 (31)
$C_6H_5^+$	77 (35)	77 (23)	77 (30)
Metastable	56.2	63.5	76.1

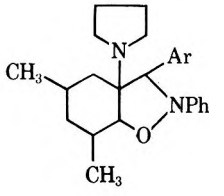
[a] Values in parentheses are intensities relative to enamine$^+$. [b] The base peak is enamine$^+$ − Me (113).

An alternative explanation which can account for all these observations is that (at least most of) the cycloadducts cleave upon electron impact into enamine molecular ion and nitrone molecule. That this type of fragmentation does in fact occur is supported by the position of the metastable peaks, *i.e.*, *m/e* 56.2 (= $137^2/334$) and 63.5 (= $151^2/348$), respectively.

We have shown that a sterically crowded enamine **5**, derived from *cis*-3,5-dimethylcyclohexanone, and **1** or α-*m*-nitrophenyl-*N*-phenylnitrone (**2**) gave the "reverse oriented" cycloadduct **8**.[7] It was expected



2 **5**



8

that **8** should show much the same fragmentation pattern upon electron impact if the retrodipolar cycloaddition mechanism is applicable to this compound since the difference in the structure between **6** or **7** and **8** is merely the location of pyrrolidine ring which should have little effect if any on the cleavage pattern of this type.

The peaks observed for **8** are also included in Table I. The base peak is not the enamine molecular ion, but (enamine$^+$ − Me) peak although the former is next to the strongest. Otherwise the fragmentation pattern is consistent with the retrocycloaddition mechanism. The nitrone peak is again weak and the metastable peak was observed at the expected position, *i.e.*, at *m/e* 76.1 (= $179^2/421$). The *m/e* 91 peak is as strong as the *m/e* 77 peak, as was observed for **6** and **7**. Thus the former peak in **6** and **7** is now assignable to $C_6H_5N^+$ rather than $C_7H_7^+$.

We suspected that this type of cleavage might be common to all 1,3-dipolar cycloadducts. It was reported, for instance, that 3,5-diphenyl-1,2,4-oxadiazole (**9**), formally a cycloadduct between benzonitrile oxide and benzonitrile, gave peaks at *m/e* (rel intensity) 222 (48), 119 (100), and 103 (61).[8] Thus, contrary to our results, the 1,3 dipole, not the dipolarophile, gave the base peak. The original author[8] claimed that the electron impact causes the migration of phenyl group from C(5) to N(4), followed by the cleavage at O(1)–N(2) and C(3)–N(4) bonds to give

(2) H. Kwart and K. King, *Chem. Rev.*, **68**, 415 (1968); R. Huisgen, H. Hauck, R. Grashey, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968); *ibid.*, **102**, 736 (1969).

(3) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 103; H. Nozaki, H. Kato, and R. Noyori, *Tetrahedron*, **25**, 166 (1969).

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(5) T. H. Kinstle and J. G. Stam, *Chem. Commun.*, 185 (1968); B. S. Larson, G. Schroll, S.-O. Lawesson, J. H. Bowie, and R. G. Cooks, *Tetrahedron*, **24**, 5193 (1968).

(6) H. J. Jakobsen, S.-O. Lawesson, J. T. B. Marshall, G. Schroll, and D. H. Williams, *J. Chem. Soc. B*, 940 (1966).

(7) Y. Nomura, F. Furusaki, and Y. Takeuchi, *Bull. Chem. Soc. Jap.*, **43**, 1913 (1970).

(8) J. L. Cotter, *J. Chem. Soc.*, 5491 (1964).

$PhNCO^+$ and PhCN. We are continuing efforts to delineate the scope of retro-1,3-dipolar cycloaddition reaction induced by electron impact.

Experimental Section

The preparation of the cycloadducts 6, 7,[4] and 8[7] was previously described. The mass spectra were determined with Hitachi RMU-6D mass spectrometer at the ionization voltage 70-eV. The temperature of the sample heater and the ionization chamber was 100 and 250°, respectively.

Registry No.—1, 1137-96-8; 3, 7148-07-4; 4, 1125-99-1; 6, 29068-11-9; 7, 16361-46-9; 8, 29348-00-3.

Conjugative and Steric Factors Affecting the Conformational Preference of Some Aromatic Sulfides

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We have had for some time evidence that the conformational preference of diphenyl sulfides and analogs could be detected by nmr, based on the fact that the diamagnetic shielding[1] of one ring on the ortho positions of the adjacent nucleus is a function of the molecular conformation.

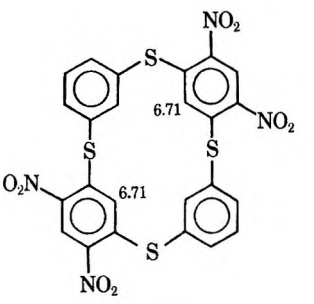
As is already well known,[2] an interesting property of the aromatic sulfides arises from the fact that unshared electrons of the bridged heteroatom may develop a resonance interaction with the π electrons of the aromatic ring.[2]

The intensity of this resonance effect and the extent to which it would affect the conformational preference of these molecules seemed to us an interesting subject of investigation. This paper is concerned with the results obtained in the case of some open-chain and cyclic aromatic sulfides bearing electron-attracting groups (nitro) eventually capable of inducing conformational preferences in these molecules.

Results and Discussion

The nmr spectra of the two novel cyclic sulfides I and II show that the protons evaluated resonate at somewhat higher field with respect to the corresponding proton in compound III (chemical shift values in parts per million). This suggests that, due to the specific conformation assumed by the cyclic structures, the protons concerned experience the diamagnetic shielding of the adjacent aromatic rings.

Furthermore, comparatively higher shieldings are found for pertinent protons in the open-chain aromatic sulfides IV–VII for which, contrary to the case of cyclic



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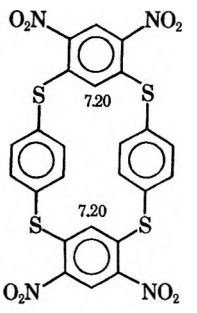

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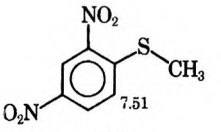
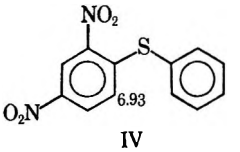


III

molecules I and II, there are no steric restraints posed on the possible molecular conformations (see below).



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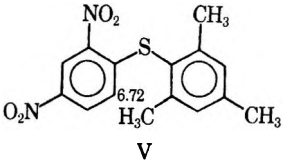
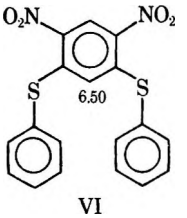
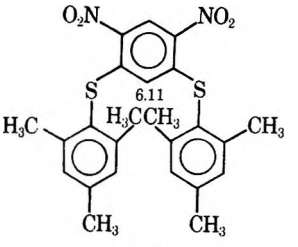


V

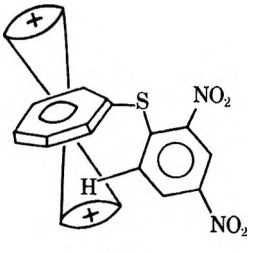


VI



VII

A satisfactory rationalization of these data is obtained considering that, due to the proximity of the aromatic rings in these molecules, the shielding of the ring current[1] of the adjacent nucleus on the ortho positions of the other ring is a function of the molecular conformation. In aromatic sulfides the possibility arises for the unshared electrons of the bridged heteroatom to develop a resonance interaction with the π electrons of the aromatic ring.[2] Here in particular, because of the concerted effect of the two strong electron-attracting groups, a partial bonding arises between π electrons localized on the bridgehead carbon atoms and the unshared electron pairs of the sulfur atom. The percentage of double bond character induced in the C_{Ar}–S bond is here high enough to cause the aromatic ring bearing the two nitro groups to lie in the C_{Ar}–S–C_{Ar} plane. Steric repulsion forces the adjacent ring out of this plane, so that the molecule assumes conformation VIII, where the ortho aromatic hydrogen lies below the



VIII

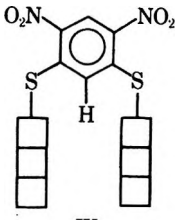
(1) C. E. Johnson and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
(2) C. C. Price and S. Oae in "Sulphur Bonding," Ronald Press, New York, N. Y., 1962, and references cited therein.

adjacent ring and experiences its diamagnetic shielding.[3]

The experimental nmr shieldings have been computed as the differences between the chemical shifts of each compound and that of compound III.

A theoretical shielding of about 1.0 ppm is calculated[1] for the aromatic proton lying below the adjacent ring (form VIII) in diphenyl sulfide. The agreement is better for compound V (Δ = 0.79 ppm) than IV (Δ = 0.58 ppm) indicating that, if the adjacent ring carries ortho substituents, form VIII receives further stabilization.

In compounds VI and VII the protons under consideration lie between two adjacent phenyl rings, and, if a conformation of type IX is present, the shielding experienced should be nearly doubled with respect to compounds IV and V.

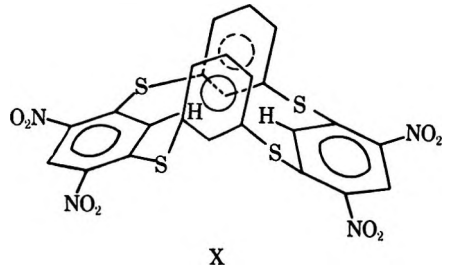


IX

The actual shieldings (Δ = 1.01 and 1.40 ppm, respectively) confirm that conformation IX is preferred in these cases, the preference being stronger for compound VII.

The lower shieldings observed for the cyclic sulfides I and II have a steric origin, we believe. In these molecules, as shown by inspection of molecular models, the cyclic structure puts steric restraints to the existence of conformations of type VIII and IX, and the inner protons are forced somewhat outside the area of maximum shielding.

Compound I is thought to exist in a form (X) for which a sensible shielding is still predictable. A similar conformation has been found in solid state[4] for an isostructural cyclic hydrocarbon.

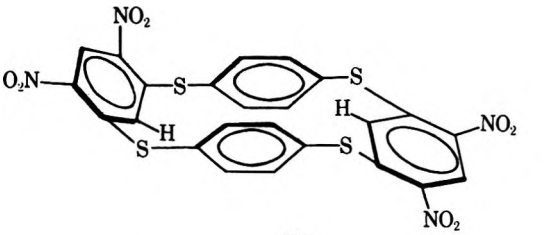


X

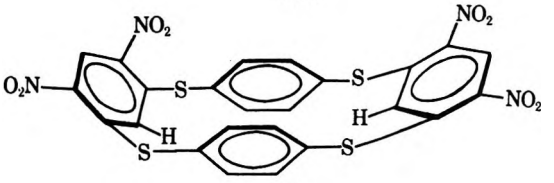
Molecular models show two structures (XIa and XIb) as equally plausible in the case of compound II.

In both forms the inner protons appear little shielded, in agreement with the experimental findings. Our results therefore show that, due to the presence of the nitro groups, a strong conjugation develops between the sulfur atom and the aromatic ring bearing the nitro groups in compounds IV–VII. The conjugation energy is strong enough to cause the internal rotation to become thermodynamically (but not kinetically) restricted, so that forms VIII and IX become preferred.

Steric factors, however, come into action for cyclic sulfides I and II, which prevent these molecules from assuming conformations of the former type.



XIa



XIb

Experimental Section

Compound I was obtained by refluxing for 1 hr very dilute ethanol solutions (20:1) of 1,3-benzenedithiol (1.7 g) with NaOH (0.9 g) and 1,3-dichloro-4,6-dinitrobenzene (2.8 g). The yellow precipitate formed was filtered, washed, and dried (yield 65%). Recrystallization from nitrobenzene afforded a product which did not melt up to 350°. *Anal.* Calcd for $C_{24}H_{12}N_4O_8S_4$ (mol wt 612): C, 47.06; H, 1.96; N, 9.16; S, 20.90. Found: C, 47.18; H, 2.20; N, 9.22; S, 21.02. Mass spectrum *m/e* 612 (M^+); nmr (DMSO-d_6, 80°) 9.02 (1 H), 7.69 (4 H), 6.71 ppm (1 H).

Compound II was obtained as above by refluxing 1,4-benzenedithiol (1.7 g), NaOH (0.9 g), and 1,3-dichloro-4,6-dinitrobenzene (2.8 g, yield 70%). The product obtained was infusible up to 350°.

Anal. Calcd for $C_{24}H_{12}N_4O_8S_4$ (mol wt 612): C, 47.06; H, 1.96; S, 20.90. Found: C, 47.24; H, 2.30; N, 9.31; S, 20.93. Mass spectrum *m/e* 612 (M^+); nmr (DMSO-d_6, 80°) 9.04 (1 H), 7.66 (4 H), 7.20 ppm (1 H).

Compounds III, IV, and V were prepared according to the literature.[5] Compound VII was obtained by refluxing 1,3-dichloro-4,6-dinitrobenzene, NaOH, and 1,3,5-trimethyl-2-benzenethiol in ethanol, similarly to the preparation described[6] for compound VI. Data for VII follow.

Anal. Calcd for $C_{24}H_{24}N_2O_4S_2$ (mol wt 468.5): C, 61.52; H, 5.16; N, 5.98; S, 13.69. Found: C, 61.71; H, 6.01; S, 13.90. Nmr ($CDCl_3$, 70°) 9.25 (1 H), 6.73 (4 H), 6.11 (1 H), 2.50 (6 H), 2.07 ppm (12 H); mp 300° (dioxane).

All the nmr measurements were performed with a Varian HA-100 spectrometer (100 MHz).

Registry No.—I, 32730-77-1; II, 32827-45-5; VII, 32827-46-6.

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A Convenient Synthesis of α-Keto Esters

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Corey and Seebach[2,3] have described a very convenient method of synthesis of aldehyde and ketone

(1) From the Ph.D. dissertation of Armando A. Hartmann, University of Notre Dame, Notre Dame, Ind., 1971.

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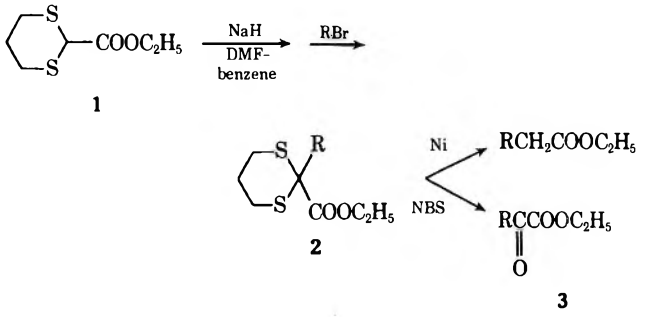
TABLE I

ETHYL 2-ALKYL-1,3-DITHIANE-2-CARBOXYLATES (2)

Alkyl group[a]	Registry no.	Yield, %	Bp, °C (mm)	$n^{20}D$	Calcd, % C	Calcd, % H	Found, % C	Found, % H
Benzyl	4882-96-6	85	145 (0.05)[b]	1.5651	59.54	6.42	59.82	6.84
n-Butyl	32557-27-0	94	90–95 (0.1)	1.5140	53.18	8.12	53.36	8.07
Isopropyl	32557-28-1	75	85–95 (0.1)	1.5205	51.24	7.74	51.19	7.70
sec-Butyl	32557-29-2	90	90–95 (0.1)	1.5208	53.18	8.12	53.23	8.11

[a] Introduced as alkyl bromide except for benzyl, which was introduced as benzyl chloride. [b] Lit.[3] bp 144° (0.01 mm).

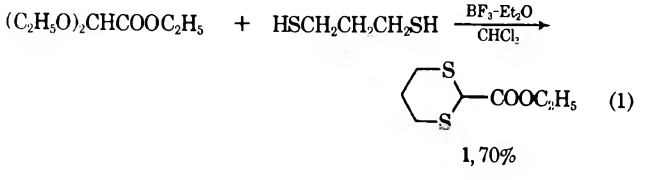
derivatives by alkylation of the lithium salts of 1,3-dithianes. When we attempted to synthesize the ester **1** by reaction of 2-lithio-1,3-dithiane with 1 mol of



ethyl chloroformate, we obtained, instead, 0.5 mol of the disubstituted product, 2,2-biscarbethoxy-1,3-dithiane, and 0.5 mol of recovered dithiane. Clearly, **1** is a strong enough acid to be converted completely into its lithium derivative by 2-lithio-1,3-dithiane.

It became apparent that the high acidity of **1** could be utilized in a rather facile alkylation in which sodium hydride in dimethylformamide (DMF)–benzene[4] is used to convert **1** into its sodium salt which is then alkylated with a primary or secondary halide in the usual way in yields of 75–95%. Desulfurization of the resulting alkylated ester **2** by means of Raney nickel provides an alternative to the malonic ester synthesis of alkylated acetic acids, with the variation that the product is obtained in the form of the ester rather than as the acid. Perhaps more significant is the conversion of **2** in good yield to the corresponding α-keto ester **3** by means of *N*-bromosuccinimide as previously described by Seebach.[3]

The significance of this α-keto ester synthesis is enhanced by the fact that the common starting material **1** has been found to be very easily available from ethyl diethoxyacetate prepared from dichloroacetic acid[5] and 1,3-propanedithiol (eq 1).



Although the present α-keto ester synthesis is quite similar to that previously described[2,3] in which the starting material is 1,3-dithiane or (if available) the appropriate 2-alkyl-1,3-dithiane, it has the advantage that a common, readily available precursor (**1**) is used for all α-keto esters and that it is not necessary to use alkyllithium reagents in the synthesis.

Experimental Section

Ethyl 1,3-Dithiane-2-carboxylate (1).—1,3-Propanedithiol, 10.8 g (0.1 mol), and 17.6 g (0.1 mol) of ethyl diethoxyacetate[6] dissolved in 20 ml of chloroform were added dropwise to a refluxing solution of 28.2 g (0.2 mol) of BF_3 etherate in 60 ml of chloroform over a period of 15 min. The solution was boiled for 0.5 hr, cooled, and washed successively with 80 ml of water, 80 ml of 20% aqueous potassium carbonate, and twice more with 80-ml portions of water. After drying over $MgSO_4$ the solution was filtered and concentrated at reduced pressure and the product was distilled, bp 75–77° (0.2 mm), yield 13.4 g (70%), $n^{20}D$ 1.5379, infrared and nmr spectrum in accordance with structure **1** [lit.[3] bp 96° (0.4 mm), $n^{25}D$ 1.5385].

General Procedure for Alkylation.—A solution of 0.1 mol (19.2 g) of **1** and 0.11 mol of the desired alkyl halide in 40 ml of DMF was added slowly to a well-stirred suspension of 0.1 mol (2.4 g) of sodium hydride in 120 ml of dry benzene cooled to 5°. The mixture was stirred in an ice bath for 1 hr and then at room temperature for 12 hr. The benzene layer was extracted three times with 200-ml portions of water, dried over $MgSO_4$, filtered, and concentrated. The crude product is suitable for desulfurization or conversion to the α-keto ester; however, the products tabulated in Table I were purified by distillation at reduced pressure, and all had the expected infrared and nmr spectra.

α-Keto Esters.—The procedure of Seebach[3] was followed. The following esters were thus obtained: ethyl phenylpyruvate, 76%, bp 145° (12 mm) [lit. bp 152° (15 mm)]; ethyl α-ketocaproate, 60%, bp 80–92° (12 mm), $n^{20}D$ 1.4187 [lit.[6] bp 74–96° (10 mm), $n^{20}D$ 1.4178]; ethyl α-ketoisovalerate, 85%, bp 63–70° (12 mm), 2,4-dinitrophenylhydrazone mp 171–172° [lit.[7] bp 72° (16 mm); lit.[8] 2,4-dinitrophenylhydrazone mp 171.5–172°]; ethyl α-ketoisocaproate, 62%, bp 76–78° (12 mm), $n^{20}D$ 1.4192 [lit.[6] bp 76–77° (10 mm), $n^{20}D$ 1.4175]. The infrared and nmr spectra of the four keto esters were compatible with the assigned structures.

Ethyl Hydrocinnamate.—To 24 g (0.1 mol) of nickel chloride hexahydrate dissolved in 80 ml of ethanol was added 7.5 g (0.2 mol) of sodium borohydride in small portions with stirring and the resulting suspension was stirred for an additional 0.5 hr. Then 2.8 g (0.01 mol) of 2-benzyl-2-carbethoxy-1,3-dithiane was added and the mixture was refluxed with stirring for 48 hr, filtered, concentrated, and distilled at reduced pressure. Ethyl hydrocinnamate boiled at 112° (12 mm), $n^{20}D$ 1.4936 [lit. bp 123° (14 mm), $n^{17}D$ 1.4941], yield 1 g (56%).

Acknowledgment.—This work was supported by Grant ARO-D-31-124-G1108 of the Army Research Office. We are grateful to Mr. Anthony Abatjoglou for checking the preparation of **1**.

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Stereospecific Dehalogenation of *vic*-Dibromides by Sodium Naphthalenide[1]

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The mechanism of the reaction of the naphthalene radical anion with organic halides has been shown to exhibit radical as well as carbanionic character.[2-4] Of synthetic interest is the observation that sodium naphthalenide serves as a convenient and efficient reagent for the dehalogenation of *vic*-dihalides to give olefins.[5] Since two-electron reductants result in stereospecific, while one-electron reductants in stereoselective, dehalogenation of *dl*-stilbene dibromides,[6] it was of synthetic as well as mechanistic interest to examine the stereochemical course of the dehalogenation of *meso*- and *dl*-stilbene dibromides by sodium naphthalenide.

When these dibromides are treated with an excess of sodium naphthalenide in dimethoxyethane (DME) and the reaction mixtures, after quenching with methanol, are submitted to glpc analysis, a complex product mixture is detected, consisting of *cis*- and *trans*-stilbene, α-bromostilbene, diphenylacetylene, and bibenzyl. These products are formed in variable proportions depending on the reaction conditions, such as concentrations, proportion of the reagents, and reaction time. Clearly, dehydrobromination into α-bromostilbene and diphenylacetylene competes with the expected debromination to give *cis*- and *trans*-stilbene. However, the formation of bibenzyl suggests immediately that the stilbenes and diphenylacetylene themselves react with the excess sodium naphthalenide leading to this reduction product after methanolysis. Indeed, a control experiment reveals that *cis*-stilbene is rapidly isomerized to *trans*-stilbene, while extended exposure of *trans*-stilbene to sodium naphthalenide produces bibenzyl after methanolysis. Furthermore, it is known that diphenylacetylene is converted to *cis*- and *trans*-stilbene on treatment with alkali metals.[7]

In view of these complications, we abandoned the stilbene system and instead examined the dehalogenation of *erythro*- and *threo*-2,3-dibromo-3-methylpentane (**1a** and **1b**), respectively. The *erythro*-dibromide **1a** of 78.6% isomeric purity was prepared from (*Z*)-3-methyl-2-pentene (**4a**) by the stereospecific addition of bromine. Similarly, the *threo*-dibromide **1b** of 87.6% isomeric purity was available from the (*E*)-3-methyl-2-pentene (**4b**). Control experiments showed that the stoichiometry of the reaction is 2 mol of sodium naphthalenide per mole of dibromide. More important, olefins **4a** and **4b** do not isomerize with sodium naphthalenide. The results of the dehalogenations are summarized in Table I.

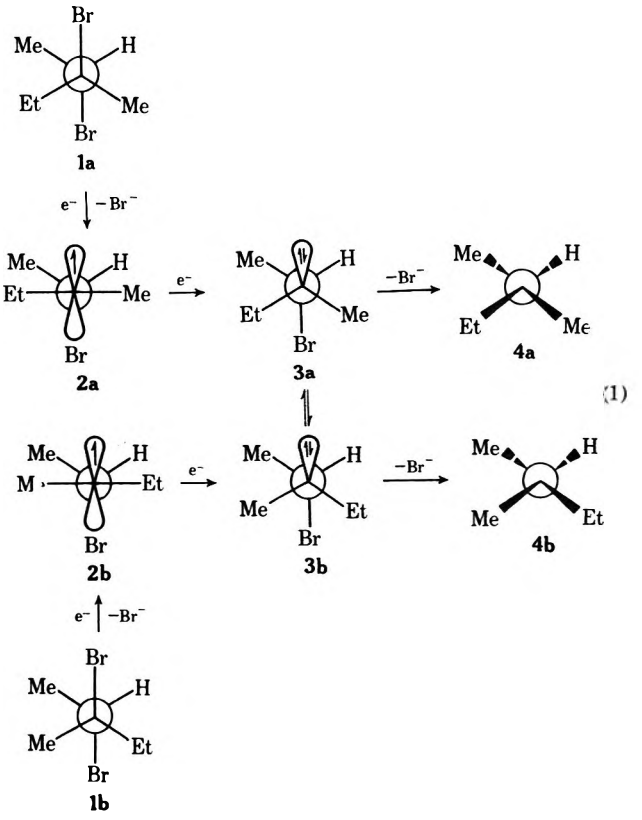
TABLE I

STEREOCHEMICAL COURSE OF THE REACTION OF *erythro*- AND *threo*-2,3-DIBROMO-3-METHYLPENTANE WITH SODIUM NAPHTHALENIDE IN DME

Reactant mixture[a] compn, %		Product mixture[b] compn, %		
erythro- (**1a**)	*threo*- (**1b**)	(*Z*)- (**4a**)	(*E*)- (**4b**)	% trans elimination[c]
12.2	87.8	15.6	84.3	92.2 ± 0.6
22.2	77.8	23.0	77.0	
78.6	21.4	61.9	38.1	75.6 ± 1.4
79.9	20.1	60.0	40.0	

[a] Determined by glpc using a 12 ft × 0.125 in. stainless steel column packed with 25% Apiezon M on 60–80 mesh Chromosorb P and operated at a column temperature of 125° and a helium flow of 25 ml/min. [b] Determined by glpc using a 24 ft × 0.125 in. stainless steel column packed with 20% Apiezon M on 60–80 mesh Chromosorb P and operated at a column temperature of 40° and a helium flow of 40 ml/min. [c] Calculated according to the equation, $E = tT + eC$, where E is % *E* olefin, t is % *threo*-dibromide, e is % *erythro*-dibromide, T is % trans elimination from *threo*-dibromide and C is % cis elimination from *erythro*-dibromide; four sets of experimental values of e, t, and E are given in the first, second, and fourth columns.

We conclude that the reaction of *vic*-dibromides **1a** and **1b** with sodium naphthalenide is a two-electron trans elimination, with a stereospecificity of 75.6 ± 1.4% for the erythro and 92.2 ± 0.6% for the threo isomer. On the basis of our results and previous work[2-4,6] we suggest that the mechanism (eq 1) for



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this reaction involves first the formation of the radicals **2a** and **2b**, respectively, from **1a** and **1b**. Before radicals **2a** and **2b** interconvert to any appreciable extent, they react with the second mole of sodium naphthalenide to produce the respective carbanions **3a** and **3b**. The rate of electron transfer between the naphthalene radical anion and free radicals is virtually diffusion controlled, since the reaction of optically active cyclopropyl bromides affords the respective cyclopropane with net retention.[8] In addition, radicals **2a** and **2b** might be expected to be stabilized by bridged structures involving the neighboring bromine and thus be prevented from interconverting by bond rotation.[9]

Finally, the lower stereospecificity in the case of the *erythro*-dibromide **1a** *vs.* the threo isomer **1b** arises from a methyl–ethyl repulsion in carbanion **3a** *vs.* a methyl–methyl repulsion in carbanion **3b**. Consequently, for **3a** bond rotation competes more effectivity with trans ejection of the bromine than for **3b**.

Experimental Section

Sodium naphthalenide was prepared according to the procedure of Scott[10] by dissolving 23 g (1.0 g-atom) of clean sodium metal in 1000 ml of dimethoxyethane (freshly distilled from the benzophenone ketyl radical) containing 134 g (1.0 mol) of naphthalene. The dark green solution was standardized by removing 2.0 ml of the stock solution by means of a calibrated syringe and quenching with 1.0 ml of methanol. The pale yellow solution was titrated with 0.100 *N* hydrochloric acid using methyl red as indicator.

erythro-**2,3-Dibromo-3-methylpentane** (**1a**) was obtained in 34% yield (79.9% isomeric purity by glpc), bp 74° (12 mm), n^{20}D 1.5126 [lit.[11] 79.5° (16 mm)], using the method of van Risseghem,[11] starting with 5.02 g (0.0597 mol) of (*Z*)-3-methyl-2-pentene [Columbia Organic, bp 67.5° (758 mm), n^{20}D 1.4021] and 9.6 g (0.060 mol) of bromine.

threo-**2,3-Dibromo-3-methylpentane** (**1b**) was obtained in 36% yield (78.6% isomeric purity by glpc), bp 75° (14 mm), n^{20}D 1.5121 [lit.[11] 75° (15 mm)], using the method of van Risseghem,[11] starting with 5.02 g (0.0597 mol) of (*E*)-3-methyl-2-pentene [Columbia Organic, bp 70° (758 mm), n^{20}D 1.4050] and 9.6 g (0.060 mol) of bromine.

General Method of Dehalogenation.—A 5-ml vial, capped with a rubber septum and supplied with a spinbar, was charged under a nitrogen atmosphere with 1.0 ml of a 2 *M* solution of the dibromide in DME (freshly distilled from the benzophenone ketyl radical). While stirring magnetically, a stoichiometric (2 mol of naphthalenide per mole of dibromide) amount of the standardized sodium naphthalenide solution was added through the rubber septum by means of a syringe. The colorless reaction mixture was stirred for 60 sec, quenched with 0.5 ml of methanol, and centrifuged to remove the sodium bromide precipitate. The supernatant liquid was submitted to glpc analysis. The results are summarized in Table I.

Registry No.—**1a**, 32675-17-5; **1b**, 32675-18-6; sodium naphthalenide, 12521-84-5.

Acknowledgments.—Financial aid by the Petroleum Research Fund, the National Science Foundation, and the Sloan Foundation is gratefully appreciated.

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Marked Differences between the Sodium–Ammonia and Calcium–Ammonia Reduction of Nitriles

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The reduction of nitriles with the alkali metals has been reported under a variety of conditions.[1-11] Normally the product isolated is the corresponding amine or the hydrocarbon resulting from reductive decyanation, a reductive fission process.[12] Recently, Arapakos, *et al.*, using sodium–ammonia or lithium–ethylamine solutions, found that tertiary nitriles give exclusive reductive decyanation products, whereas primary and secondary nitriles give both the expected amine as well as decyanation products.[10,11] In particular, dodecyl cyanide was reduced to dodecane (35%) and tridecylamine (65%).[11]

While working on another problem it became necessary to learn the fate of various aliphatic nitriles in the presence of calcium–ammonia solutions. For a direct comparison to the results reported for the alkali metal–ammonia or amine reductions,[10,11] dodecyl cyanide was chosen for the initial studies with calcium–ammonia solutions. In the presence of this reducing medium, dodecyl cyanide gave trace amounts of dodecane. Tridecylamine was the major product, accompanied by small amounts of 1-dodecyl-1-aminotridecane. Because of the marked difference in the amount of reductive decyanation found using calcium–ammonia solutions in comparison to the results reported using sodium–ammonia or lithium–ethylamine solutions,[10,11] other nitriles were reduced by addition of the nitrile to a heterogeneous solution of isooctane, calcium, and ammonia to see if this observation was a general phenomenon.

The results are shown in Table I. For convenience, the more volatile amines were isolated as derivatives from the isooctane solutions after removal of ammonia and represent the minimum amount of amine actually produced. No effort was made to measure the hydrocarbons or HCN produced by reductive fission due to the solvent used, the method of work-up and the *pyrophoric nature* of the calcium residues.

The alkali metal–ammonia or amine reductions of primary, secondary, and tertiary nitriles give increasing quantities of decyanation products (hydrocarbon

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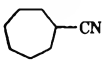
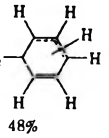
TABLE I

REDUCTION OF NITRILES WITH CALCIUM–AMMONIA SOLUTIONS

Nitrile	Product	Yield, %
$CH_3CH_2CH_2CN$	$CH_3CH_2CH_2CH_2NH_2$[a]	31–46
$(CH_3)_2CHCN$	$(CH_3)_2CHCH_2NH_2$[a]	32–43.5
$(CH_3)_3CCN$	$(CH_3)_3CCH_2NH_2$[b]	42.0
$CH_3CH_2CH_2CH_2CN$	$CH_3CH_2CH_2CH_2CH_2NH_2$[a]	40–65
		63
$(C_6H_5)_2CHCN$	$(C_6H_5)_2CH_2$ (52%) +  (48%)	100.0[c]
$(C_6H_5)_2CHCN$ (Na^0)	$(C_6H_5)_2CH_2$	100.0[c]
$NC(CH_2)_4CN$		39

[a] Isolated from isooctane as *n*-phenylthiourea derivative. [b] Isolated from isooctane as benzamide derivative. [c] Based on consumed starting material.

or olefin) and decreasing quantities of amine in the order listed.[10,11] In contrast to these results, the calcium–ammonia system reduced primary, secondary, and tertiary nitriles to give modest, synthetically useful amounts of the expected amine product and little decyanation based on the result obtained with dodecylcyanide. Under the same reaction conditions employed with calcium, a heterogeneous solution of sodium–ammonia in isooctane reduced diphenylacetonitrile to diphenylmethane in accord with earlier reports.[10,11] However, the calcium–ammonia system gave nearly equal amounts of diphenylmethane and further reduction products of diphenylmethane as a result of partial reduction of the aromatic nuclei. A dinitrile, adiponitrile, reacted with calcium–ammonia solutions to give 2-cyanocyclopentanone after a hydrolytic work-up.

The results obtained employing calcium–ammonia solutions are similar to those reported for reductions of nitriles with sodium and alcohol solutions[3,8,9] or sodium–ammonia solutions containing an alcohol.[4] In all cases, the blue metal–ammonia solutions could be effectively "titrated" with the nitrile, the blue color being instantly discharged. Calcium amide, the by-product of reduction, is produced rapidly. The isolation of 2-cyanocyclopentanone as the major hydrolysis product from adiponitrile attests to this fact as it is the expected hydrolysis product from the well-known base-catalyzed cyclization of adiponitrile.[13] The intermediate imine apparently tautomerizes rapidly in the basic medium to the enamine and is not reduced further.[13]

$$2Ca + 12NH_3 + RCN \longrightarrow RCH_2NH_2 + 8NH_3 + 2Ca(NH_2)_2$$

In metal–ammonia reductions, the solvated electron is considered to be the reducing specie.[12] However, the differences between the alkali metal–ammonia (or amine) solutions and calcium–ammonia solutions in the reduction of nitriles have also been observed in similar metal–ammonia reductions of monothioketals,[14] monothioacetals,[14] 1,3-dithiolanes,[15] and 1,3-dithianes.[15] This suggests that factors, such as the coordinating ability of the substrate toward the metal, or the degree of aggregation of the metal, may be of importance.

All derivatives prepared were found to be identical (nmr, ir, melting point) with authentic samples synthesized from commercially available amines.

Experimental Section

General Procedure for Nitrile Reduction.—Calcium (8.0 g, 0.2 mol) was charged to a dry, nitrogen-purged reactor. Ammonia (100 ml) was added slowly with adequate cooling to control the highly exothermic reaction. Isooctane (Phillips ASTM grade, redistilled from 4A molecular sieves, under N_2, 200 ml) was added slowly to the reactor. The rapidly stirred blue mixture was cooled to −50°. Nitrile (0.1 mol) was added rapidly dropwise. The blue color could be essentially titrated with the nitrile. The cooling bath was removed and the gray slurry was allowed to come to room temperature, venting the ammonia. Isooctane (300 ml) was added in portions (100 ml) during this time. In a nitrogen-filled drybox the reaction mixture was gravity filtered. The appropriate derivatizing agent (0.1 mol) was added to the filtrate. Usually the amine derivative rapidly precipitated, was filtered and recrystallized from an appropriate solvent.

Note. The calcium residue should be placed under a nonprotic solvent in the drybox and destroyed by the careful and slow addition of isopropyl alcohol to the slurry in a well-vented hood (HCN is liberated in some cases). In air, the semidry calcium residue is pyrophoric if not treated in the above manner.

Reduction of Cycloheptylnitrile.—Cycloheptylnitrile (12.3 g, 0.1 mol) was reduced as described above. After removal of ammonia, dilute HCl (20%, 400 ml) was added slowly with cooling (−10 to −20°). The water layer was extracted with 100 ml of ether. The aqueous layer was made strongly basic with 50% sodium hydroxide and extracted with ether (five 100-ml portions). The ethereal extract was washed with 100 ml of a saturated aqueous solution of sodium chloride, dried (Na_2SO_4), concentrated, and distilled, giving 8.0 g (63%) of cycloheptylmethylamine, bp 101° (35 mm). The *n*-phenylthiourea derivative was prepared, mp 125.5–127°.

Anal. Calcd for $C_{15}H_{22}N_2S$: C, 68.66; H, 8.45; N, 10.68. Found: C, 68.50; H, 8.38; N, 10.64.

Reduction of Adiponitrile.—Adiponitrile (10.8 g, 0.1 mol), calcium (4.0 g, 0.1 mol), and 500 ml of isooctane were placed in a reactor equipped with a high-speed stirrer and cooled to −35 to −40°. Approximately 100 ml of ammonia was added as rapidly as possible. The heterogeneous solution turned blue and then white; 20 ml of *tert*-butyl alcohol was added; and stirring was continued for 20 min. The ammonia was weathered off. Product was obtained by acidifying (10% diluent HCl), extraction of water layer ($CHCl_3$), concentration of organic layers, and vacuum distillation to give 4.39 g of 2-cyanocyclopentanone (39%), bp 67–69° (<1 mm) [lit.[16] bp 125–130° (4 mm)], semicarbazone mp 195–197° (lit. mp 192–195°).

Reduction of Dodecyl Cyanide.—Dodecyl cyanide (32.1 g, 0.15 mol) was reduced with calcium (0.15 mol) in 300 ml of ammonia. Isooctane (1000 ml) was added and the ammonia was weathered off. Water (0.2 mol) was added. The hydrocarbon layer was concentrated and distilled. Dodecane was isolated by glc and identified by mass spectroscopy, identical in all respects with the published spectrum. Tridecylamine had bp 80° (1.5 mm), mass spectrum parent mass 199.229989 (calcd, 199.229959). The benzoyl derivative was made, mp 69.5–70.5° (lit. mp 71.0°). The ir and nmr spectra were in agreement with the structure. Acetic anhydride was added to the distillation residue. Recrystallization from ethanol gave the acetamide of 1-dodecyl-1-aminotridecane, mp 105.5–106.0°. *Anal.* Calcd for $C_{27}H_{55}NO$: C, 79.14; H, 13.53; N, 3.42. Found: C, 79.16; H, 13.49; N, 3.46. Ir (KBr) 3.05 (NH), 3.42, 3.50 (CH_3–, CH_2–), 6.09 (NHC=O), 7.31 (CH_3CO), 13.82 μ (–CH_2–); nmr ($CDCl_3$) δ 0.87 (t, 6, CH_3–), 1.26 (s, 40, –CH_2–), 1.97 (s, 3, CH_3CO), 3.93 (broad signal, 1, CHN), 5.15 (m, 1, NH); mass spectrum A.E.I. MS-9 (70 eV) *m/e* (rel intensity)

(13) C. F. Hammer and R. A. Hines, *J. Amer. Chem. Soc.*, **77**, 3649 (1955).
(14) E. L. Eliel and T. W. Doyle, *J. Org. Chem.*, **35**, 2716 (1970).
(15) B. C. Newman and E. L. Eliel, *ibid.*, **35**, 3641 (1970).
(16) S. M. McElvain and R. D. Mullineaux, *J. Amer. Chem. Soc.*, **74**, 1811 (1952).

M+ 409.428630 (1.4) (calcd, 409.428344), 366 (1), 240 (100), 198 (81); m* (409 → 240) 140.83; m* (240 → 198) 163.65.

Registry No.—Sodium, 7440-23-5; calcium, 7440-70-2; ammonia, 7664-41-7; cycloheptylnitrile, 32730-85-1; cycloheptylmethylamine, 4448-77-5, 32730-87-3 (*N*-phenylthiourea derivative); adiponitrile, 111-69-3; dodecyl cyanide, 629-60-7; tridecylamine, 2869-34-3; acetamide of 1-amino-1-dodecyltridecane, 32730-89-5.

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A New Synthesis of Unsymmetrical Azo Compounds[1]

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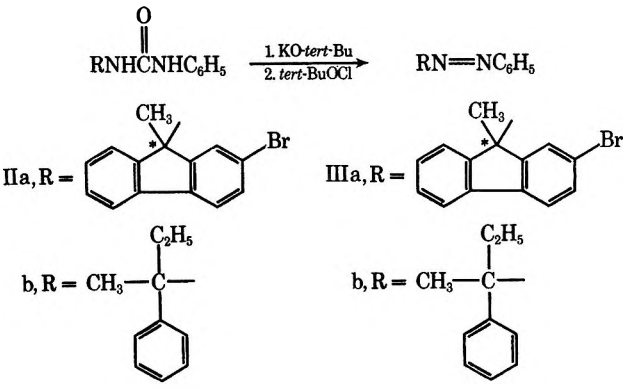
The relative rates of bond breaking of the two carbon–nitrogen bonds in the thermal decomposition of unsymmetrical azo compounds has been investigated recently.[2] This and other studies have resulted in the modification of old and development of new synthetic procedures for the preparation of the requisite unsymmetrical azo compounds.[3]

In connection with our studies, we required an azo compound of the general formula I in which the tertiary carbon is optically active. Since none of the existing methods for the preparation of unsymmetrical azo compounds could be modified to give a compound of type I, we explored new routes to this structure.[4]

RN=NAr
I, R = *tert*-alkyl

The treatment of unsymmetrical ureas (IIa,b) with potassium *tert*-butoxide in *tert*-butyl alcohol followed by the addition of *tert*-butyl hypochlorite at room temperature for 15 min produced azo compounds IIIa,b in approximately 20% yield. The ureas are readily obtained by the reaction of phenyl isocyanate with a *tert*-alkylamine. In addition, IIIa was produced optically active by beginning with resolved 2-bromo-9-methyl-9-aminofluorene, which was prepared from 2-bromofluorenone.



This method resembles the sequence which Greene[5] reported in the synthesis of diaziridones. However, it is not known if a diaziridone is an intermediate in this reaction.

Experimental Section[6]

2-Bromofluorenone.—2-Bromofluorene was oxidized according to the procedure of Ross and coworkers[7] to give 2-bromofluorenone in 73% yield, mp 144–146° (lit.[7] mp 146–148°), after recrystallization from ethanol.

2-Bromo-9-methylfluoren-9-ol.—To 22 g of 2-bromofluorenone in 700 ml of dry benzene was added 100 ml of CH_3MgBr (Aldrich, 2.2 *M*) over 20 min. The solution was stirred at room temperature for 1 hr and poured into 1 *N* H_2SO_4. The benzene layer was separated and the acid extracted with benzene. The benzene was dried ($MgSO_4$) and evaporated and the residue crystallized from chloroform–petroleum ether (bp 30–60°) to give 15.7 g (67%) of product, mp 143.5–144.5° (lit.[8] mp 148–149°).

2-Bromo-9-methyl-9-azidofluorene.—2-Bromo-9-methylfluoren-9-ol was converted to the azide according to the procedure of Coombs[9] in 85% yield and used as the oil without further purification: nmr spectrum (CCl_4) δ 1.67 (s, CH_3) and 7.1–7.8 (m, aromatics).

2-Bromo-9-methyl-9-aminofluorene.—To 9 g of $LiAlH_4$ (Ventron) in 225 ml of dry ether cooled in an ice bath was added with stirring 51.4 g of 2-bromo-9-methyl-9-azidofluorene at a rate which maintained vigorous refluxing. After addition was complete the reaction mixture was stirred at room temperature for 30 min. The excess $LiAlH_4$ was decomposed by the *slow* addition of 39 ml of 20% NaOH to the cooled reaction mixture. The white granular precipitate was filtered and the ether evaporated (frothing!) to give 42 g (89%) of a very viscous nearly colorless oil: nmr spectrum (CCl_4) δ 1.55 (s, CH_3), 7.1–7.8 (m, 7 aromatic H's), 1.41 (s, broad, NH_2).

Resolution of 2-Bromo-9-methyl-9-aminofluorene.—The amine (27.4 g) in 350 ml of ethyl ether was added to 12.5 g of *d*-10-camphorsulfonic acid in 50 ml of ethyl alcohol. The solution was allowed to stand at room temperature for 2 hr and at 16° for 1 hr and filtered to give 12.1 g of the camphorsulfonate salt. The amine from this salt was used to prepare the (+) azo compound. The filtrate was evaporated and the amine liberated. To 19.4 g of this amine was added 10.6 g of *d*-tartaric acid in 350 ml of ethanol. This was allowed to stand at 25° overnight and yielded 11.9 g of the tartrate salt. The amine liberated from this salt was used to prepare the (−) azo compound. In order to ascertain the rotation of the respective amines, they were each converted to the urea with phenyl isocyanate as described below and the rotations measured. The urea from the camphor-

(1) Research performed under the auspices of the U. S. Atomic Energy Commission.

(2) S. Seltzer and F. T. Dunne, *J. Amer. Chem. Soc.*, **87**, 2628 (1965); S. Seltzer, *ibid.*, **83**, 2625 (1961), **85**, 14 (1963); S. Seltzer and S. G. Mylonakis, *ibid.*, **89**, 6584 (1967); S. E. Scheppele and S. Seltzer, *ibid.*, **90**, 358 (1968); S. G. Mylonakis and S. Seltzer, *ibid.*, **90**, 5487 (1968); S. Seltzer, personal communication; W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, **92**, 5403 (1970), **89**, 1741 (1967); N. A. Porter, M. E. Landis, and L. J. Marnett, *ibid.*, **93**, 795 (1971).

(3) For a summary of the synthetic methods which have been used in the preparation of azo compounds, see C. G. Overberger, J. P. Anselme, and J. G. Lombardino, "Organic Compounds with Nitrogen–Nitrogen Bonds," Ronald Press, New York, N. Y., 1966, Chapter 4; H. Zollinger, "Azo and Diazo Chemistry, Aliphatic and Aromatic Compounds," Interscience, New York, N. Y., 1961, Chapter 9. For specific examples of unsymmetrical azo compounds, see S. G. Cohen, F. Cohen, and C. H. Wang, *J. Org. Chem.*, **28**, 1479 (1963); S. Seltzer and F. T. Dunne, ref 2; N. A. Porter, M. E. Landis, and L. J. Marnett, ref 2.

(4) Since this method was developed Porter, *et al.*,[2] have reported a synthetic sequence which also leads to this type of compound and involves the unsymmetrical sulfamide.

(5) F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.*, **34**, 2254 (1969).

(6) Melting points were taken on a Reichert melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60 instrument and ultraviolet spectra were recorded on a Cary Model 14 spectrophotometer. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. 11377.

(7) S. D. Ross, M. Finkelstein, and R. C. Petersen, *J. Amer. Chem. Soc.*, **80**, 4327 (1958).

(8) A. Weizmann, *J. Org. Chem.*, **16**, 1851 (1951).

(9) M. M. Coombs, *J. Chem. Soc.*, 3454 (1958).

sulfonate salt gave $\alpha_{DMF}^{5461\,\text{Å}}$ = +26° and the urea from the tartrate salt gave $\alpha_{DMF}^{5461\,\text{Å}}$ = −28°. A second crystallization of the salts gave ureas with $\alpha_{DMF}^{5461\,\text{Å}}$ = +40° and $\alpha_{DMF}^{5461\,\text{Å}}$ = −40°. For preparation of optically active azo compounds various batches of +(−) ureas having specific rotation from +(−)23 to +(−)40° were used.

N-Phenyl-*N'*-2-bromo-9-methyl-9-fluorenylurea (IIa).—To 1.98 g of 2-bromo-9-methyl-9-aminofluorene in 40 ml of benzene was added 0.79 ml of phenyl isocyanate. The solution was heated to boiling on a steam bath and allowed to cool, and 2.4 g of colorless crystals was collected, mp 269.5–270°, after two crystallizations from acetone.

Anal. Calcd for $C_{21}H_{17}BrN_2O$: C, 64.13; H, 4.36; N, 7.12. Found: C, 64.67; H, 4.41; N, 7.09.

2-Bromo-9-methyl-9-fluorenylazobenzene (IIIa).—Potassium *tert*-butoxide (2.70 g) was dissolved in 430 ml of *tert*-butyl alcohol, 9.65 g of *N*-phenyl-*N'*-2-bromo-9-methyl-9-fluorenylurea was added, and the resulting slurry was stirred for 15 min at room temperature. *tert*-Butyl hypochlorite (4.58 ml) was added dropwise from a syringe over 2 min. The reaction mixture became bright yellow and the temperature rose to 30°. Stirring was continued for 15 min and the mixture poured onto ice and water and extracted with ether until the water was colorless. Some unreacted urea remained suspended at the interface. The ether was thoroughly washed with water (2 l.) to remove the *tert*-butyl alcohol. (Since emulsions result from shaking while extracting, it is better to pour the water through the ether and not to shake it.) The ether is filtered from 2.7 g of unreacted urea and dried with K_2CO_3 and evaporated leaving a red oil. This was chromatographed using a cold dry column of alumina eluting with 20% benzene in petroleum ether (bp 30–60°).[10] The fractions of the chromatograph were monitored by tlc. The first few fractions contained two faster running compounds in addition to the yellow azo compound and these fractions were discarded. The yield of azo compound was 1.5 g (23% based on recovered urea). This material could be crystallized with difficulty from petroleum ether, mp 67–73° dec. However, the oil and crystals had identical infrared and nmr, and the elemental analyses of the oil and the solid were identical. The nmr spectrum ($CDCl_3$) showed δ 1.85 (s, CH_3) and 7.26–8.05 (m, aromatic H's), and the uv spectrum of the oil showed λ^{EtOH} 404 nm (ε 202).

Anal. Calcd for $C_{20}H_{15}BrN_2$ (oil): C, 66.12; H, 4.16; N, 7.71. Found: C, 66.34; H, 4.24; N, 7.63.

The azo compound prepared from the partially resolved ureas gave $\alpha_{EtOH}^{5461\,\text{Å}}$ = +(−)150°. The optical purity of the azo compound was not determined. However, when attempts were made to recrystallize the partially resolved material it was found that the racemate crystallized leaving a more highly resolved oil in the mother liquors. Hence the oil was used without crystallization.

[(α-Phenyl-α-methyl)propyl]azobenzene (IIIb).—To 2.36 g of IIb[11] in 100 ml of *tert*-butyl alcohol was added 1.06 g of potassium *tert*-butoxide. This was stirred for 15 min at room temperature and 2.04 ml of *tert*-butyl hypochlorite was added dropwise over 2 min. After the addition was complete the reaction mixture was poured into 120 ml of cold water and extracted with petroleum ether. The petroleum ether extracts were washed well with water, then dried, and evaporated. The petroleum ether soluble portion of the residue was chromatographed over neutral alumina and 0.6 g of a yellow oil was eluted with petroleum ether. Nmr showed this material to be a 1:3 mixture of an unidentified compound and azo compound IIIb. The analytical sample was prepared by fractional molecular distillation: nmr (CCl_4) δ 0.77 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.57 (s, 3 H, CH_3), 2.12 (q, 2 H, J = 7 Hz, CH_2CH_3); uv λ_{vis}^{EtOH} 410 nm (ε 120).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.38; N, 11.65. Found: C, 80.22; H, 7.82; N, 11.59.

Registry No.—IIa, 32659-22-6; (±)-IIa, 32659-23-7; (+)-IIIa, 32659-24-8; (−)-IIIa, 32659-25-9; IIIb, 32722-87-5; 2-bromo-9-methyl-9-azidofluorene, 32670-62-5; 2-bromo-9-methyl-9-aminofluorene, 32659-26-0.

(10) The alumina used for the dry column (240 g) was deactivated by the addition of 7 ml of water to 380 g of neutral alumina and heating the resulting mixture at ~50° for 1 hr on the rotary evaporator. The jacketed chromatograph column (1.2 × 14 in.) was cooled with an ice–water mixture.

(11) M. Thiel, W. Schafer, and F. Asinger, *Justus Liebigs Ann. Chem.*, **618**, 128 (1958).

The Synthesis of 3-Alkyl-2-pyrazinyl Methyl Ketones and Related Compounds

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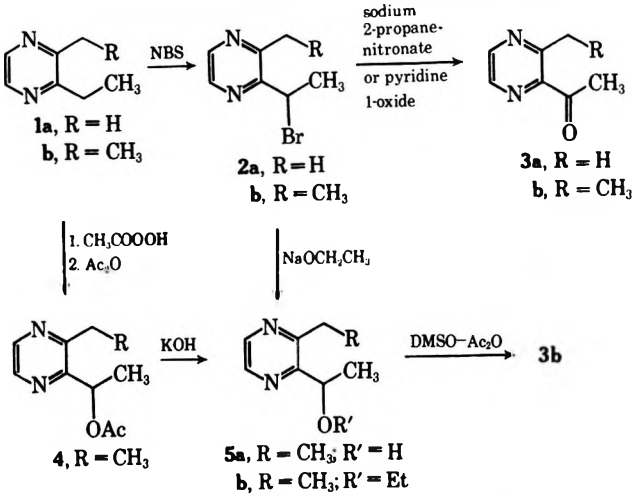
Acetylpyrazines, which are important flavoring materials,[1a–d] are not readily available. The literature contains no convenient synthetic route involving less than four steps.

We now report a simple two-step synthesis of acetylpyrazines from the corresponding alkylpyrazines. Monobromoalkylpyrazines, obtained by treatment of alkylpyrazines with *N*-bromosuccinimide (NBS),[2,3] are readily oxidized to the corresponding ketones by either sodium-2-propanenitronate[4] or pyridine 1-oxide.[5] Thus, 2-ethyl-3-methylpyrazine (**1a**) on treatment with NBS in the presence of benzoyl peroxide gave 2-(1-bromoethyl)-3-methylpyrazine (**2a**) (≈100%) which in turn was converted to ketone **3a**[1c] by both sodium 2-propanenitronate and pyridine 1-oxide in 66 and 25% overall yield, respectively. Similarly, 2-(1-bromoethyl)-3-ethylpyrazine (**2b**), obtained from 2,3-diethylpyrazine (**1b**), was converted to ketone **3b** in 54% overall yield with sodium 2-propanenitronate. When bromide **2b** was treated with excess sodium ethoxide in ethanol, ethyl ether **5a** was obtained in 43% yield.



In another experiment ketone **3b** was prepared from **1b** using the *N*-oxide rearrangement.[6] Treatment of **1b**

(1) (a) D. L. Roberts, to R. J. Reynolds Tobacco Co., U. S. Patent 3,402,051 (Sept 17, 1968); *Chem. Abstr.*, **72**, 11496*d* (1970); (b) M. Winter, F. Gautschi, I. Flament, and M. Stoll, to Firmenich et Cie., French Patent 1,530,436 (June 28, 1968); *Chem. Abstr.*, **71**, 90131*m* (1969); (c) Polak's Frutal Works, U. S. Patent Application 666,980; (d) V. K. Smith, Jr., P. River, and S. Kushner, to American Cyanamid Co., U. S. Patent 2,677,686 (May 4, 1954).

(2) *N*-Chlorosuccinimide has previously been used for the chlorination of 2,3-dimethylpyrazine: R. A. Pages and P. E. Spoerri, *J. Org. Chem.*, **28**, 1702 (1963).

(3) For bromination of methylpyrimidine derivatives with *N*-bromosuccinimide, see M. Hasegawa, *Pharm. Bull.*, **1**, 387 (1953); *Chem. Abstr.*, **49**, 10970*g* (1955).

(4) H. B. Hass and M. L. Bender, *J. Amer. Chem. Soc.*, **71**, 1767 (1949); *Org. Syn.*, **30**, 99 (1950).

(5) W. Feely, W. L. Lehn, and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).

(6) G. Kobayashi and S. Furukawa, *Pharm. Bull.*, **1**, 347 (1953); *Chem. Abstr.*, **49**, 10948*e* (1955); V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954); B. Klein, J. Berkowitz, and N. E. Hetman, *J. Org. Chem.*, **26**, 126 (1961).

with 1 mol of peracetic acid and excess acetic anhydride gave acetoxypyrazine **4** (42%) which was saponified to hydroxypyrazine **5a** (77%) and oxidized to ketone **3b** by the acetic anhydride–dimethyl sulfoxide method.[7] It should be mentioned that our attempts to oxidize alcohol **5a** to ketone **3b** with either the Jones reagent[8] or chromium trioxide–pyridine[9] were unsuccessful.

Experimental Section

Vapor phase chromatographic (vpc) analyses were performed on an F & M 810 instrument using 5% Carbowax 20M and 5% silicone SE-30 packed stainless steel columns (1/4 in. × 25 ft). The following spectrometers were used: infrared (ir), Beckman IR-5A and IR-4; nuclear magnetic resonance (nmr), Varian A-60 and HA-100 (TMS as internal standard); mass spectrometer, CEC Model 21-103C and AEI MS9. Mass spectral major fragmentation peaks are listed in decreasing order of intensity except for the molecular ion peak which is listed first. Five per cent deactivated silicic acid (Grace, 100–200 mesh), made by adding 5 ml of water to 95 of silicic acid, and acid alumina (activity I, Fisher Scientific, 80–200 mesh) were used for column chromatography. Anhydrous magnesium sulfate was used as drying agent.

2-(1-Bromethyl)-3-methylpyrazine (2a).—A solution of **1a** (24.4 g, 0.2 mol) in carbon tetrachloride (400 ml) containing NBS (35.6 g, 0.2 mol) and benzoyl peroxide (0.5 g) was refluxed for 90 min, cooled, filtered, and solvent stripped under reduced pressure to give 40.5 g (~100%) of crude orange-brown oil. Vpc (Carbowax) indicated the complete conversion of **1a** to bromide **2a**. Pure bromide was isolated by vpc (silicone): ir (neat) 3.3, 3.4, 3.45, 5.85, 6.55, 6.95, 7.12, 7.3, 7.55, 7.95, 8.4, 8.55, 8.85, 9.22, 9.45, 9.61, 10.3, 11.5, 11.75, 12.7, 13.2, 13.7 μ; nmr ($CDCl_3$) δ 2.07 (d, 3, $-CHBrCH_3$), 2.6 (s, 3, C-3 methyl H), 5.2 (q, 1, $-CHBrCH_3$), 8.3 (s, 2, C-5 and C-6 H); mass spectrum *m/e* 200 (molecular ion), 121, 39, 93, 42, 52.

Anal. Calcd for $C_7H_9BrN_2$: *m/e* 199.9949. Found: *m/e* 199.9954.

3-Methyl-2-pyrazinyl Methyl Ketone (3a). A. With Sodium 2-Propanenitronate.—2-Nitropropane (18.7 g, 0.21 mol) was added to a solution of sodium ethoxide, prepared by the reaction of sodium (4.6 g, 0.2 g-atom) with absolute ethanol (200 ml). After the mixture was stirred for 30 min at room temperature, crude bromide **2a** (40.5 g) was added and the resulting slurry, which gradually thinned out and darkened during heating, was refluxed for 2 hr. The mixture was cooled and the solid was filtered. Removal of solvent under reduced pressure yielded 36.1 g of residue which was distilled, giving 18.1 g (66.5%) of pale yellow oil **3a**: bp 56° (0.5 mm); ir (neat) 3.3, 3.4, 3.45, 5.92 (>C=O), 6.48, 6.55, 6.95, 7.09, 7.19, 7.3, 7.41, 7.82, 8.05, 8.42, 8.6, 9.23, 9.45, 9.7, 9.9, 10.2, 10.6, 11.7 μ; nmr ($CDCl_3$) δ 2.7 (s, 3, $-C(=O)CH_3$), 2.8 (s, 3, methyl H), 8.5 and 8.6 (two d, 2, C-5 and C-6 H); mass spectrum *m/e* 136 (molecular ion), 43, 94, 93, 42.

Anal. Calcd for $C_7H_8N_2O$: *m/e* 136.0636. Found: *m/e* 136.0641.

B. With Pyridine 1-Oxide.—A solution of crude **2a** (40.5 g) and pyridine 1-oxide (38 g) in acetonitrile (300 ml) was refluxed for 5 hr and then cooled. The solvent was stripped under reduced pressure leaving a dark residue behind, to which 10% aqueous potassium hydroxide solution (150 ml) was added. The aqueous layer was extracted with ether. The organic extract was dried, concentrated, and distilled to afford a fraction (8.9 g), bp 57–64° (3–5 mm), which was further purified by column chromatography (100 g silicic acid): 20–50% ether in hexane (500 ml) eluted 6.8 g (25%) of ketone **3a**.

2-(1-Bromoethyl)-3-ethylpyrazine (2b).—A solution of **1b** (68.1 g, 0.5 mol) in carbon tetrachloride (1 l.) containing NBS (89 g, 0.5 mol) and benzoyl peroxide (1 g) was refluxed for 90 min, cooled, filtered, and solvent stripped under reduced pressure to give 108.3 g (~ 100%) of crude bromide **2b**. Pure bromide was isolated by vpc (silicone): ir (neat) 3.3, 3.35, 3.42, 3.5, 6.52, 6.85, 6.9, 6.93, 7.1, 7.29, 7.5, 7.6, 7.9, 8.1, 8.39, 8.62, 8.89, 9.2, 9.42, 9.6, 9.73, 10.3, 11.65, 13.8 μ; nmr ($CDCl_3$) δ 1.35 (t, 3, $-CH_2CH_3$), 2.1 (d, 3, $-CHBrCH_3$), 2.75 (q, 2, $-CH_2CH_3$), 5.39 (q, 1, $-CHBrCH_3$), 8.0 (s, 2, C-5 and C-6 H); mass spectrum *m/e* 214 (molecular ion), 135, 39, 119, 52, 54, 136.

Anal. Calcd for $C_8H_{11}BrN_2$: *m/e* 214.0006. Found: *m/e* 214.0009.

3-Ethyl-2-pyrazinyl Methyl Ketone (3b).—2-Nitropropane (62.3 g, 0.7 mol) was added to a solution of sodium ethoxide, prepared by the reaction of sodium (12.7 g, 0.55 g-atom) with absolute ethanol (600 ml). After the mixture was stirred for 30 min, crude bromide **2b** (108.3 g) was added and the resulting slurry, which gradually thinned out, was refluxed for 2 hr. After the usual work-up and distillation, 40.5 g (54%) of pale yellow oil **3b** was obtained: bp 55° (1.1 mm); ir (neat) 3.3, 3.39, 3.41, 5.5, 5.9 (>C=O), 6.05 (very weak), 6.45, 6.55, 6.85, 7.09, 7.14, 7.4, 7.6, 7.85, 8.02, 8.45, 8.6, 8.7, 9.2, 9.3, 9.45, 9.72, 10.3, 10.5, 11.65 μ; nmr ($CDCl_3$) δ 1.28 (t, 3, $-CH_2CH_3$), 2.69 (s, 3, $-C(=O)CH_3$), 3.15 (q, 2, $-CH_2CH_3$), 8.44 and 8.61 (two d, 2, C-5 and C-6 H); mass spectrum *m/e* 150 (molecular ion), 43, 107, 52, 79, 27.

Anal. Calcd for $C_8H_{10}N_2O$: *m/e* 150.0793. Found: *m/e* 150.0799.

3-Ethyl-α-methyl-2-pyrazinemethanol Acetate (4).—To a solution of **1b** (27.2 g, 0.2 mol) in acetic acid (100 ml) was added slowly 40% peracetic acid (38 g, 0.2 mol) at 75–80°. After stirring for 1 hr at 75° the acetic acid was stripped under reduced pressure, acetic anhydride (150 ml) was added to the residue, and the reaction mixture was refluxed for 4 hr. The acetic anhydride was removed under reduced pressure to obtain a dark residue which was taken up in ether and poured into water. The ether extract was washed with sodium bicarbonate and sodium chloride solutions, dried, evaporated, and distilled to yield 16.5 g (42.5%) of colorless oil **4**: bp 107–110° (0.4 mm); ir (neat) 3.3, 3.35, 3.41, 3.45, 5.75, 6.85, 7.05, 7.29, 7.59, 8.05, 8.6, 8.75, 9.2, 9.35, 9.45, 9.75, 9.9, 10.25, 10.55, 11.6, 11.75 μ; nmr ($CDCl_3$) δ 1.3 (t, 3, $-CH_2CH_3$), 1.56 (d, 3, $-OCHCH_3$), 2.06 (s, 3, $-OOCCH_3$), 2.9 (q, 2, $-CH_2CH_3$), 6.1 (q, 1, >CHOAc), 8.4 (m, 2, C-5 and C-6 H); mass spectrum *m/e* 194 (molecular ion), 43, 151, 152, 134, 133, 135.

Anal. Calcd for $C_{10}H_{14}N_2O_2$: *m/e* 194.1055. Found: *m/e* 194.1058.

3-Ethyl-α-methyl-2-pyrazinemethanol (5a).—To a solution of **4** (11.7 g, 0.06 mol) in methanol (75 ml) was added slowly 20% aqueous potassium hydroxide (30 ml) and the solution was stirred for 2 hr at room temperature. The reaction mixture was poured into water and extracted with ether. The dried extract was concentrated to give 9.7 g of crude material which was distilled to afford 7.1 g (77.7%) of colorless oil **5a**: bp 70–71° (1.5 mm); ir (neat) 3.0 (–OH), 3.3, 3.39, 3.41, 3.49, 6.51, 6.9, 7.1, 7.3, 7.6, 7.9, 8.6, 9.2, 9.7, 9.85, 10.3, 11.1, 11.7, 12.2, 12.7, 13.7 μ; nmr ($CDCl_3$) δ 1.33 (t, 3, $-CH_2CH_3$), 1.45 (d, 3, $-OCHCH_3$), 2.82 (q, 2, $-CH_2CH_3$), 5.05 (q, 1, >CHOH), 8.34 and 8.45 (two d, 2, C-5 and C-6 H); mass spectrum *m/e* 152 (molecular ion), 137, 107, 52, 45, 80.

Anal. Calcd for $C_8H_{12}N_2O$: *m/e* 152.0949. Found: *m/e* 152.0953.

3-Ethyl-2-pyrazinyl Methyl Ketone (3b). DMSO–Ac_2O Method.—A solution of **5a** (2.28 g, 0.015 mol) in dimethyl sulfoxide (27 ml) and acetic anhydride (18 ml) was allowed to stand at room temperature for 24 hr. The reaction mixture was poured into water and basified with 10% aqueous hydroxide solution. The mixture was extracted with methylene chloride. The organic extract was dried and concentrated to give a residue which was dissolved in hexane, washed with water, and dried. Removal of solvent gave 1.75 g of oil which showed one major peak by vpc (Carbowax) due to **3b**.

3-Ethyl-2(1-ethoxyethyl)pyrazine (5b).—Crude bromide **2b**, obtained by reacting **1b** (13.6 g, 0.1 mol), NBS (17.8 g, 0.1 mol), and benzoyl peroxide (0.2 g) in carbon tetrachloride in the usual manner, was added to a solution of sodium ethoxide (4.6 g, 0.2 g-atom of sodium in 250 ml of dry ethanol) and refluxed for 1 hr. The reaction mixture was cooled, filtered, and distilled to obtain 7.75 g (43%) of colorless oil **5b**: bp 44–50° (0.5 mm); ir (neat) 3.3, 3.4, 3.42, 3.49, 5.72, 6.5, 6.85, 7.1, 7.29, 7.45, 7.58, 7.89, 8.0, 8.62, 9.05, 9.3, 9.4, 9.9, 10.3, 10.6, 11.65 μ; nmr ($CDCl_3$) δ 1.2 (t, 3, $-OCH_2CH_3$), 1.3 (t, 3, $-CH_2CH_3$), 1.5 (d, 2, $EtOCHCH_3$), 2.94 (q, 2, $-CH_2CH_3$), 3.4 (m, 2, $-OCH_2-CH_3$), 4.76 (q, 1, $EtOCHCH_3$), 8.4 (s, 2, C-5 and C-6 H); mass spectrum *m/e* 180 (molecular ion), 136, 45, 73, 121, 133, 27.

(7) J. D. Albright and L. Goldman, *J. Amer. Chem. Soc.*, **87**, 4214 (1965).
(8) K. Bowden, I. M. Heilbron, E. R. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(9) K. Biemann, G. Büchi, and B. H. Walker, *J. Amer. Chem. Soc.*, **79**, 5558 (1957).

Anal. Calcd for $C_{10}H_{16}N_2O$: *m/e* 180.1262. Found: *m/e* 180.1265.

Registry No.—**2a**, 32974-89-3; **2b**, 32974-90-6; **3a**, 23787-80-6; **3b**, 32974-92-8; **4**, 32974-93-9; **5a**, 32974-94-0; **5b**, 32974-95-1.

Acknowledgment.—The authors express their appreciation to Dr. W. I. Taylor for his interest in this project. We also thank Mr. W. Ledig for his technical assistance and Messrs. H. Bondarovich and M. Jacobs for doing high-resolution mass spectrometric analyses and nmr analyses.

New Deamination in a Benzyne Addition to *N*-Benzylaziridine

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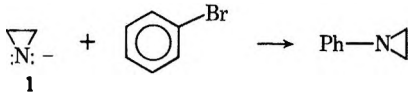
Aziridine chemistry is receiving widening attention since the recent discovery[1] of an economic access to the parent compound in 1963. However, the only likely aryne reaction reported in the literature is a simple amide elimination–addition of **1** to bromobenzene.[2]



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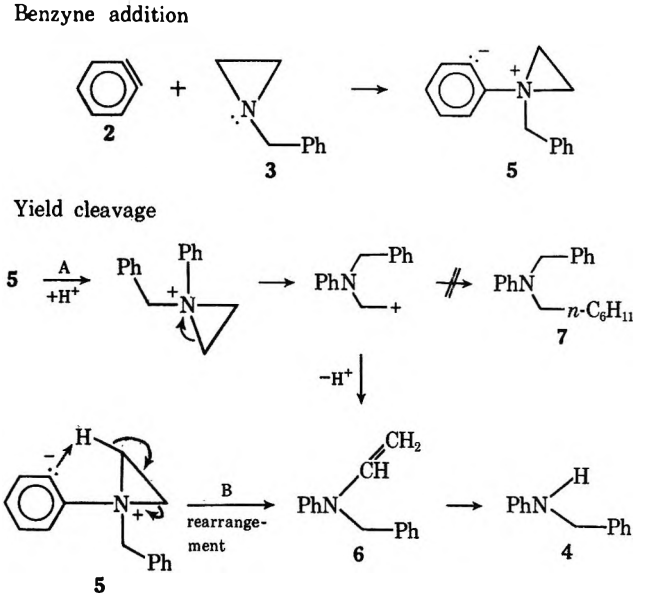
In a continuing interest in the chemistry of ammonium ylides, we endeavored to add benzyne (**2**), generated *in situ* by the fluorobenzene–butyllithium route,[3] to *N*-benzylaziridine (**3**) in the hope of producing α-ylides, whose subsequent fate might have been of definite synthetic interest.

Surprisingly, the addition reaction followed quite a different course, the main product being *N*-benzylaniline (**4**) to the exclusion of amounts larger than 0.1% of the theoretical yield of rearranged products.[4] Amine **4** was identified by glc retention time ratio *vs.* a known standard, enhancing technique, by mass spectrometry, and, on a separated analytical sample, by ir and pmr spectroscopy.

The obvious rationalization of this unexpected product is a benzyne addition to the tertiary aziridine **3**, followed by the formal elimination of ethylene from the activated amine ring. Two mechanisms may be envisaged for the latter reaction (Scheme I, A and B). Both routes lead to a common intermediate **6** from the initial ortho ylide **5**; **6** should in turn eliminate acetylene.[5] Route A involves a less likely[6] ring opening of the SN1 type of the aziridinium ion **5**; in this context it is rather strange that no substitution product, *i.e.*, *N*-(*n*-hexyl)-*N*-benzylaniline (**7**), was formed. Thus, route B, a one-step concerted Hofmann elimination, appears at this time a more satisfactory alternative.[7]

SCHEME I



Interestingly, all known deamination reactions of aziridines are thermal dissociation[8] of tertiary aziridines bearing activating nitrogen substituents and a photochemical dissociation of a highly substituted aziridine;[9] all these reactions yielded an olefin product.

Research is now under way in our laboratory in order to elucidate the reaction mechanism of this new deamination and widen the scope of the reaction.

Experimental Section

Glc analyses were performed with a Perkin-Elmer 900 gas chromatograph equipped with a flame ionization detector, using the internal standard method for qualitative and quantitative determinations. Calibration factors (area/weight coefficients) as well as authentic retention time ratios were evaluated with genuine pure samples. Ratio agreements were within 0.5%. The ideal column for these analyses was found to be a 0.5 × 200 cm column packed with 5% SF-96 on Chromosorb P (80–100 mesh) operating between 80 and 220°. Ir spectra were recorded with a Beckman IR-5 spectrometer (neat compound for

(1) "Ethylenimine," Dow Chemical Co., 1965, p 3.

(2) R. G. Kostyanovskii and O. A. Pan'shin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1554 (1964).

(3) This method afforded reasonable yields of ylides, as deduced from cleavage and rearrangement products of the reaction between dimethylbenzylamine and benzyne: A. G. Giumanini and A. R. Lepley, *Bull. Chem. Soc. Jap.*, **42**, 2359 (1969).

(4) "Expected" rearranged products are those from Stevens (ring enlargement and benzyl group migration), Sommelet, and perhaps 1,3 shift (to the aniline ring with ring enlargement or benzyl migration).

(5) A. Lattes and M. Rivière, *C. R. Acad. Sci.*, **262**, 1797 (1966), found that *N*-(β-chloroethyl)-*N*-methylaniline, treated with *n*-butyllithium, gave *N*-methylaniline. No mechanism was advanced for this reaction, which should involve the sequential steps of a dehydrohalogenation and devinylation. Devinylation by excess of a strongly basic reagent is simply the reverse reaction for the synthesis of *N*-vinylamines from acetylene and secondary amines in the presence of a trace of a basic catalyst: C. E. Schildkneckt, "Vinyl and Related Polymers," Wiley, New York, N. Y., 1952, pp 653, 654.

(6) An excellent presentation of the available evidences for the mechanism of aziridine ring opening is given in the book by O. C. Dormer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y., 1969, p 206 ff. Carbon unsubstituted aziridines open the ring according to an SN2 mechanism.

(7) J. P. N. Brewer, H. Heaney, and J. M. Jablonski, *Tetrahedron Lett.*, 4455 (1968), observed benzyne reactions of ethers and tertiary amines leading to C–O and C–N bond cleavage, respectively, which were rationalized in terms of an analogous sequence, *i.e.*, addition followed by internal β-proton abstraction with simultaneous alkene elimination. For other pertinent references, see A. R. Lepley and A. G. Giumanini, "Mechanisms of Molecular Migrations," B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1971.

(8) Reference 5, p 293 ff.

(9) A. Padwa and L. Hamilton, *J. Amer. Chem. Soc.*, **89**, 102 (1967).

liquid samples, KBr pellet for solids). Pmr spectra were recorded with a JEOL 60 spectrometer. Mass spectra were recorded with a low-resolution Perkin-Elmer 270 instrument equipped with gas chromatographic eluate direct inlet into the ion source, with target temperatures ranging from 100 to 220°, electron energy 75 eV, and acceleration potential 2 kV. Ten highest peaks are reported (*m/e* values, relative intensity, and eventual ion interpretation are given in brackets).[10]

Aziridine was purchased from Fluka (Switzerland). *N*-Benzylaniline was prepared in 60% yield according to a method described in the literature:[11] ir 3310 m, 3010 m, 2830 w, 1603 s, 1500 s, 1455 s, 1430 m, 1360 m, 1320 s, 1265 s broad, 1180 m, 1155 m, 1095 m, 1075 m, 1060 m, 1030 m, 985 m, 865 w, 745 s broad, and 690 cm^{-1} s; mass spectrum (glc inlet, target 220°) 91 (100, C_7H_7), 183 (52, parent peak), 182 (19, immonium ion), 106 (18, loss of C_6H_5, methylene immonium ion), 77 (17, C_6H_5), 65 (17), 92 (9), 104 (9), 184 (8), and 51 (8).

***N*-Benzylaziridine.**—Aziridine (386 mmol) was added dropwise under stirring below 0° to a hexane solution of *n*-butyllithium (0.96 *N*, 386 mmol) in an atmosphere of dry argon. To this mixture in the same conditions benzyl chloride (386 mmol) was added dropwise. The resulting mixture was stirred during 12 hr at room temperature, then chilled to −10°, and treated with cold brine, and the organic layer separated. The organic layer was extracted with 15% hydrochloric acid at −15°, the separated aqueous extract was dropped carefully into 40% aqueous KOH kept at −10°, and the mixture extracted with ether, dried over sodium sulfate, and vacuum distilled. **3** was obtained as a colorless liquid: bp 87–89° (12 Torr);[12] yield 46.8%; glc homogeneous; ir 3080 m, 3000 m, 2850 w, 2680 w, 1500 w, 1460 m, 1275 m, 1160 w, 1032 w, 1010 m, 821 w, 778 s, 695 cm^{-1} s; pmr (CCl_4, τ values in ppm from TMS) 2.74 (m, 5 Ar H), 6.77 (s, 2 H), 8.38 (def t, 2 cis-H), and 9.02 (def t, 2 trans H); mass spectrum (glc inlet, target 100°) 42 (100, C_2H_4N), 91 (60, C_7H_7), 65 (15, C_5H_5), 132 (14, loss of H, immonium ion), 51 (12), 105 (10, C_7H_7N), 77 (8, C_6H_5), 39 (8, C_3H_3), 133 (7, parent peak), and 103 (5, C_7H_5N).

Benzyne Addition to *N*-Benzylaziridine.—*n*-Butyllithium (1.13 *M* in hexane, 76 mmol) was added dropwise at −13° to a well-stirred solution of fluorobenzene (23 mmol) in the amine (38 mmol) under argon. The reaction appeared slightly exothermic and the mixture promptly acquired a lively red color which eventually faded to pale yellow. The mixture was kept at −13° during 15 hr and then quenched with cold water. Hydrochloric acid (15%, 2 equiv) chilled at −15° was used to extract the amines from the organic solution chilled at −10°; the aqueous solution with the amine salts was immediately carefully added to a solution of 40% potassium hydroxide (4 equiv) in water at −15° and the resulting mixture was extracted with ether. The hexane solution containing the neutral compounds revealed only little *n*-butylbenzene at the glc analysis. It was quickly identified by mass spectrometry.[13] Glc analysis of the amine solution showed unreacted **3** (28% recovery) and *N*-benzylaniline (**4**) (14%). At higher glc temperature an amine of apparent mol wt 266 (highest *m/e* peak in its mass spectrum)[14] in *ca.* 2% yield was detected. The identifications of **3** and **4** were made on the basis of glc enhancing technique, the mass spectra, and ir and pmr spectra on samples of sufficient purity obtained by distillation.

Attempts to prepare the assumed intermediate **6**, *N*-benzyl-*N*-vinylaniline, a hitherto unknown compound, met with failure.[15]

Registry No.—**2**, 462-80-6; **3**, 1074-42-6; **4**, 103-32-2.

Acknowledgment.—This work was supported in part by the Italian National Research Council (CNR) under Contract No. 7000143/03.

(10) We are indebted to Mrs. Armida B. Giumanini of the Center for Mass Spectrometry of this University for recording the spectra.

(11) F. G. Wilson and T. S. Wheeler, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1948, p 102.

(12) A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, **80**, 5203 (1958), reported bp 86–88° (12 Torr).

(13) H. M. Grubb and S. Meyerson, "Mass Spectrometry of Organic Ions," F. W. McLafferty, Ed., Academic Press, New York, N. Y., 1963, p 455 ff.

(14) The mass spectrum of this compound is inducive of a structure dimeric of **3** with peaks at the following *m/e* values: 91 (100), 120 (100), 175 (100), 266 (45), 134 (54), 92 (41), 146 (41), 65 (39), 132 (39), 119 (31), 42 (28), and 104 (27).

(15) Complete details will be reported at a later time.

Disproportionation of 2-Iodothiophene in Dimethyl Sulfoxide

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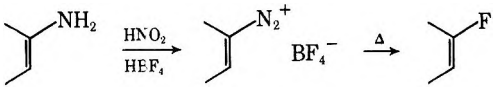
Fluorination of aromatic and heteroaromatic compounds is vested with both a theoretical and a practical interest. The method of choice for the introduction of fluorine into such structures is the two-step sequence of the preparation of a diazonium fluoroborate followed by its decomposition (Schiemann).



This method suffers from two serious drawbacks: the starting amine may not be readily available and not always do diazotation and decomposition follow the desired course.[2] A different access to fluorinated heteroaromatics in particular would therefore be desirable and with this goal we attempted to prepare 2-fluorothiophene[3] (**1**).

We attempted to make use of a nucleophilic displacement of the iodide ion by the fluoride ion in DMSO at near reflux temperature, treating 2-iodothiophene (**2**) with ammonium fluoride. To our surprise, no evidence of even trace amounts of **1** was found by gas chromatography–mass spectrometry, but a few new higher boiling compounds were formed together with some thiophene (**3**) and dimethyl sulfide. The two major higher boiling components were identified on the basis of their mass spectra as 2,5-diiodothiophene (**4**, 25%) and 5-iodo-2-thiophenaldehyde (**5**, 1.5%). Vpc–mass spectrometric inspection of other minor components of the reaction mixture ruled out the presence of isomeric diiodothiophenes and of other polyiodothiophenes. Since the spectra of the four isomeric diiodothiophenes show very similar fragmentation patterns with only tiny intensity differences, the 2,4 and 3,4 isomers were ruled out on the basis of vpc retention time ratios (Table I) and enhancing technique. Final identification of **4** was achieved by ir and pmr on an analytical sample. Vpc properties and mass spectral fragmentation of **5** were identical with those of a sample prepared by an independent route. Two well-separated minor vpc peaks eluted at much higher temperature had an identical mass spectrum fitting the elemental composition and the expected fragmentation pattern for *x*,*x*′-diiododithienylmethanes (**6**).

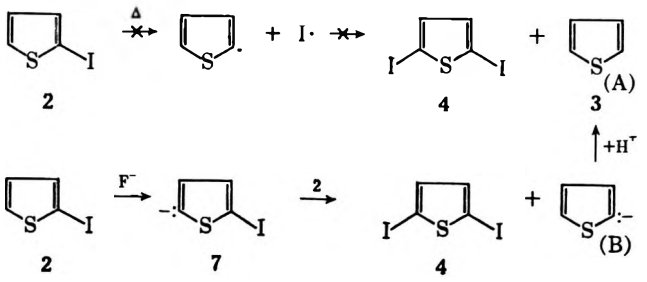
The formation of **4** may be rationalized either according to a radical mechanism (Scheme I, route A) or an

(1) (a) Work supported in part by CNR Contract 7000143-03. (b) Chemistry student.

(2) A. Roe, *Org. React.*, **5**, 194 (1949).

(3) All fluorinated thiophenes are known, but their syntheses are very costly and difficult. Compound **1** was prepared in 10–15% yield by chlorine–fluorine exchange with SbF_3 [R. T. Van Vleck, *J. Amer. Chem. Soc.*, **71**, 3256 (1949)] or by reaction of the dangerous $FClO_3$ with 2-thienyllithium at −72° in 52% yield [R. D. Shuetz, D. D. Taft, J. P. O'Brien, J. L. Shea, and H. M. Mork, *J. Org. Chem.*, **28**, 1420 (1963)]. The latter method, also used to prepare the 3 isomer, gives an inseparable mixture of the desired compound with thiophene and is therefore impractical.

SCHEME I



ionic pathway (Scheme I, route B) with catalysis by ammonium fluoride, which may be considered a strong base in cation solvating dipolar aprotic solvents. The intermediate iodinated anion **7** would then undergo iodine exchange with **2**. This type of exchange was recently observed and studied in detail by M. Reinecke,[4a] who interpreted and extended previous findings by Vaitiekunas.[4b]

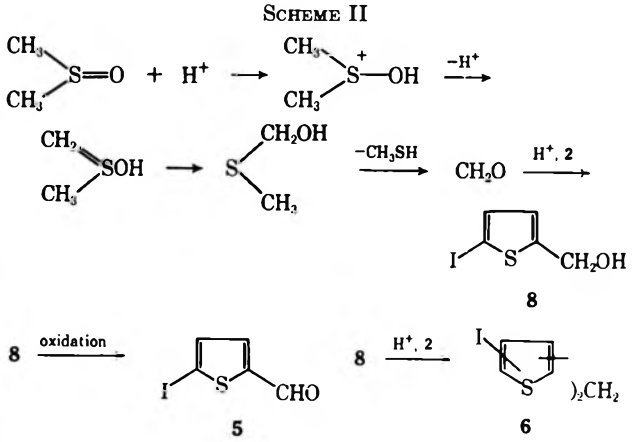
In order to establish the actual route to **4**, we first checked whether the reaction was purely thermal. Prolonged heating of pure **2** at reflux temperature did not yield any **4**. Uv irradiation was ineffective as well. This is in agreement with the fact that our reaction ran with equal yield in the dark. When **2** was heated with *N*,*N*-dimethylaniline, the expected products of a radical attack by the iodine atom or the thienyl radical on this substrate failed to materialize. Moreover, the absence of substantial amounts of free iodine and of the radical coupling product, 2,2′-dithienyl, run counter to the radical mechanism.

At this stage it was interesting to determine the role of DMSO and therefore we carried out the reaction of **2** in DMSO without fluoride. The diiodo derivative **4** was again formed in comparable yields. Parallel experiments with and without fluoride at exactly the same conditions of temperature and concentration showed that the fluoride reaction was much faster. From these results we believe that the reaction is ionic, since it is favored by presence of a base (F^-). DMSO itself may act as a proton acceptor[5] in a much less efficient way; indeed more drastic conditions and longer reaction times were required to achieve comparable yields.

The formation of the diiodothiophene **4** may be explained by a third alternative route, shown to be the mechanistic pathway through which some 2-bromothiophenes undergo selective disproportionation to thiophenes and 2,5-dibromothiophenes and discovered by Wynberg[6] recently. Though at present it is not possible to clearly rule out this possibility on a rigorous experimental basis, it must be noted that the medium for Wynberg's reaction is strongly acidic, a condition which is not realized for either DMSO alone or the DMSO–ammonium fluoride system.

The production of the iodoaldehyde **5** must involve the material participation of DMSO, which contributes the new carbon and oxygen atom. Its appearance is therefore to be related to a reaction of **2** with a decomposition product of DMSO. We propose the mechanism outlined in Scheme II. It moves its steps from

SCHEME II



the acid-catalyzed rearrangement–decomposition of DMSO in acidic solution.[7] Formaldehyde thus formed reacts under acidic catalysis (better than neutral, more likely than basic) with **2** to yield the iodo alcohol **8**, which displays reductive properties towards some of the species present in solution in going to the observed product **5** or alkylating properties to yield **6**. The latter reaction is a well known side reaction in the analogous preparation of 2-thenyl chloride from thiophene and formaldehyde in hydrochloric acid.[8] The fact that **5** and **6** are also present when the reaction was run without fluoride may be interpreted by the assumption of a high-temperature self-ionization of DMSO or assuming that a trace of an acidic product (HI) may trigger the usual decomposition of DMSO.

Experimental Section

Materials and Apparatus.—2-Iodothiophene (**2**) (Eastman) was washed with aqueous sodium thiosulphate, dried, and distilled before use; glc analysis ruled out the presence of isomeric and polyhalogenated material. Anhydrous ammonium fluoride (kept in a desiccator with P_2O_5), DMSO, and *N*,*N*-dimethylaniline were purchased from Erba (Italy). *N*-(2-Thenyl)-*N*-methylaniline was available from previous work.[9] Pure samples of 2,4- and 3,4-diiodothiophene were kindly supplied by Professor M. Tiecco of this university. Gas–liquid chromatography analyses were performed with a Perkin-Elmer 900, using a flame ionization detector on a variety of columns. Optimal results were obtained on an SF 96 4% Chromosorb P (60–80 mesh) 2-m column, to which data in Table I refer. Product yields were determined with 3,4-diiodothiophene as internal standard. Mass spectra were recorded with a Perkin-Elmer 270 equipped with glc and solid inlet operating at 75 eV and 100 mA, acceleration voltage 2000 V, target temperature 150–220°. Infrared spectra were recorded with a Beckman IR-5 on the neat compounds (liquids) or with the KBr pellet technique. Proton

TABLE I

GLC RETENTION TIME RATIOS AT 140° OF COMPOUNDS RELATED TO THE 2-IODOTHIOPHENE REACTION IN DMSO

5-Iodo-2-thiophenaldehyde (**5**)	0.80
2,5-Diiodothiophene (**4**)	1.00
2,4-Diiodothiophene	1.10
3,4-Diiodothiophene	1.32

(4) (a) M. Reinecke, *J. Amer. Chem. Soc.*, **90**, 511 (1968), and private communication; (b) A. Vaitiekunas and F. F. Nord, *ibid.*, **75**, 1764 (1953).

(5) DMSO exhibits excellent complexing properties toward cations and superior hydrogen bonding properties even with organic compounds; see, *e.g.*, the hydrogen bonding with acetylenes. The solvating power for the anion is much lesser, thus leading to enhancement of the nucleophilicity of the relatively free anions.

(6) R. M. Kellogg, A. P. Shaap, E. T. Harper, and H. Wynberg, *J. Org. Chem.*, **33**, 2902 (1963).

(7) V. J. Traynelis and W. C. Hergenrother, *ibid.*, **29**, 221 (1964); *J. Amer. Chem. Soc.*, **86**, 298 (1964).

(8) Y. Inaba, G. Kimura, and M. Kinoene, Japanese Patent 9586 (1962).

(9) A. G. Giumanini and G. Lercker, unpublished results.

magnetic resonance spectra were recorded with a JEOL 60 in $CDCl_3$. Melting points were determined with a Kofler apparatus and are not corrected.

2-Iodothiophene (2) and NH_4F in DMSO.—2-Iodothiophene (2, 6.49 g, 30.9 mmol), ammonium fluoride (0.31 g, 8.5 mmol), and DMSO (6 ml) were stirred in a round-bottom flask with reflux condenser and calcium chloride valve at 170–175° (oil bath) during 6 hr. The reaction course was followed by glc and a continuous buildup of 2,5-diiodothiophene was observed during this time. The dark reaction mixture was taken up with boiling ether, filtered with Celite, washed with water, dried with sodium sulfate, and analyzed. Glc analysis of the mixture revealed unreacted 2 without contamination by the 3 isomer and a new major peak preceeded by a small peak and followed by other smaller impurities at much higher retention times. The first new peak had a retention time ratio of 0.80 (see Table I) and was identified on this basis, by enhancing technique, and by its mass spectrum as belonging to 5-iodothiophenealdehyde (5). The glc-determined yield of 5 was 1.5%. The largest new peak was analogously identified as 2,5-diiodothiophene (4, 25%, retention time ratio 1.00). While no detectable peaks had molecular ions which fitted the polyiodothiophene molecular composition, two small but still appreciable peaks had identical mass spectra with prominent ions at m/e values of 432 (M^+), 305 (−I, base peak), 178 (−2I, base peak in the less retained isomer), 134 ($-CI_2S$), 96 (C_5H_4S), and 82 (C_4H_2S). Distillation of the mixture allowed recovery of pure 2-iodothiophene, uncontaminated by the 3 isomer as shown by its ir.[10] The residue from this distillation was chromatographed on a 1.8 × 21 cm silica gel column using n-hexane as eluent; a white solid was obtained, which was recrystallized from ethanol, mp 36–37°, mmp with 2,5-diiodothiophene (4) 38.5–39.5°. This compound, which corresponds to the product with retention time ratio 1.00, had an ir spectrum identical with that of authentic 4. The pmr spectrum showed a single peak as expected at τ 3.12 ppm. The reaction mixture showed no peak for either isomeric diiodothiophenes or fluorothiophenes, but small amounts of thiophene and dimethyl sulfide were detected by glc and confirmed by mass spectrometry. No attempts to optimize the yield of 4 were made, but lower and higher temperatures were found to give too slow a reaction and extensive tarring, respectively.

2-Iodothiophene in DMSO.—2 (7.45 g, 35.4 mmol) and DMSO (5.50 g, 70.5 mmol) were heated in the dark at 190–195° during 18 hr to yield 18% (glc) of 2,5-diiodothiophene (4), whose identification was carried out as described in the fluoride experiment. Thiophene and dimethyl sulfide were present in the reaction mixture as well as the two isomers 6 and the aldehyde 5 in tiny amounts. Isomeric diiodothiophenes were absent.

Irradiation of 2-Iodothiophene (2).—2 was irradiated during 18 hr without solvent at room temperature with a 254-nm mercury lamp. No 4 was formed.

"Parallel" Reactivity Tests of 2-Iodothiophene.—2 (30 mmol) was heated in DMSO (75 mmol) with and without ammonium fluoride (11 mmol) at 165–170° during 6 hr to yield, respectively, 5 and 0.5% 4. In either case only traces of free iodine were present.

Thermal Stability of 2-Iodothiophene (2).—2 was heated without solvent during 15 hr at 190° (gentle reflux). No new compound could be detected by glc analysis.

2-Iodothiophene (2) and N,N-Dimethylaniline.—2 (4.08 g, 19.4 mmol) and N,N-dimethylaniline (3.47 g, 28.8 mmol) were heated from 100 to 180° during 1.5 hr without any color change. Glc analysis showed no changes in the composition of the mixture. After 20 min at 180° the mixture turned dark blue, but glc analysis ruled out the formation of 4 and of N-(2-thenyl)-N-methylaniline (9). Heating the above mixture at 160° during 1 hr caused complete solidification; ether extraction did not yield any 4; and digestion with aqueous sodium bicarbonate at 100° and extraction with ether gave a mixture which did not contain either 4 or 9.

2,5-Diiodothiophene (4).—This compound was prepared in 17% yield from thiophene (0.121 mol), iodine (0.243 mol), and mercuric oxide (0.184 mol) in benzene according to a procedure described in the literature for 2-iodothiophene.[11] The product was recrystallized from ethanol: mp 39–40° (lit.[12] 40°); pmr ($CDCl_3$) singlet at τ 3.12 ppm; ir (KBr) 2825 (w), 2300 (w), 1380 (w), 1198 (w), 947 (m), 918 (w), 783 (s), and 727 cm^{-1} (w). The mass spectrum was essentially identical with that reported in the literature.[13] Distillation of the reaction mixture gave 24% of pure 2-iodothiophene (2).

5-Iodo-2-thiophenaldehyde (5).—This compound was prepared (18%) by treatment of 2 with n-butyllithium at −70°, followed by reaction with dry dimethylformamide in ether–hexane according to a described procedure:[14] mp 52° (lit.[15] 51–52°); ir (KBr) 1528 (s), 1503 (w), 1404 (s), 1370 (m), 1288 (m), 1223 (s), 1190 (w), 1043 (s), 950 (m), 807 (s), 743 (s), 675 (w), and 664 cm^{-1} (s); pmr ($CDCl_3$) singlets at δ 7.40 and 9.76 ppm; mass spectrum (75 eV, solid inlet 50°, chamber 150°) m/e 238 (M^+, base peak), 237 (2-I-thenoyl), 210 (C_4H_4SI), 209 (C_4H_3SI), 128 (HI), 127 (I), 111 (−I), 110 (−HI), 82 (−I, −CHO), 57, 45, 39.

Registry No.—DMSO, 67-68-5; **2**, 3437-95-4; **4**, 625-88-7; **5**, 5370-19-4.

(10) The ir spectra of the isomeric monoiodothiophenes are very different with most bands not overlapping: S. Gronowitz and R. Håkansson, *Ark. Kemi*, **16**, 309 (1960).

(11) V. Meyer and H. Kreis, *Ber.*, **17**, 1558 (1884); W. Minnis, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 357.

(12) J. Volhard, *Justus Liebigs Ann. Chem.*, **267**, 172 (1892).

(13) S. Gronowitz and B. Åkesson, *Ark. Kemi*, **28**, 155 (1967).

(14) R. Guilard, P. Fournari, and M. Person, *Bull. Soc. Chim. Fr.*, 4121 (1967).

(15) R. E. Atkinson, R. F. Curts, and J. A. Taylor, *J. Chem. Soc. C*, 578 (1967).

N-Phenyl-1-thio-1,2-azetidinedicarboximide, the Phenylthiohydantoin of Azetidine-2-carboxylic Acid[1]

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L-Azetidine-2-carboxylic acid (1), a naturally occurring antimetabolite of proline[2] that has been isolated from the Liliaceae,[3] is unstable in mineral acids and the four-membered azetidine ring undergoes degradative ring-opening reactions.[4] Derivatives of 1 prepared in acidic media are thus suspect unless the integrity of the azetidine moiety can be shown to be intact. In our studies on the behavior of ring homologs of α-imino acids related to proline and their 2,4-dinitrophenyl-, 6-dimethylaminonaphthalene-1-sulfonyl-, and 3-phenyl-2-thiohydantoin (PTH) derivatives in various chromatographic systems,[5] it was necessary to prepare such derivatives of 1 including the PTH derivative **7a**, since 1 is the first member of this homologous series.

The procedure of Edman[6] as modified by Sjöquist[7] for the preparation of PTH amino acids, which involves the cyclization of the phenylthiocarbamoyl amino acid in aqueous acetic acid–hydrogen chloride, when applied to 1 did not yield 7a. Heating 1 in toluene with excess phenyl isothiocyanate[8] likewise gave intractable mixtures when examined by tlc. The feasibility of cycliz-

(1) Supported in part by Grant CA-06432, United States Public Health Service.

(2) L. Fowden, D. Lewis, and H. Tristam, *Advan. Enzymol.*, **28**, 89 (1967).

(3) (a) L. Fowden, *Nature (London)*, **176**, 347 (1955); (b) A. I. Virtanen, *ibid.*, **176**, 984 (1955).

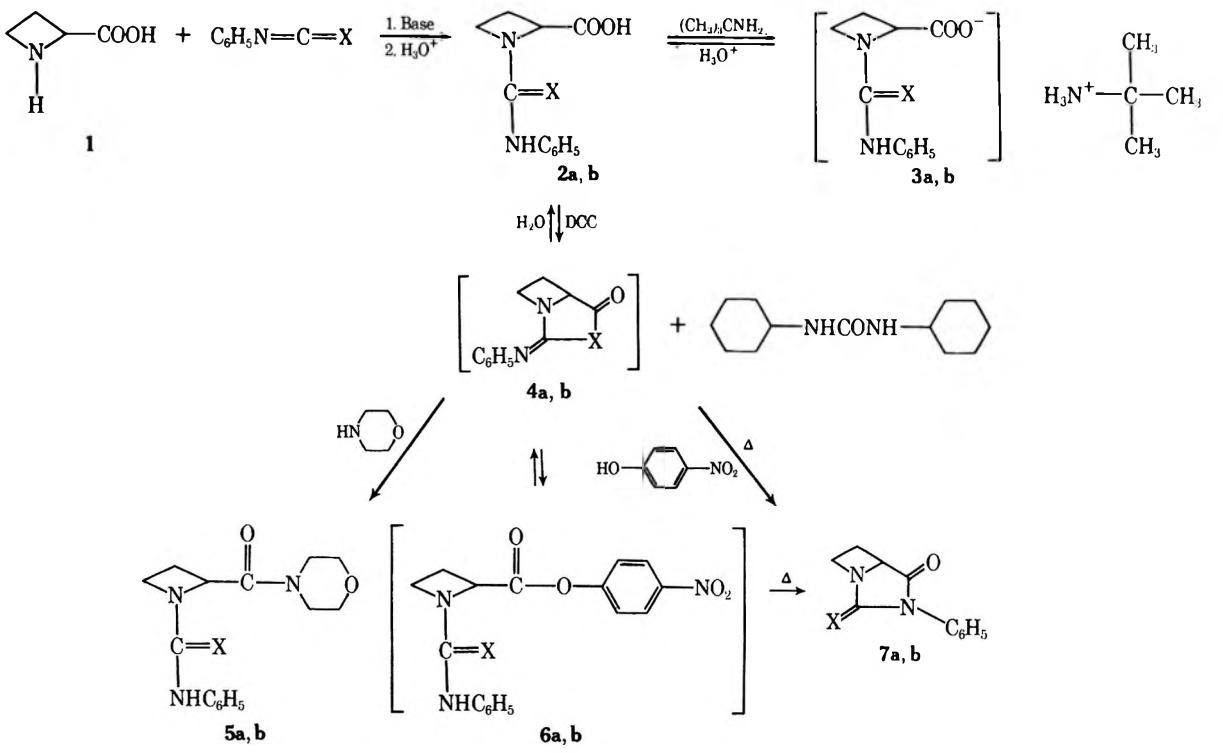
(4) L. Fowden, *Biochem. J.* **64**, 323 (1956).

(5) H. T. Nagasawa, P. S. Fraser, and J. A. Elberling, *J. Chromatogr.*, **44**, 300 (1969).

(6) P. Edman, *Acta Chem. Scand.*, **4**, 277 (1950).

(7) J. Sjöquist, *Ark. Kemi*, **11**, 129 (1957).

(8) H. T. Nagasawa, J. A. Elberling, P. S. Fraser, and N. S. Mizuno, *J. Med. Chem.*, **14**, 501 (1971).



a, series, X = S
b, series, X = O

ing the phenylthiocarbamoyl derivative **2a** under mild conditions to the 2-phenyliminothiazolidin-5-one **4a**, followed by *thermally* rearranging[9] the latter to **7a** in anhydrous aprotic solvents, was then investigated.

Reaction of **2a** with dicyclohexylcarbodiimide (DCC) in dry acetonitrile at room temperature gave an immediate reaction as evidenced by the precipitation within 30 min of dicyclohexylurea in 80% yield. The formation of the expected 2-phenylimino-5-thiazolidinone **4a**, a compound tautomeric with the 2-anilino-5-thiazolinones proposed by Edman[9] as the intermediate in the acid-catalyzed cleavage of phenylthiocarbamoyl peptides, was adduced by the appearance of a broad peak at 235 nm (shoulder, 275 nm) in the uv spectrum (Figure 1). The reactivity of **4a**, cogently demonstrated by its acylation of morpholine at room temperature (**4a** → **5a**), precluded its isolation.

Heating the solution of **4a** under reflux gave rise to gradual formation of **7a** with an absorption maximum at 277 nm (Figure 1). The appearance of isosbestic points at 253 and 295 nm was indicative of the presence of only two ultraviolet-absorbing compounds in the reaction mixture, *viz.*, **4a** and **7a**. After 4 hr, the latter was isolated. This thermal rearrangement of **4a** was highly unpredictable, leading frequently to racemized **7a** (see Experimental Section), and another route to **7a** was investigated. The *p*-nitrophenyl ester of the phenylthiocarbamoyl imino acid, *viz.*, **6a**, prepared *in situ* from **4a**, more readily rearranged to **7a**. In fact, **6a** proved to be a superior intermediate; not only was the reaction time reduced considerably, but **7a** was obtained with retained optical activity.[10]

(9) P. Edman, *Acta Chem. Scand.*, **10**, 761 (1956).

(10) Since the reaction proceeds smoothly whether the *p*-nitrophenol is added after the imino thiazolidinedione is formed, or before the addition of DCC itself, the intermediate here must be the *p*-nitrophenyl ester **6a**, and the accelerated reaction is not due merely to catalysis by *p*-nitrophenol. In the latter mode of addition, the formation of **4a** is likely bypassed to give **6a** directly.

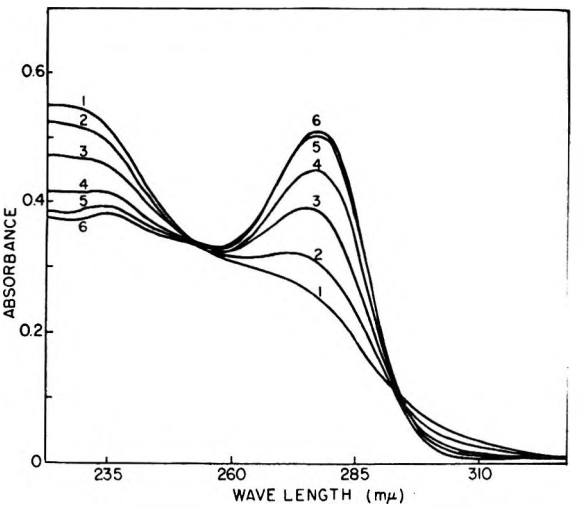


Figure 1.—The conversion of **4a** to **7a**. Aliquots of the reaction mixture were diluted with acetonitrile and scanned (1) immediately after removal of dicyclohexylurea, (2) after heating under reflux for 5 min, (3) for 15 min, (4) for 30 min, (5) for 60 min, and (6) for 120 min.

In order to correlate the major infrared bands of **7a** with that of the higher ring homologs already described[8,11] and to identify its fragmentation ions on electron impact, the corresponding oxygen analog **7a** was prepared for comparison. In this sequence (**b** series), **4b** was so reactive that it rapidly absorbed traces of moisture and hydrolyzed back to **2b** on prolonged heating, and **7b** could not be prepared except through the *p*-nitrophenyl ester **6b**.

The fragmentation pattern exhibited by **7a** on electron impact was quite analogous to the mass spectrum of PTH proline.[12] The peak at *m/e* 55, which can be

(11) L. K. Ramachandran, A. Epp, and W. B. McConnell, *Anal. Chem.*, **27**, 1734 (1955).

(12) B. W. Melvas, *Acta Chem. Scand.*, **23**, 1679 (1969).

ascribed to the four-membered 1-azetine radical ion, (**8**) appears to be characteristic for this compound in the same manner as the 1-pyrroline radical ion (**9**, *m/e* 69) is for PTH proline.[12] The oxygen analog **7b** fragments to give the phenyl isocyanate radical ion, $C_6H_5NCO\cdot^+$ (*m/e* 119, $\%\Sigma_{40}$ 25.3), as base peak; and again, the diagnostic **8** appeared as a fairly intense peak at *m/e* 55.

8

9

The 2,4-dinitrophenyl- and the 6-dimethylaminonaphthalene-1-sulfonyl derivatives of **1** have also been prepared and are reported here. These, as well as **7a**, are useful derivatives for the chromatographic and/or mass spectrographic identification of azetidine-2-carboxylic acid (**1**) in biological systems.[4,8]

Experimental Section

Melting points were taken on a Mettler FP-2 apparatus and are corrected; optical rotations were determined in a Perkin-Elmer Model 141 polarimeter. Spectrophotometers used were: uv, Beckman DK-2A; ir, Beckman IR-10; nmr, Varian A-60A; mass spectra, Hitachi Perkin-Elmer RMU-6. Microanalyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y., and Galbraith Laboratories, Knoxville, Tenn.

***tert*-Butylammonium 1-(Phenylthiocarbamoyl)-L-azetidine-2-carboxylate (3a).**—**1**[13] (303 mg, 3.0 mmol), 30 ml of CH_3CN, 10 ml of dry pyridine, and 0.42 g (3.1 mmol) of C_6H_5NCS were heated under reflux for 4 hr and then concentrated to a syrup under reduced pressure. The residue was diluted with 5% $NaHCO_3$ solution, then extracted three times with ether. The bicarbonate extract was acidified to pH 2 with 6 *N* HCl and extracted repeatedly with *ca.* 100-ml portions of EtOAc, and the combined EtOAc extracts were washed (H_2O), dried (Na_2SO_4), and evaporated to dryness. The residue was recrystallized from MeOH containing 2 ml of *tert*-butylamine by addition of ether, 844 mg and 24 mg (crop 2), yield 93%. The analytical sample was recryst from MeOH–ether, mp (broad) 170–182°, $[\alpha]^{27}D$ −367° (*c* 1.47, 95% EtOH).

Anal. Calcd for $C_{15}N_{23}N_3O_2S$: C, 58.2; H, 7.49; N, 13.58; S, 10.36. Found: C, 58.06; H, 7.58; N, 13.44; S, 10.17.

***N*-Phenyl-1-thio-1,2-azetidinedicarboximide (7a). By Thermal Rearrangement of 4a.**—Free **2a** was obtained from **3a** (155 mg, 0.50 mmol) by extracting a pH 2 solution of the latter with EtOAc. The extract was dried (Na_2SO_4) and evaporated to dryness below 30°, and the residue was further dried *in vacuo* (128 mg) and dissolved in 10 ml of spectrophotometric grade CH_3CN; to this was added 103 mg (0.50 mmol) of dicyclohexylcarbodiimide (DCC). After 30 min the precipitate of dicyclohexylurea (89 mg, 80%, mp 231–232°) was removed by filtration and rinsed with CH_3CN, and the combined filtrate (29.7 ml) was heated under reflux in a volumetric t-tube. Aliquots (100 μl) were taken after 0, 5, 15, 30, 60, and 120 min of reflux, diluted to 50 ml with CH_3CN, and the uv spectra recorded (Figure 1). After 2 hr of additional reflux, the reaction solution was evaporated to dryness ad the product was purified by preparative tlc on 1 mm thick silica gel PF_{254} (dried at 110° for 4 hr just before use) using $CHCl_3$ as solvent (four passes). and recrystallized from CH_2Cl_2–petroleum ether (bp 30–60°): yield 55 mg; mp 128–130°; $[\alpha]^{28}D$ −65.1° (*c* 0.335, CH_3CN); uv max (EtOH) 235, 279 nm (log ε 3.96, 4.14); ir (KBr) 1755, 1740 (C=O), 1375 (CH_2), 1325 cm^{-1} (C=S); ir (CH_2Cl_2) 1760 (C=O). 1375 (CH_2), 1330 cm^{-1} (C=S); nmr ($CDCl_3$) δ 2.83 (m, 2, H-3), 4.31 (m, 2, H-4), 4.90 (t, 1, $J_{2,3}$ = 8 Hz, H-2); mass spectrum (70 eV, 100°) *m/e* (rel intensity) 218 (M^+, 56.7), 189 (5.1), 162 (11.5), 149 (17.5), 137 (6.1), 135 (100), 132 (15.5), 104 (14.1), 91 (10.0), 77 (65.5), 72 (16.1), 67.5 (4.3), 55 (26.3), 51 (37.8). Crop 2 contained 17 mg, mp 125–126° (66% yield).

Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.54; H, 4.63; H, 13.00; S, 14.73.

(13) Purchased from Calbiochem Corp., Los Angeles, Calif. The optical rotation of this sample lot was reported to be $[\alpha]^{31}D$ −123° (c 3.5, H_2O).

This thermal rearrangement was unpredictable, especially when the solvents were EtOAc, dioxane, or a less pure grade of CH_3CN, and reaction times up to 72 hr were necessary for completion. Prolonged reaction times and multiple chromatographic manipulations caused racemization, which was reflected in the *rise* in melting point of the product: thus, for mp 131–134°, $[\alpha]^{28}D$ −59.5°; mp 134–138°, $[\alpha]^{28}D$ −46.8°; mp 160–166°, $[\alpha]^{28}D$ −15.8°; mp 163–166°, $[\alpha]^{28}D$ −11.0°; mp 166–167°, $[\alpha]^{28}D$ 0. The racemic product was analyzed, uv max (EtOH) 235, 279 nm (log ε 3.97, 4.14).

Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.53; H, 4.68; N, 12.88; S, 14.70.

7a *via* *p*-Nitrophenyl Ester 6a.—**2a** was coupled with DCC as above. After removal of the dicyclohexylurea, 278 mg (2.0 mmol) of *p*-nitrophenol was added, and the reaction mixture was heated under reflux for 2 hr and then diluted with EtOAc. The mixture was extracted repeatedly with 5% Na_2CO_3 solution until no more yellow color was extracted, washed (H_2O), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The product was purified by preparative tlc as above and recrystallized from CH_2Cl_2–petroleum ether, 61 mg, mp 130–132°, and crop 2, 14 mg, mp 126–127° (69% yield), $[\alpha]^{27}D$ −62.4° (*c* 1.05, CH_3CN).

7a was also obtained in reasonable yield when excess *p*-nitrophenol (1.0 g) was added *before* the DCC and the reaction was allowed to proceed at room temperature overnight. After work-up essentially as above, 44 mg was obtained, mp 128–130°, $[\alpha]^{28}D$ −66.5° (*c* 0.783, CH_3CN), and 15 mg, mp 126–127°, $[\alpha]^{28}D$ −67.2° (*c* 0.603, CH_3CN). The ir, uv, nmr, and mass spectra of the **7a** prepared *via* the *p*-nitrophenyl ester here were identical with the spectra of the optically active **7a** prepared above by the thermal rearrangement of **4a**.

Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83; S, 14.69. Found: C, 60.43; H, 4.73; N, 13.11; S, 14.82.

1-(Phenylthiocarbamoyl)-L-azetidine-2-carbomorpholide (5a).—**2a** was coupled with DCC as above. After removal of the dicyclohexylurea, 0.50 g of morpholine was added to the intermediate **4b**. Tlc ($CHCl_3$–88% HCOOH, 100:5; silica gel F_{254}) of an aliquot of the reaction mixture 40 min after addition of morpholine indicated that a new product, R_f 0.31, had formed. After overnight reaction at room temperature, the mixture was diluted with water and extracted four times with $CHCl_3$, and the combined $CHCl_3$ extract was washed (H_2O), dried (Na_2SO_4), and evaporated to dryness. Recrystallization of the residue from CH_2Cl_2–petroleum ether gave 128 mg (84%) of **5a**, colorless needles, mp 194–197° dec. After two more recrystallizations, the product melted at 195–198° dec; $[\alpha]^{28}D$ −284° (c 1.09, CH_3CN); ir (KBr) 3305 (NH), 1650 (amide C=O), 1550 (NCS I), 1400 cm^{-1} (NCS II).

Anal. Calcd for $C_{15}H_{19}N_3O_2S$: C, 58.99; H, 6.27; N, 13.76; S, 10.50. Found: C, 58.76; H, 6.33; N, 13.66; S, 10.60.

1-(Phenylcarbamoyl)-L-azetidine-2-carboxylic Acid (2b).—To a solution of 808 mg (8.0 mmol) of **1** in 60 ml of H_2O containing 3.39 g of KOH was added at room temperature a fivefold excess of phenyl isocyanate in three equal portions over 1.5 hr. After 4 hr of stirring at room temperature, the reaction mixture was worked up as for **3a** above and the product was recrystallized from acetone–hexane: 1.48 g (84%); mp (after recrystallization again from acetone–hexane), 147–151°; $[\alpha]^{27}D$ −163° (*c* 1.55, 95% EtOH); ir (KBr) 3400 (NH), 1745, 1725 (COOH), 1620 (amide I), 1535 cm^{-1} (amide II).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.85; H, 5.60; N, 12.91.

L-*N*-Phenyl-1,2-azetidinedicarboximide (7b).—To a solution of 440 mg (2.0 mmol) of **2b** in 40 ml of CH_3CN (spectrophotometric grade) was added 412 mg (2.0 mmol) of DCC, whereupon dicyclohexylurea precipitated almost immediately. *p*-Nitrophenol (1.0 g) was then added and the reaction mixture was heated under reflux for 24 hr. Crude **7b** was obtained by work-up similar to the procedure for **7a** and was recrystallized from CH_2Cl_2–petroleum ether: yield 82 mg; mp 117–118°; $[\alpha]^{29}D$ −20.3° (c 0.777, CH_3CN); ir (KBr) 1785, 1710 (C=O's), 1380 cm^{-1} (CH_2); ir (CH_2Cl_2) 1790, 1725 (C=O's), 1380 cm^{-1} (CH_2); nmr ($CDCl_3$) δ 2.78 (m, 2, H-3), 4.01 (m, 2, H-4), 4.73 (t, 1, $J_{2,3}$ = 8 Hz, H-2); mass spectrum (70 eV, 100°) *m/e* (rel intensity) 202 (M^+, 33.1). 174 (19.0), 146 (4.8), 119 (100), 104 (12.9), 91 (25.6), 77 (15.0), 64 (16.2), 55 (18.0). Crop 2 contained 41 mg: mp 115–117°; $[\alpha]^{29}D$ −19.7° (*c* 0.910, CH_3CN); total yield 30% (best yield was 49%).

Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.40; H, 4.91; N, 13.77.

1-(Phenylcarbamoyl)-L-azetidine-2-carbomorpholide (5b).—The intermediate **4b** was prepared from 220 mg (1.0 mmol) of **2b** and 206 mg (1.0 mmol) of DCC in 25 ml of CH_3CN as above. Morpholine (0.50 g) was added after 3 min. The reaction time and work-up followed the procedure for **5a**. The product was purified by preparative tlc on 1 mm silica gel PF_{254} using $CHCl_3$–HOAc (95:5) (5–7 passes) and recrystallized from CH_2Cl_2–petroleum ether, 73 mg (25% yield), mp 186–187°. After recrystallization twice from CH_2Cl_2–petroleum ether, the product had mp 188–189°; $[\alpha]^{28}D$ −201° (c 1.11, CH_3CN); ir (KBr) 3260 (NH), 1665, 1640 (amide C=O's), 1535 cm^{-1} (amide II).

5b was obtained in 53% yield when 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride[14] was substituted for DCC in this reaction. The crude product was recrystallized directly without prior purification by tlc after removal of the water-soluble urea: mp 186–188°, $[\alpha]^{28}D$ −197° (*c* 1.05, CH_3CN).

Anal. Calcd for $C_{15}H_{19}N_3O_3$: C, 62.27; H, 6.62; N, 14.52. Found: C, 62.19; H, 6.91; N, 14.61.

1-(2,4-Dinitrophenyl)-L-azetidine-2-carboxylic Acid.—This DNP derivative of **1** was prepared in 80% yield according to the dinitrophenylation procedure of Rao and Sober,[15] and recrystallized from H_2O-saturated CH_2Cl_2–hexane, mp 119–120°.

Anal. Calcd for $C_{10}H_9N_3O_6$: C, 44.95; H, 3.40; N, 15.73. Found: C, 44.87; H, 3.26; N, 15.57.

1-(5-Dimethylaminonaphthalene-1-sulfonyl)-L-azetidine-2-carboxylic Acid, Cyclohexylammonium and Piperidinium Salts.—The dansyl derivative of **1** was prepared in the same manner as for the higher ring homologs[8] except that the free imino acid instead of the methyl ester was used. Recrystallization of the dansyl derivative from EtOH containing excess cyclohexylamine afforded the cyclohexylammonium salt in 80% yield, mp (broad) 170–181° after recrystallization from EtOH. Tlc[5] indicated that this product was homogeneous.

Anal. Calcd for $C_{22}H_{31}N_3O_4S$: C, 60.95; H, 7.21; N, 9.69. Found: C, 61.08; H, 7.02; N, 9.71.

The piperidinium salt was prepared in 89% yield by substituting piperidine for cyclohexylamine in the above procedure, and recrystallized from CH_2Cl_2–petroleum ether, mp 117–123°.

Anal. Calcd for $C_{21}H_{29}N_3O_4S$: C, 60.12; H, 6.97; N, 10.02. Found: C, 59.94; H, 7.17; N, 9.79.

Registry No.—**2b**, 32970-20-0; **3a**, 32970-21-1; **5a**, 32970-22-2; **5b**, 32970-23-3; **7a**, 32970-24-4; **7b**, 32970-25-5; 1-(2,4-dinitrophenyl)-L-azetidine-2-carboxylic acid, 32970-26-6; 1-(5-dimethylaminonaphthalene-1-sulfonyl)-L-azetidine-2-carboxylic acid, 32970-27-7 (cyclohexylammonium salt), 32970-28-8 (piperidinium salt).

Acknowledgment.—We are indebted to Mrs. O. Hamerston for the ir spectra, Miss F. N. Shirota for the nmr spectra, and Mr. J. McMahon for the mass spectra.

(14) J. C. Sheehan, J. Preston, and P. A. Cruickshank, *J. Amer. Chem. Soc.*, **87**, 2492 (1965).

(15) K. R. Rao and H. A. Sober, *J. Amer. Chem. Soc.*, **76**, 1328 (1954).

Beckmann Rearrangements of Tetrahydro-α-santonin Oximes

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The Beckmann rearrangement[1,2] of cis- and trans-fused tetrahydro-α-santonin oximes has been carried out. Cis- and trans-fused tetrahydro-α-santonins (I) were prepared by the reported method,[3] and converted to their oximes (II) by the usual method.

The Beckmann rearrangement of *cis*-tetrahydro-α-santonin oxime (IIa) with *p*-toluenesulfonyl chloride at 50° afforded only 4-aza-*A*-homo-*cis*-tetrahydro-α-santonin (IIIa). No other isomeric products were found by tlc or by ir spectral examination of the mother liquor after separation of IIIa. This indicates that the cis-fused tetrahydro-α-santonin oxime (IIa) has the *E* configuration (anti form) (Chart I).

The oxime from *trans*-4β-tetrahydro-α-santonin oxime (IIb), mp 199–202°, showed two spots on tlc at R_f 0.36 and 0.26 (1:4 ratio). The oxime from *trans*-4α-tetrahydro-α-santonin oxime (IIc), mp 221–225°, showed two spots with the same R_f value of 0.36 and 0.26 but in a different ratio (5:1). Mixture melting point determination of these trans oximes (IIb and IIc) showed a depression. Therefore, the trans-fused tetrahydro-α-santonin oximes (IIb and IIc) are two different syn–anti mixtures, with IIb having the 4β configuration (H-4, δ 3.60 ppm) and IIc having the 4α configuration (H-4, δ 2.46 ppm).[4] This was further confirmed by the observed ratio of Beckmann rearrangement products. Although IIb and IIc did not react under the conditions described for IIIa, they did react with thionyl chloride in dioxane at 70° (Chart II).

The product of the Beckmann rearrangement of *trans*-4β-oxime (IIb) showed two spots on tlc (R_f 0.43 and 0.24, chloroform–methanol). The product from IIb was chromatographed on silica gel and yielded a 4-aza lactam (IIIb, R_f 0.43) and a 3-aza lactam (IIIc, R_f 0.24) in a ratio of 2:3. On the other hand, the Beckmann rearrangement product of *trans*-4α-oxime (IIc) gave a mixture of 4-aza lactam (IIIb) and 3-aza lactam (IIIc) in the ratio of 2:1.

The Schmidt reaction of *cis*-tetrahydro-α-santonin (Ia) produced 4-aza-*A*-homo-*cis*-tetrahydro-α-santonin (IIIa) in good yield, while *trans*-4α-tetrahydro-α-santonin (Ic) gave 4-aza-*A*-homo-*trans*-tetrahydro-α-santonin (IIIb) in 40% yield. These lactams were identical with those obtained from the Beckmann rearrangement.

The stereochemistry of the Beckmann rearrangement products (IIIa, b, and c) was confirmed by analysis of their nmr spectra. In the case of 4-aza-*A*-homo-*cis*-tetrahydro-α-santonin (IIIa), a doublet at δ 5.99 ppm (J = 4.5 Hz) could be assigned to the amide hydrogen. The angle between the amide hydrogen and H-5 should be approximately 53° (a)[5] from the Karplus equation.[6] When the amide hydrogen was irradiated, the multiplet (1 H) at 3.76 ppm changed to a double quartet ($J_{5,14}$ = 6.7 and $J_{5,6}$ = 9.0 Hz), and could therefore be attributed to the H-5. Irradiation of the H-7 at 4.36 ppm (1 H, dd, $J_{7,6}$ = 4.3 and $J_{7,8}$ = 11.0

(1) S. D. Levine, *J. Org. Chem.*, **35**, 1064 (1970).

(2) K. Oka and S. Hara, *Chem. Ind. (London)*, 168 (1969).

(3) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955); M. Yanagita and H. Ogura, *ibid.*, **22**, 1092 (1957).

(4) H. Saito, I. Terasawa, M. Ohno, and K. Nukada, *J. Amer. Chem. Soc.*, **91**, 6696 (1969).

(5) In this case, a value of the vicinal coupling constant was obtained by parameters in the equations

$$J = 6.6\cos^2\phi + 2.6\sin^2\phi \quad (0° \leq \phi \leq 90°)$$

$$J = 11.6\cos^2\phi + 2.6\sin^2\phi \quad (90° \leq \phi \leq 180°)$$

[E. W. Garbish, *J. Amer. Chem. Soc.*, **86**, 5561 (1964)].

(6) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, p 280.

CHART I

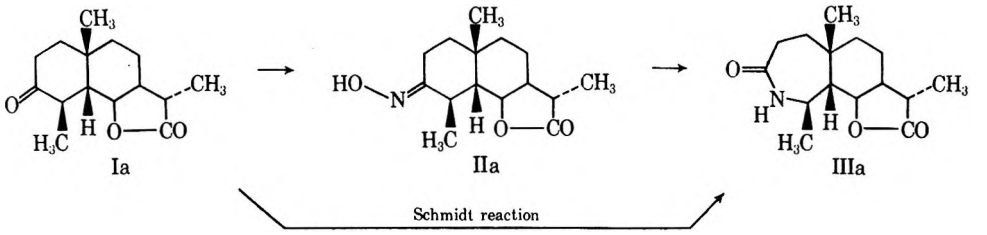


CHART II

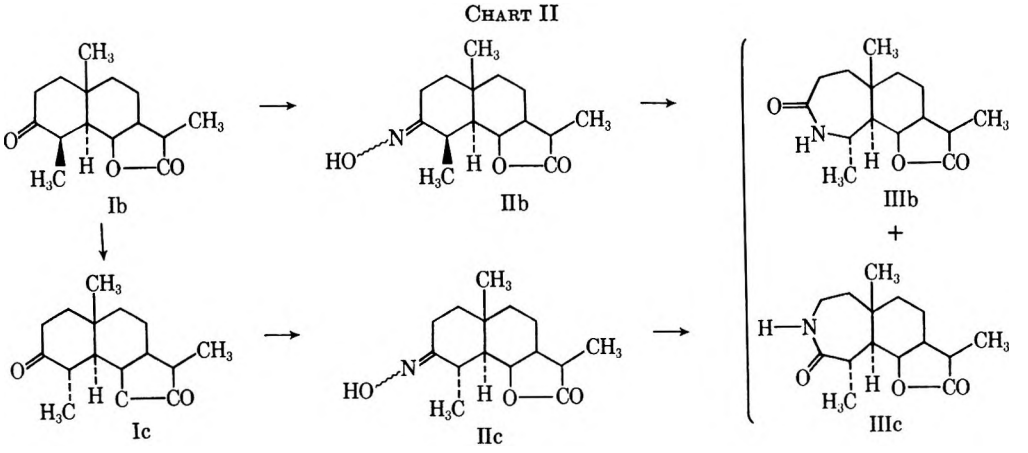
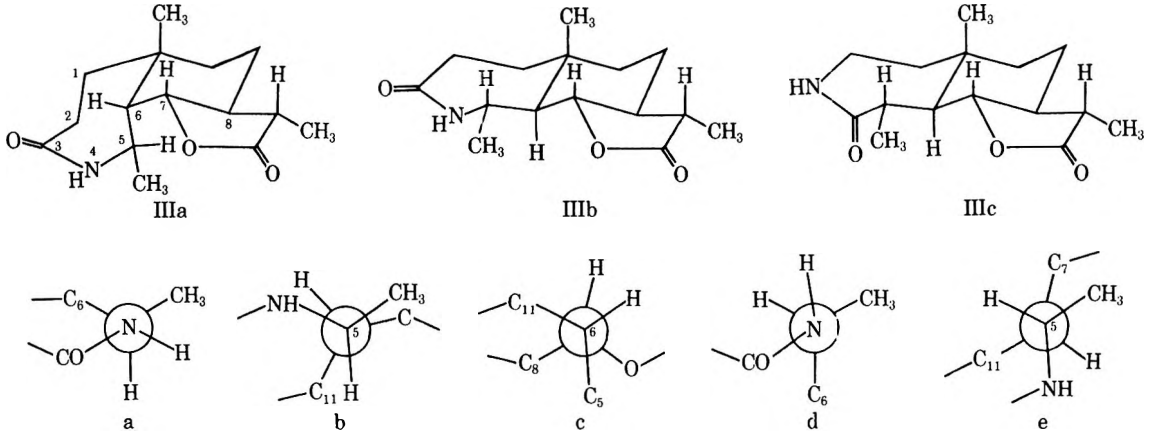


CHART III



Hz) resulted in simplification of a signal at 2.05 ppm (dd, $J_{6,7}$ = 4.3 and $J_{6,5}$ = 9.0 Hz) to a doublet (J = 9.0 Hz); hence the proton at 2.05 ppm was assigned to H-6 whose coupling to H-5 (J = 9.0 Hz) indicated a trans configuration (b). On the other hand, the value of $J_{6,7}$ = 4.3 Hz suggested a cis relationship between H-6 and H-7 (c)[6] (Chart III).

The stereochemistry of 4-aza-*A*-homo-*trans*-tetrahydro-α-santonin (IIIb) was also confirmed by nmr measurements. A doublet at 5.97 ppm (J = 4.0 Hz) was assigned to an amide hydrogen; the relationship of the amide and H-5 hydrogen is therefore as shown in d. Irradiation of the amide hydrogen changed a multiplet (2 H) at 3.75 ppm. This showed that one proton in this multiplet is H-5. Irradiation of H-5 resulted in collapse of the amide hydrogen resonance (5.97 ppm) and a methyl doublet at 1.35 ppm to singlets. Moreover, on double decoupling of the amide hydrogen (5.97 ppm) and the C-5 methyl, the band at 3.75 ppm changed to a doublet ($J_{5,6}$ = 6.5 Hz) and a double doublet (J = 7.0 and 11.5 Hz, H-7). This shows that the C-5 methyl group occupies the quasi-equatorial configuration. By analogy with the H-6,-H-7 and the H-7,H-8 splitting in the cis compound (IIIa), the splitting of 7.0 Hz was assigned to the coupling between H-6 and H-7, and the splitting of 11.0 Hz to that between H-7 and H-8. Values near 11 Hz are generally characteristic for $J_{7,8}$ in the santonin series (α-santonin 9.0 Hz, β-santonin 10.9 Hz, artemisin 11.6 Hz).[7] On the basis of these results, the conformation of N–C_5–C_6 is considered to be that shown in d and e (Chart III).

In the case of 3-aza-*A*-homo-*trans*-tetrahydro-α-santonin (IIIc), a triplet at 6.74 ppm (J = 5.3 Hz) was attributed to the amide hydrogen and a band of 2.83 ppm (multiplet) was attributed to the H-5. This was confirmed by the change in the band at 2.83 ppm on addition of deuterium oxide. When the H-5 was irradiated, a methyl doublet at 1.27 ppm (J = 7.4 Hz) changed to a singlet; decoupling at 1.27 ppm changed the band at 2.83 ppm to a doublet (J = 8.0 Hz).

Decoupling of the band at 1.57 ppm (m) in deuter-

(7) J. T. Pinhey and S. Sternhell, *Aust. J. Chem.*, **18**, 543 (1965).

ated IIIc changed the H-2 signal to a quartet and the double doublet at 3.86 ppm to a doublet (J = 8.6 Hz). From these results, the band at 3.86 ppm was assigned to H-7, and a multiplet at 1.57 ppm to H-2 (J_{gem} = −15.2 Hz). In conclusion, configuration and conformational structures of these lactams (IIIa,b,c) are shown in Chart III.

Experimental Section

All melting points are uncorrected. Optical rotations were measured in a 0.1-dm tube with a JASCO automatic polarimeter DIP-SL, unless otherwise noted. Nmr spectra were recorded in deuteriochloroform at 100 MHz with a Varian Associate H-100 spectrometer and tetramethylsilane was used as an internal reference. Mass spectra were taken with a Japan Electron Optics JMS-01S high-resolution spectrometer with a direct inlet system.

cis-**Tetrahydro-α-santonin Oxime (IIa).**—To a solution of hydroxylamine hydrochloride (1.0 g) in ethanol (5 ml) and pyridine (5 ml) was added 1.0 g of *cis*-tetrahydro-α-santonin (Ia) and the resulting solution was warmed under reflux for 3 hr. After evaporation of organic solvents under a reduced pressure, ice water was added and white crystals precipitated. Recrystallization from methanol afforded IIa in 80–90% yield as colorless prisms: mp 175°; ir ν_{max}^{Nujol} 3230 (OH), 1670 cm^{-1} (C=N); $[\alpha]^{26}D$ −30.0° (*c* 1.8, EtOH), −12.0° (*c* 1.5, $CHCl_3$).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.81; H, 8.87; N, 5.07.

trans-4β-**Tetrahydro-α-santonin Oxime (IIb).**—4β-Tetrahydro-α-santonin (Ib) was treated in the same manner as for IIa. Recrystallization from benzene gave *trans*-4β-oxime (IIb) in 70% yield as colorless plates: mp 199–202°; $[\alpha]^{20}D$ −9.1° (*c* 1.0, $CHCl_3$); tlc R_f 0.26 and 0.36 (4:1) in benzene–acetone (5:1); ir ν_{max}^{KBr} 3320 (OH), 1655 cm^{-1} (C=N); nmr (DMSO-d_6) δ 3.60 ppm (m, 1, H-4).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.63; H, 8.72; N, 5.14.

A mixture melting point with *trans*-4α-oxime (IIc, mp 219–224°) was depressed to 174–182°.

trans-4α-**Tetrahydro-α-santonin Oxime (IIc).**—4α-Tetrahydro-α-santonin (Ic) was treated in the same way as IIa. Recrystallization from methanol–water gave *trans*-4α-oxime (IIc) in 80% yield as colorless plates: mp 221–225° dec; $[\alpha]^{20}D$ −29.9° (*c* 1.0, $CHCl_3$); tlc R_f 0.26 and 0.36 (1:5) in benzene–acetone (5:1); ir ν_{max}^{KBr} 3440 (OH), 1635 cm^{-1} (C=N); nmr (DMSO-d_6) δ 2.46 ppm (m, 1, H-4).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.76; H, 8.64; N, 5.11.

Beckmann Rearrangement of *cis*-**Tetrahydro-α-santonin Oxime (IIa).**—A solution of IIa (1.0 g) and *p*-toluenesulfonyl chloride (1.0 g) in pyridine (6 ml) was warmed on a water bath at 50° for 1 hr. After evaporation of pyridine under reduced pressure, the resulting residue was treated with ice water and extracted with chloroform. Evaporation of the dried chloroform solution and recrystallization of the residue from methanol afforded 4-aza-*A*-homo-*cis*-tetrahydro-α-santonin (IIIa) in 76% yield as colorless prisms: mp 222°; $[\alpha]^{25}D$ +27.5° (*c* 1.5, $CHCl_3$); ir ν_{max}^{Nujol} 3200, 3070 (NH), 1763 (lactone), 1679 cm^{-1} (C=O); nmr δ 5.99 (d, 1, J = 4.5 Hz, NH), 4.36 (dd, 1, $J_{7,6}$ = 4.3, $J_{7,8}$ = 11.0 Hz, H-7), 3.76 (m, 1, $J_{5,4}$ = 4.5, $J_{5,6}$ = 9.0, $J_{5,\text{C-5 CH}_3}$ = 6.7 Hz, H-5), 2.05 (dd, 1, $J_{6,5}$ = 9.0, $J_{6,7}$ = 4.3 Hz, H-6), 1.24 (d, 3, J = 6.7 Hz, C-5 CH_3), 1.23 (d, 3, J = 6.75 Hz, C-12 CH_3), 1.16 ppm (s, 3, C-11 CH_3); mass m/e 265 (M^+).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28; mol wt, 265.169. Found: C, 68.06; H, 8.90; N, 5.20; mol wt, 265.167.

Beckmann Rearrangement of *trans*-4β-**Tetrahydro-α-santonin Oxime (IIb).**—To the warmed (70°) solution of *trans*-4β-oxime (1.0 g) in dioxane (20 ml), thionyl chloride (0.6 ml) was added dropwise during 20 min with stirring. After standing at room temperature for 30 min the reaction mixture was neutralized with sodium bicarbonate solution and then extracted with chloroform. The chloroform solution was dried and evaporated under reduced pressure. The residue was treated with methyl acetate and gave a crude lactam (IIIb + IIIc) in 30% yield, tlc R_f 0.24 and 0.43 (2:3) in chloroform–methanol (10:1). This crude lactam was chromatographed on silica gel and eluted with benzene–chloroform (3:2).

From the first eluate **4-aza-*A*-homo-*trans*-tetrahydro-α-santonin (IIIb)** was obtained as colorless plates from benzene: mp 214–218°; $[\alpha]^{24}D$ −3.92° (*c* 0.9, $CHCl_3$); ir ν_{max}^{KBr} 3240, 3090 (NH), 1770 (lactone), 1675 cm^{-1} (C=O); nmr δ 5.97 (d, 1, J = 4.0 Hz, NH), 3.75 (m, 1, $J_{5,4}$ = 4.0 Hz, $J_{5,\text{C-5 CH}_3}$ = 6.9, $J_{5,6}$ = 6.5 Hz, H-5), 3.75 (dd, 1, $J_{7,6}$ = 7.0, $J_{7,8}$ = 11.0 Hz, H-7), 2.18 (dd, 1, $J_{6,5}$ = 6.5, $J_{6,7}$ = 7.0 Hz, H-6), 1.35 (d, 3, J = 6.9 Hz, C-5 CH_3), 1.20 (d, 3, J = 6.75 Hz, C-12 CH_3), 1.09 ppm (s, 3, C-11 CH_3); mass m/e 265 (M^+).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28; mol wt, 265.169. Found: C, 67.95; H, 8.63; N, 5.13; mol wt, 265.167.

From the second eluate, **3-aza-*A*-homo-*trans*-tetrahydro-α-santonin (IIIc)** was obtained as colorless plates from benzene: mp 211–213°; $[\alpha]^{23}D$ +10.9° (*c* 1.0, $CHCl_3$); ir ν_{max}^{KBr} 3570, 3440, 3310 (NH), 1770 (lactone), 1655 cm^{-1} (C=O); nmr δ 6.74 (t, 1, J = 5.3 Hz, NH), 3.86 (dd 1, $J_{7,6}$ = 8.6, $J_{7,8}$ = 11.0 Hz, H-7), 2.83 (m, 1, J_5, C-5 CH_3 = 7.4, $J_{5,6}$ = 8.0 Hz, H-5), 2.25 (dd, 1, $J_{6,5}$ = 8.0, $J_{6,7}$ = 8.6 Hz, H-6), 1.27 (d, 3, J = 7.4 Hz, C-5 CH_3), 1.17 (d, 3, J = 7.0 Hz, C-12 CH_3), 1.14 ppm (s, 3, C-11 CH_3); mass m/e 265 (M^+).

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28; mol wt, 265.169. Found: C, 67.62; H, 8.73; N, 5.11; mol wt, 265.167.

Schmidt Reaction of *cis*-**Tetrahydro-α-santonin (Ia).**—To a cooled solution of Ia (1.0 g) in chloroform (6 ml) was added dropwise concentrated sulfuric acid (2 ml), and then sodium azide (0.55 g) was added during 30 min at −10° with stirring. After stirring for 30 min at room temperature, the reaction mixture was allowed to stand overnight at room temperature. Crushed ice was added to the reaction mixture, which was neutralized with sodium carbonate and extracted with chloroform. Evaporation of dried chloroform solution left 4-aza-*cis*-lactam (IIIa) in 85% yield, mp 220°, $[\alpha]^{21}D$ +23.8° (*c* 1.0, EtOH), which was identified with the product (IIIa) of Beckmann rearrangement by comparison of their ir spectra and by mixture melting point determination.

Schmidt Reaction of *trans*-4α-**Tetrahydro-α-santonin (Ic).**—Ic (1.0 g) was treated in the same manner as Ia. Recrystallization from methanol gave 4-aza-*A*-homo-*trans*-tetrahydro-α-santonin (IIIb) in 40% yield, mp 228–229°, $[\alpha]^{23}D$ −5.0° (*c* 1.0, $CHCl_3$), which was identified with a sample described above in the Beckmann rearrangement, 4-aza compound IIIb, by comparison of their ir spectra and by mixture melting point determination.

Registry No.—IIa, 32979-73-0; IIb, 32979-74-1; IIc, 32979-75-2; IIIa, 32979-76-3; IIIb, 32979-77-4; IIIc, 32979-78-5.

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Hydrogenolysis of Mixed Ketals of Norcamphor by Dichloroalane

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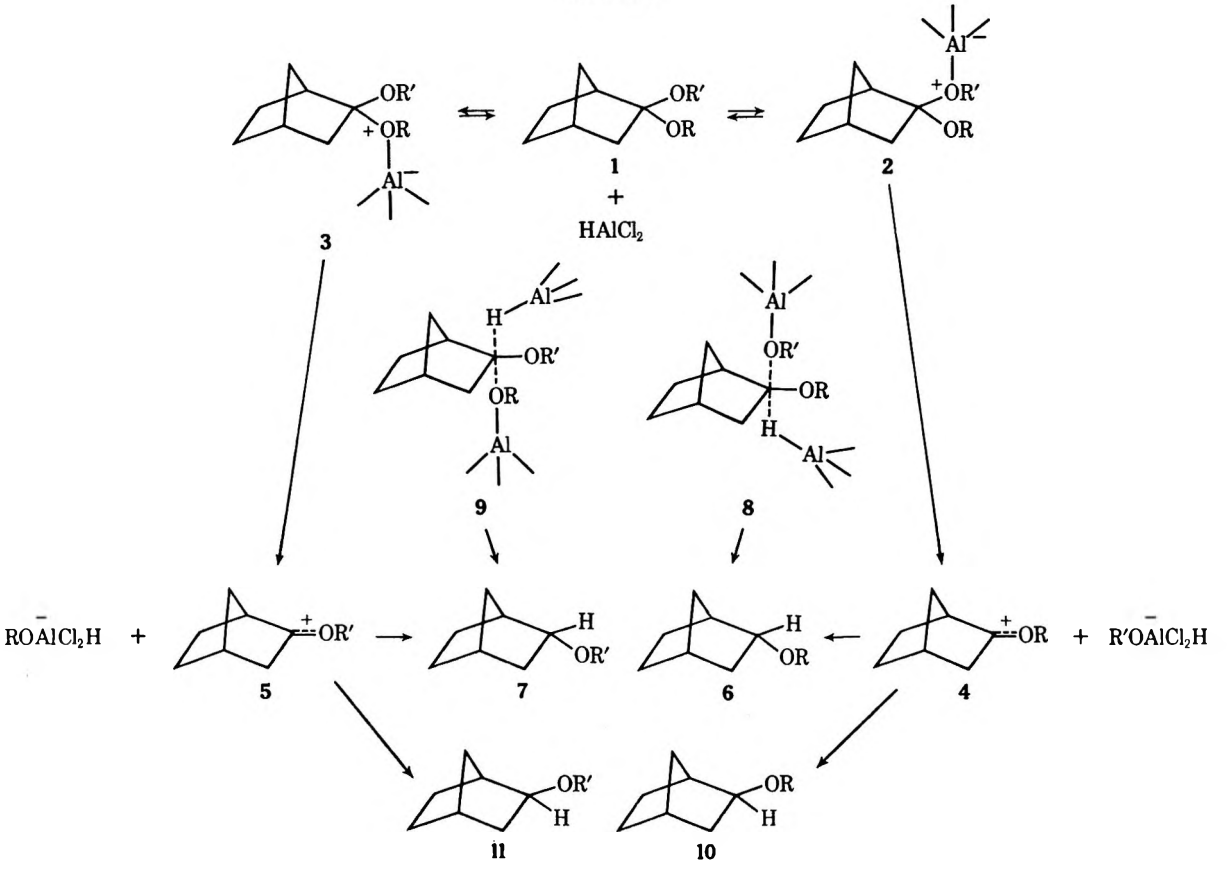
Hydrogenolysis of ketals by "mixed hydrides" ($LiAlH_4$–$AlCl_3$) gives ethers as the products. Studies on the hydrogenolysis of 4-substituted 1,3-dioxolanes,[1] a steroidal propylene ketal,[2] and 2-substituted tetra-

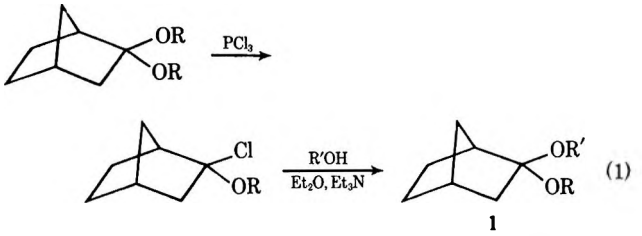
(1) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **42**, 990 (1964).
(2) M. S. Ahmad and S. C. Logani, *Aust. J. Chem.*, **24**, 143 (1971).

SCHEME I



hydropyranyl and tetrahydrofuranyl ethers[3,4] have shown that the product which results from the more inductively stabilized oxocarbonium ion intermediate usually predominates. From the data obtained on the hydrogenolysis of cycloalkanone dimethyl ketals[5] it has been suggested that in the medium ring sizes (8–12) there is a steric hindrance, due to transannular repulsion, to the formation of a ketal–dichloroalane complex, which is the first step of the hydrogenolysis reaction. Recent evidence has led to the suggestion that ortho esters[6] and one of the two isomeric norcamphor isobutylene ketals[7] are hydrogenolyzed by back-side attack of a hydride. In an effort to better understand the steric and electronic conditions which control the mechanism of hydrogenolysis, we have synthesized a series of mixed ketals of norcamphor and subjected these compounds to hydrogenolysis by dichloroalane.

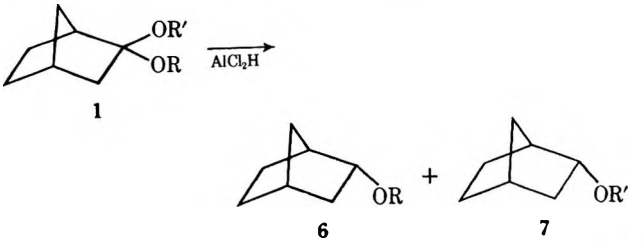
The mixed ketals are synthesized from the dimethyl, diethyl, and diisopropyl ketals of norcamphor, respectively. When these starting ketals are allowed to react with PCl_3, the corresponding 2-chloronorbornyl ethers are formed. When the chloro ethers are allowed to react with an alcohol and an organic base in a nonpolar medium, they are converted to the mixed ketals (eq 1). The addition of the alcohol is from the exo side, giving a mixed ketal (**1**) of high isomeric purity. The



(1)

mixed ketals synthesized and their hydrogenolysis products, the ethers, are tabulated in Table I.

TABLE I
HYDROGENOLYSIS OF MIXED KETALS OF NORCAMPHOR BY A 1:3 MIXTURE OF LiAlH–$AlCl_3$ IN ETHER AT ROOM TEMPERATURE



Compd	R	R′	Compd	R	Yield, %	Compd	R′	Yield, %
1a	CH_3	CD_3	**6a**	CH_3	67	**7a**	CD_3	33
1b	CH_3	Et	**6b**	CH_3	20	**7b**	Et	80
1c	CH_3	*i*-Pr	**6c**	CH_3	2	**7c**	*i*-Pr	98
1d	CH_3	*tert*-Bu	**6d**	CH_3	8	**7d**	*tert*-Bu	83[a]
1e	Et	CH_3	**6e**	Et	86	**7e**	CH_3	14
1f	*i*-Pr	CH_3	**6f**	*i*-Pr	99	**7f**	CH_3	1

[a] 9% *endo*-norborneol also isolated.

All the ethers produced by the hydrogenolysis of the mixed ketals were identified as endo ethers (Scheme I, **6** and **7**). The norbornyl ethyl ether from nor-

(3) E. L. Eliel, B. E. Nowak, R. A. Daignault, and V. G. Badding, *J. Org. Chem.*, **30**, 2441 (1965).
(4) U. E. Diner and R. K. Brown, *Can. J. Chem.*, **45**, 2547 (1967).
(5) W. W. Zajac, Jr., and K. J. Byrne, *J. Org. Chem.*, **35**, 3375 (1970).
(6) S. S. Bhattacharjee and P. A. J. Gorin, *Can. J. Chem.*, **47**, 1195 (1969).
(7) P. C. Loewen, W. W. Zajac, Jr., and R. K. Brown, *ibid.*, **47**, 4059 (1969).

TABLE II
PROPERTIES OF MIXED KETALS

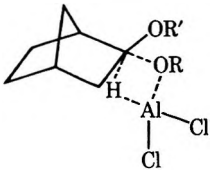
Mixed ketal	Bp, °C (mm)	Isomeric purity,[a] %	Calcd, % C	Calcd, % H	Found, % C	Found, % H	Nmr (CCl_4),[b] cps, CH_3O
1a[c]	84–86 (30)	94					186.0
1b	103–104 (40)	97	70.55	10.66	70.33	10.60	186.4
1c	112–114 (40)	97	71.70	10.94	71.76	10.96	189.3
1d	89–90 (8.6)	99	72.68	11.18	72.60	10.92	188.4
1e	78–80 (13)	97	70.55	10.66	70.74	10.78	184.6
1f	104–108 (40)	90	71.70	10.94	71.92	11.09	187.0

[a] The isomeric purity was determined by the integration of the methoxyl signals in the nmr. [b] Positions are given downfield of TMS. The relative positions were determined in mixtures of these compounds. The positions for the endo and exo methoxyls of norcamphor dimethyl ketal are 186.0 and 184.4 cps, respectively. [c] The molecular ion peak is 159, by mass spectroscopy.

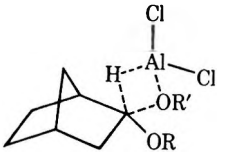
camphor *exo*-ethyl *endo*-methyl ketal (**1b**) and norcamphor *endo*-ethyl *exo*-methyl ketal (**1e**) and the norbornyl methyl ether from all the ketals had ir and nmr identical with those of the unequivocally synthesized endo ethers. The norbornyl isopropyl and *tert*-butyl ether produced by the hydrogenolysis of norcamphor *endo*-methyl *exo*-isopropyl ketal (**1c**), and norcamphor *exo*-methyl *endo*-isopropyl ketal (**1f**), and norcamphor *exo*-*tert*-butyl *endo*-methyl ketal (**1d**), respectively, are assigned as the endo isomers on the basis of their nmr spectra. The C-2 hydrogen of the norbornyl system is a multiplet centered around 185 and 195 ppm for the methyl and ethyl exo ethers and 215 and 220 ppm for the two endo ethers. The norbornyl isopropyl and *tert*-butyl ethers have a C-2 hydrogen signal centered around 230 ppm. Furthermore, the nmr spectra of *exo*-norbornyl methyl and ethyl ethers show that the chemical shifts of the C-1 and C-4 hydrogens are similar and give rise to a single complicated multiplet. For the endo ethers the same two hydrogens are sufficiently different to give rise to two adjacent complicated multiplets. The spectra published by Loewen, *et al.*,[7] show a similar behavior of the tertiary hydrogens of some endo and exo norbornyl ethers. Both the norbornyl isopropyl and *tert*-butyl ethers have two adjacent complicated multiplets for the C-1 and C-4 hydrogens which agree with the endo assignment. Furthermore, the norborneol which was produced during hydrogenolysis of **1d** was the endo alcohol and could only arise by the further hydrogenolysis of *endo*-norbornyl *tert*-butyl ether. A similar hydrogenolysis of a tertiary *exo*-norbornyl ether has been reported to give *exo*-norborneol.[7] The hydrogenolysis of norcamphor *endo*-methyl *exo*-methyl-d_3 ketal (**1a**) gave only one glpc peak, which was examined by mass spectroscopy to determine the ratio of products. *endo*-Norbornyl methyl ether has a molecular ion peak of 126. *endo*-Norbornyl methyl-d_3 ether with a molecular peak of 129 is easily determined. The results obtained by integrating the methoxyl group against the C-2 hydrogen downfield and against all the other hydrogens upfield together were in close agreement with the mass spectral analysis of the hydrogenolysis reaction mixture.

The hydrogenolysis of norcamphor dimethyl ketal is known to give 95% *endo*-methyl ether and 5% *exo*-methyl ether.[8] Other reactions[8-10] of the norbornyl system where C-2 is sp^2 hybridized in the rate-controlling step show high selectivity for approach from the exo side. The results of the hydrogenolysis of **1a** (Scheme I, R = CH_3; R′ = CD_3) indicate that even one atom removed from C-2 the approach to form the complexes (**2** and **3**), which are the first steps in the hydrogenolysis, is easier from the exo side because the deuterated methoxyl is lost to the extent of 67%. For the ethyl methyl ketals (**1b**, R = CH_3; R′ = Et) (**1e**, R = Et; R′ = CH_3) the methoxyl group is lost to the extent of 86% when it is exo and 80% when it is endo. For the methyl isopropyl ketals (**1c**, R = CH_3; R′ = *i*-Pr) (**1f**, R = *i*-Pr; R′ = CH_3) the methoxyl group is lost to the extent of 99% when it is exo and 98% when it is endo. This is in agreement with the principle that the more inductively stabilized oxocarbonium ion (**4** and **5**) will predominate. Clearly the stabilizing abilities of the alkoxyl groups are *tert*-BuO > *i*-Pro > EtO > MeO, whereas the ease of complexation is in the opposite order. Along with the electronic effects, then, part of the observed trend is undoubtedly due to the ease of complexing the methoxy group whether it is in an exo or endo position.

It has been suggested that hydrogenolysis can proceed through a four-center transition state resulting in net retention of configuration.[7] In this case a four-center transition state such as **12** or **13** would be required. Transition state **12** is clearly ruled out by the results since no exo ethers (**10**, **11**) are observed as products.



12



13

Furthermore, it would not be consistent to invoke a four-center transition state (**13**) to account for the endo ethers **6a–d** from the ketals **1a–d** and at the same time to invoke an oxocarbonium ion **5** to account for the other endo ether products **7a–d** resulting from hydrogenolysis of the same ketals **1a–d**.

The results of this investigation can be uniformly explained as arising from the attack of dichloroalane from the least hindered side (exo) on an intermediate oxocarbonium ion which can be formed by the decomposition of a ketal complexed with either the exo or endo alkoxy group (see Scheme I, paths **1** → **3** → **5** → **7** and **1** → **2** → **4** → **6**).

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(8) T. G. Traylor and C. L. Perrin, *J. Amer. Chem. Soc.*, **88**, 4934 (1966).
(9) E. L. Eliel and D. Nasipuri, *J. Org. Chem.*, **30**, 3809 (1965).
(10) W. W. Zajac, Jr., B. Rhee, and R. K. Brown, *Can. J. Chem.*, **44**, 1547 (1966).

Mass spectra were obtained through the courtesy of Dr. J. F. Siuda, University of Pittsburgh.

Analytical glpc was carried out on an F and M Model 700 using a 0.25 in. × 6 ft 10% Carbowax column. Preparative glpc was done on a 0.50 in. × 12 ft 10% SE-30 column. The percentage yields reported correspond to peak area. Nmr spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as an internal standard.

Glassware used in the handling of the mixed ketals was washed with dilute sodium hydroxide and oven dried.

exo-Norbornyl methyl ether and ethyl *exo*-norbornyl ether were prepared by the acid-catalyzed addition of methanol and ethanol, respectively, to norbornene.[11] *endo*-Norbornyl methyl ether and *endo*-norbornyl ethyl ether were prepared by the reaction of *endo*-norborneol[12] and sodium hydride in dimethoxyethane with methyl iodide and ethyl iodide, respectively.

Starting Ketals.—The dimethyl, diethyl, and diisopropyl ketals of norcamphor are most easily prepared by the acid-catalyzed reaction of norcamphor and trimethyl orthoformate, triethyl orthoformate, and triisopropyl orthoformate,[13] respectively, in the appropriate alcohol. The reaction of triisopropyl orthoformate and norcamphor was followed by the appearance of the formate hydrogen and the disappearance of the orthoformate hydrogen in the nmr. The equilibrium mixture has about one-third conversion to the product.

2-Chloronorbornyl Ethers.—The preparative procedure was to add the starting norcamphor ketal to a 5% molar excess of PCl_3 which is stirring in an ice bath. The ice bath was removed and the mixture was stirred for 1.5 hr. The mixture was distilled using an oil bath which was kept below 65°. Fractionation was accomplished by reducing the pressure of the distillation. The receiving flask was in an ice–calcium chloride slurry, and the pump was protected by a Dry Ice–acetone trap and a liquid nitrogen trap. Yields were high and free of starting ketals, but norcamphor, which appears to be a thermal decomposition product, accounts for *ca.* 10% of the products.

Mixed Ketals.—The preparation of norcamphor *exo*-ethyl *endo*-methyl ketal (**1b**) is representative and is given here. To 4.60 g (100 mmol) of ethanol, 20 ml of triethylamine, and 100 ml of diethyl ether mechanically stirred in an ice bath, 11.0 g (68 mmol) of 2-chloronorbornyl methyl ether in 20 ml of diethyl ether was added over 10 min. A thick white precipitate of triethylamine hydrochloride formed. The ice bath was removed and after 15 min 80 ml of 10% sodium carbonate was added. The ether layer was separated and washed twice with 20 ml of water. The ether was dried ($CaSO_4$), concentrated, and distilled.

When the alcohol being added was isopropyl alcohol, and particularly *tert*-butyl alcohol, a larger excess of alcohol was necessary to minimize the dehydrohalogenation product, norbornenyl methyl ether.

Distillation through a vacuum-jacketed column typically gave yields of 60–70%. Physical data for the mixed ketals is tabulated in Table II.

endo-Norbornyl isopropyl ether was collected by glpc from the hydrogenolysis reaction. *Anal.* Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.70; H, 11.62.

endo-Norbornyl *tert*-butyl ether was collected by glpc from the hydrogenolysis reaction. *Anal.* Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.39; H, 11.90.

Hydrogenolysis of Mixed Ketals.—After 0.12 g of $LiAlH_4$ had refluxed for 1 hr in 20 ml of diethyl ether, the solution was added to a solution of 1.20 g of $AlCl_3$ and 15 ml of ether in an ice bath. This yields 12.0 mmol of dichloroalane, which is stirred for 0.5 hr without the ice bath. Then 6.29 mmol of a mixed ketal (1.00 g of 1a, 1.07 g of 1b and 1e, 1.16 g of 1c and 1f, and 1.25 g of 1d) in 5 ml of ether was added over 5 min. After 10 min of stirring 20% NaOH was added until the ether was clear and the aluminum salts were precipitated. The products were determined by glpc and all products were collected by preparative glpc. Retention times, ir spectra, and nmr spectra were obtained for all products. A mass spectrum was obtained for the hydrogenolysis product of 1a.

(11) S. J. Cristol, W. K. Seifert, D. W. Johnson, and J. B. Jutale, *J. Amer. Chem. Soc.*, **84**, 3918 (1962).

(12) H. C. Brown and H. R. Deck, *ibid.*, **87**, 5620 (1965).

(13) Prepared by the distillation of methanol from an acid-catalyzed trimethyl orthoformate and isopropyl alcohol mixture. Dynamitnoble A.-G., Netherlands Appl. 6,500,507; *Chem. Abstr.*, **64**, 601g (1966).

Registry No.—**1a**, 33016-02-3; **1b**, 33016-03-4; **1c**, 33016-04-5; **1d**, 33016-05-6; **1e**, 33068-14-3; **1f**, 33016-06-7; **6f**, 33016-07-8; **7d**, 33016-08-9; $AlCl_2H$, 13497-97-7.

On the Mechanism of the Reaction of 1-*tert*-Butyl-3-azetidinyl Tosylate with Methanolic Potassium Cyanide and with Solvent[1]

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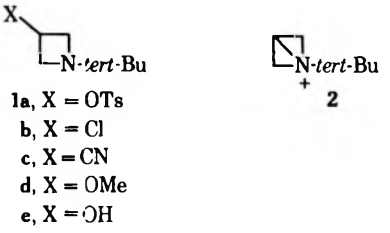
Received August 6, 1971

Recently Chen, *et al.*, described the synthesis[2] and some reactions[2,3] of 1-*tert*-butyl-3-azetidinyl tosylate (**1a**). Deyrup and Moyer[4] have determined the solvolysis rate of **1a** in ethanol and concluded that **1a** underwent assisted ionization, probably by transannular nitrogen participation forming intermediate **2**. A similar conclusion was drawn by Gaertner,[5] who studied the solvolysis of **1b** in 50% aqueous ethanol.



1a, X = OTs
b, X = Cl
c, X = CN
d, X = OMe
e, X = OH

2

As a continuation of our studies[6] of the reactions of functionally substituted azetidines, we have reexamined the solvolysis reactions of **1a**, since previous studies[4,5] have not clearly demonstrated the importance (or lack thereof) of direct nucleophilic attack on the substrate by solvent, nor have previous rate data been sufficiently precise for computation of activation parameters, which might be compared with those of the solvolysis reactions of cyclobutyl tosylates.

Results and Discussion

If it could be shown that the rate of the reaction of **1a** with nucleophiles, which are more nucleophilic than solvent, were independent of the concentration of nucleophile (and first order in substrate), it could safely be deduced that direct nucleophilic displacement of tosylate by the poorer nucleophile, solvent, was unimportant. Furthermore, except for a small "salt

(1) Presented in part at the 80th Annual Meeting of the Nebraska Academy of Sciences, Lincoln, Nebraska, April 1970.

(2) T.-Y. Chen, T. Sanjiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Jap.*, **40**, 2401 (1967).

(3) T.-Y. Chen, H. Kato, and M. Ohta, *ibid.*, **41**, 712 (1968).

(4) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968).

(5) V. R. Gaertner, *J. Org. Chem.*, **35**, 3952 (1970).

(6) See, for example, (a) E. Doomes and N. H. Cromwell, *J. Heterocycl. Chem.*, **6**, 153 (1969); (b) *J. Org. Chem.*, **34**, 319 (1969); (c) R. M. Rodebaugh and N. H. Cromwell, *J. Heterocycl. Chem.*, **6**, 439 (1969); (d) **8**, 19 (1971).

effect," the first-order rate constant (k_1) for the reaction of **1a** with nucleophile should be identical with the rate of solvolysis of **1a** in the same solvent.

We chose to follow the reaction of **1a** with methanolic potassium cyanide.[2] This nucleophile and solvent were chosen because the resulting nitrile[2] has been shown to be a useful intermediate in the preparation of 3-aroylazetidines[6a,7,8] and 1-*tert*-butylazetidine-3-carboxylic acid.[2]

The reaction of **1a** with methanolic potassium cyanide yielded **1c** (determined by glc and pmr analysis of crude product); however, small quantities of **1d** and an unidentified substance were formed when the reaction mixture was injected into the glc before the reaction was complete.

The reaction of **1a** with methanolic potassium cyanide at 30° was found to be too rapid for accurate determination of cyanide ion (by titrating aliquots of the reaction mixture with silver nitrate, Liebig determination). Consequently, the reaction was followed at 0°. First-order and second-order rate constants were calculated for this reaction; see Table I. These data are

TABLE I

RATE CONSTANTS[a] CALCULATED FOR THE REACTION OF **1a** WITH METHANOLIC POTASSIUM CYANIDE AT 0°

$[\mathbf{1a}]^a \times 10^2$	$[CN^-]^b \times 10^2$	k_1,[c] sec^{-1}	k_2,[d] l. mol^{-1} sec^{-1}
7.579	7.574	8.13×10^{-7}	1.51×10^{-5}
7.579	10.08	8.80×10^{-7}	0.94×10^{-5}
5.001	7.595	8.35×10^{-7}	1.16×10^{-5}

[a] Single determinations. [b] In mol/l. [c] For rate = $k_1[\mathbf{1a}]$. [d] For rate = $k_2[\mathbf{1a}][CN^-]$.

clearly much more consistent with the unimolecular reaction than with the bimolecular reaction, thus supporting an ionic intermediate as was assumed by Gaertner[5] and Deyrup and Moyer.[4]

It appeared advisable to determine the relative basicities of **1a** and the products arising from solvolysis of **1a** under the conditions of the solvolysis reaction, such that appropriate corrections could be made, if necessary, in the rate equation for protonated **1a**. The solvolysis products are substantially better bases than **1a**, indicating that the concentration of protonated **1a** is always relatively low. Furthermore, the relative basicities are reasonably independent of temperature (see Table II).

TABLE II

RELATIVE BASICITIES OF **1a** AND THE SOLVOLYSIS PRODUCTS

Temp, °C	Solvent	(K_a of **1a**/ K_a of **1d**)[a,b]	(K_a of **1a**/ K_a of **1e**)[b,c]
25	Methanol	63.5	
	60% Aqueous acetone		863
36.2	Methanol	48	
	60% Aqueous acetone		851

[a] Obtained as the antilog of differences in pK_a's of **1d** and **1a**. [b] See Experimental Section for the methods of pK_a determination. [c] Obtained as the antilog of differences in pK_a's of **1e** and **1a**.

Methanolysis of **1a**, both in the absence of and in the presence of a tenfold excess of triethylamine, yielded

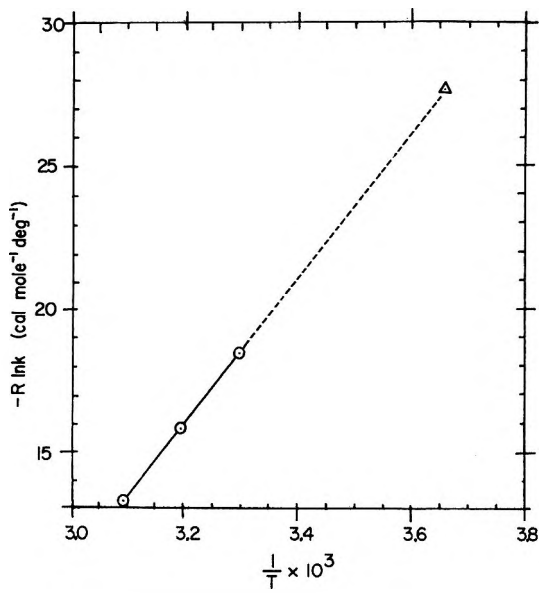


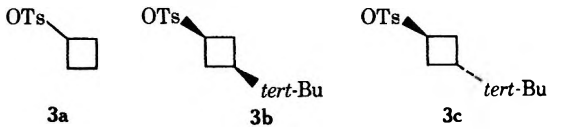
Figure 1.—Activation plot for reactions in methanol: ⊙, for solvolysis reactions; △, for reaction with methanolic potassium cyanide.

only **1d** (by pmr and glc); no ring contraction[5,9] or ring-opened[8] products were observed. Furthermore, no enhancement of the rate of methanolysis was observed in the presence of triethylamine; rate enhancement would be anticipated if the reaction involved direct displacement of tosylate.

The rate of methanolysis of **1a**, at 30°, is in reasonable agreement with the qualitative estimate (6×10^{-5} sec^{-1}, see above) of the rate of the reaction of **1a** with methanolic potassium cyanide. Indeed the data for the reaction of **1a** with methanolic potassium cyanide at 0° fall on the extrapolation of the line in the activation plot (see Figure 1) for the methanolysis reaction. We feel that these facts are indicative of the similarity in rates and presumably intermediates for these reactions.

The data in Table III result from application of the simple first-order rate law (rate = $k_1[\mathbf{1a}]$). The similarity in the rates of methanolysis with and without the presence of added amine indicate that the rate expression is adequately represented by the simple first-order rate law.

The hydrolysis of **1a** in aqueous acetone gave **1e** as the only product (by glc). The data for the hydrolysis in 60% aqueous acetone may be compared with those reported[10] for cyclobutyl tosylates (**3a–c**). A moderate



3a **3b** **3c**

increase in the hydrolysis rate of the heterocyclic tosylate relative to **3a**[10] or **3c**[10] (a large increase relative to **3b**[10]) is apparent. In view of the rather large uncertainty in $\Delta H^{\pm}$ in our investigation, it is not possible to quantitatively compare the activation parameters (or their significance) for the solvolysis reactions of **1a** and **3a–c** in 60% aqueous acetone. However, it is apparent that the enthalpies of activation for the

(7) R. H. H., Ph.D. Dissertation, University of Nebraska, Lincoln, Nebraska, 1971.

(8) R. H. Higgins, E. Doomes, and N. H. Cromwell, *J. Heterocycl. Chem.*, in press.

(9) V. R. Gaertner, *Tetrahedron Lett.*, 5919 (1968).

(10) P. v. R. Schleyer, P. Le Perches, and D. J. Raber, *ibid.*, 4389 (1969).

TABLE III
MEAN CONDUCTIMETRIC SOLVOLYSIS RATES OF 1-*tert*-BUTYL-3-AZETIDINYL TOSYLATE

Solvent	Temp, °C	Rate, sec^{-1}	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
MeOH	30.0	$(9.09 \pm 0.39) \times 10^{-5}$		
MeOH + Et_3N[a]	30.0	$(9.00 \pm 0.17) \times 10^{-5}$	25.3 ± 1	6.3[b]
	40.0	$(3.38 \pm 0.03) \times 10^{-4}$		
	50.0	$(1.29 \pm 0.07) \times 10^{-3}$		
50% aqueous acetone	15.0	$(4.88 \pm 0.10) \times 10^{-5}$	22.8 ± 0.5	0.8
	30.0	$(3.61 \pm 0.08) \times 10^{-4}$		
	45.5	$(2.42 \pm 0.05) \times 10^{-3}$		
60% aqueous acetone	15.0	$(3.49 \pm 0.14) \times 10^{-5}$	22.05 ± 1	2.2[b]
	30.0	$(2.69 \pm 0.11) \times 10^{-4}$		
	45.5	$(1.55 \pm 0.03) \times 10^{-3}$		

[a] Contains a tenfold excess of triethylamine. [b] In view of the rather large variance in $\Delta H^{\pm}$, $\Delta S^{\pm}$ is probably valid to only ± 3 eu.

solvolyses of the carbocyclic (**3a,b**) and heterocyclic (**1a**) tosylates are very similar in 60% aqueous acetone, and that the rate increase observed in the solvolysis of **1a** relative to **3a–c** is primarily due to $\Delta S^{\pm}$.

It is interesting that the enthalpies of activation for these tosylates compare so favorably. The enthalpy of activation for the solvolysis of **1a** may be the result of a delicate balance of inductive electron withdrawal from the cationic site by the nitrogen atom and stabilization of the cation by charge dispersal to the nitrogen atom by anchimeric assistance.[11] It seems fortuitous that $\Delta H^{\pm}$ for the solvolysis of **1a** and of **3a** or **3b** are identical, within experimental error, particularly in view of the uncertainty[12] surrounding the nature of the intermediate in the solvolysis of cyclobutyl tosylates.

The large values of $\Delta S^{\pm}$ observed in the solvolysis reactions of **1a** may be interpreted as additional support for an ionic intermediate.[13] Indeed, one is tempted to argue that the value of $\Delta S^{\pm}$ (in 60% aqueous acetone), relative to **3a–c**, is indicative of the significance of anchimeric assistance[14] by the nitrogen atom *in the transition state* involved in the solvolysis of **1a**.

The effects of substitution of C-2 on the solvolysis rates and product distribution are presently being pursued. The results of this study may give a more definitive insight into the nature of the N–C-3 bond.

Experimental Section

1-*tert*-Butyl-3-azetidinyl Tosylate (1a).—The synthesis of this compound has been described.[8]

Absolute Methanol.—Commercial absolute methanol was further dried by distillation from magnesium methoxide.[15]

Relative Basicities.—Absolute pK_a values were not determined (the null point of the pH meter being arbitrarily set at 7.07 and 7.00 for solvent at 25 and 36.25°, respectively).

The "basicity constants" of **1d** (in methanol) and **1e** (in 60% aqueous acetone) were determined by recording the "pH" of a solution of the azetidine while hydrogen chloride, in the appropriate solvent, was added at constant rate. The "pK_a" is the "pH" at the half-equivalence point.

The "basicity" constants of **1a** were determined by dissolving 1 equiv of **1a** in a solution of the appropriate solvent containing 0.5 equiv of anhydrous *p*-toluenesulfonic acid and immediately determining the "pH."

Method of Determining Remaining Cyanide.—Aliquots (5 ml) of the methanolic reaction mixture were added to *ca.* 30 ml of ice water. The resulting solution was covered with *ca.* 10 ml of ether and titrated with 0.05–0.1 *N* silver nitrate solutions (the volumes being recorded to 0.001 ml). The reaction with cyanide was followed through *ca.* one half-life; the solvolysis reactions were followed for 4–10 half-lives.

Registry No.—**1a**, 17358-65-5; methanol, 67-56-1; potassium cyanide, 151-50-8; acetone, 67-64-1; triethylamine, 121-44-8.

Acknowledgments.—The authors wish to thank Mr. Gary M. Underwood for the use of his computer program for determining solvolysis rates and Dr. C. A. Kingsbury for his valuable discussions and suggestions. This research was supported in part by Grant CA-02931 from the National Cancer Institute of the United States Public Health Service and by the University of Nebraska Damon Runyon Memorial Fund for Cancer Research.

(11) We have no evidence for participation of nonclassical ions in the solvolysis of **1a**.

(12) See, for example, R. H. Mazur, W. N. White, D. A. Semenov, C. C. Lee, M. S. Silver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **81**, 4390 (1959); R. E. Davis and A. Ohno, *Tetrahedron*, 2063 (1968).

(13) E. F. Jenny and S. Winstein, *Helv. Chim. Acta*, **41**, 807 (1958); S. Winstein and R. Heck, *J. Amer. Chem. Soc.*, **78**, 4801 (1956); D. J. Cram, *ibid.*, **86**, 3767 (1964).

(14) Anchimeric assistance, *via* phenonium ions, seems to increase the value of $\Delta S^{\pm}$. See the data of C. J. Kim and H. C. Brown, *ibid.*, **91**, 4287 (1969); **91**, 4289 (1969); C. J. Lancelot and P. v. R. Schleyer, *ibid.*, **91**, 4291 (1969).

(15) A. I. Vogel, "A Text-Book of Practical Organic Chemistry, 3rd ed, Wiley, New York, N. Y., 1957, p 169.

C-Alkylation of Active Methylene Compounds by Means of Alcohols. VII.[1] Synthesis of α-Substituted Phenylacetonitriles from α-Phenylacetoacetonitrile

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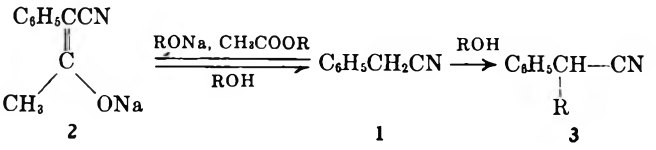
Received July 2, 1971

In a preceding paper of this series we have reported that phenylacetonitrile **1** is readily alkylated by means of four to five times the calculated amount of alcohols in the presence of metallic sodium and appropriate ester to give α-substituted phenylacetonitrile **3**. Having demonstrated that the alkylation proceeds *via* α-phenylacetoacetonitrile sodium salt **2** (Scheme I, **1** → **2** → **1** → **3**), we now wished to study the possibility that the reaction starting with **2** might be of general application for the preparation of α-substituted phenylacetonitrile **3**. By simply heating a mixture of **2** and alcohol, a series of α-substituted phenylacetonitrile

(1) Paper VI: S. Miyano and N. Abe, *J. Org. Chem.*, **36**, 2948 (1971).

(2) To whom inquiries should be sent.

SCHEME I



was obtained in excellent yields and this route of preparation is now established.

As compared with the previous method[1] the procedure was thus simplified considerably, since the use of sodium and appropriate acetic ester was not required.

Our results are summarized in Tables I and II. Obviously 2 underwent alcoholysis to give 1 which, in turn, was alkylated to give 3 as a final product.

TABLE I

ALKYLATION BY LOWER ALIPHATIC AND ALICYCLIC ALCOHOLS (PROCEDURE A)

Expt	Registry no.	Alcohol	Product: Bp (18 mm) or mp, °C	Product: Yield, %[a]
1	769-68-6	Ethyl	120–123	62.1
2	5558-78-1	*n*-Propyl	132–135	76.1
3	3508-98-3	*n*-Butyl	140–145	79.2
4	5558-31-6	Isobutyl	134–138	78.0
5	5558-33-8	*n*-Amyl	149–154	81.8
6	5558-34-9	Isoamyl	143–149	79.7
7[b]	3753-59-1	Cyclopentyl	44–45[c]	33.5
8[b]	3893-23-0	Cyclohexyl	54–56[d]	47.2

[a] Based on phenylacetoacetonitrile sodium salt 2. [b] Heated at 230–240° for 2 hr. [c] A fraction boiling at 125–135° (2 mm) solidified on cooling, and was recrystallized from petroleum ether (bp 30–60°) as colorless needles, literature mp 50°: G. Vasiliu, V. Pumitorescu, and H. Valcan, *Bul. Soc. Chim. Romania Stiinte, Bul. Stiinte Fiz.*, **2**, 3A, 54 (1941). *Anal.* Calcd for $C_{13}H_{15}N$: C, 84.28; H, 8.16; N, 7.56. Found: C, 84.29; H, 8.23; N, 7.42. [d] Colorless needles from petroleum ether.

In the alkylations with lower alcohols (from ethyl to amyl) the procedure consists in heating the reaction mixture at 210–220° in an autoclave for 1 hr (procedure A). Yields are slightly improved over those of the method starting with phenylacetonitrile (Table I). However, in the alkylations with secondary alcohols such as isopropyl, *sec*-butyl, cyclopentyl, and cyclohexyl alcohols the products were contaminated with α-alkylidenephenylacetonitrile, which is an intermediate in the alkylation sequence,[1] and isolation by fractional distillation proved difficult. Only α-cyclopentylphenylacetonitrile and cyclohexylphenylacetonitrile, which can be crystallized out from the distillate, were secured.

With higher alcohols (higher than *n*-heptyl) that do not require an autoclave the procedure is extremely simple: when a mixed slurry of 2 and 1.5 times the calculated amount of alcohol was maintained at 210° for a few minutes a vigorous reaction was induced and the subsequent heating brought the overall reaction into completion in a surprisingly short period, approximately 30 min (procedure B). Yields are excellent and comparable to those of the previous method (Table II).

Alkylations with *n*-hexyl and 2-ethylhexyl alcohols are two exceptions: 30-min heating of the reactants failed, only starting nitrile being recovered, presumably because of the low boiling point of the former and steric hindrance involved in the latter, respectively.

TABLE II

ALKYLATION BY HIGHER ALIPHATIC AND ARALKYL ALCOHOLS (PROCEDURE B)

Expt	Registry no.	R	Product: Bp (2 mm) or mp, °C	Product: Yield, %[a]
9[b]	5558-35-0	*n*-Hexyl	127–130	70.6
10	5558-36-1	*n*-Heptyl	138–145	69.8
11	15601-30-6	*n*-Octyl	147–151	82.1
12[b]	17178-81-3	2-Ethylhexyl	136–141	70.5
13	17179-16-7	*n*-Nonyl	151–162	79.0
14	30889-57-7	3,5,5-Trimethylhexyl	140–144	75.7
15	17179-17-8	*n*-Decyl	174–180	74.7
16	17179-18-9	Lauryl	191–194	71.6
17	3333-14-0	Benzyl	56–57[c,d]	62.8
18	32970-77-7	4-Methylbenzyl	58–59[c,e]	67.0
19	32970-78-8	4-Anisyl	86–87[c,f]	54.0
20	32970-79-9	4-Chlorobenzyl	109.5–110.5[c,g]	67.9
21	32970-47-1	3,4-Dimethoxybenzyl	94–95.5[c,h]	59.2
22		3,4-Methylenedioxybenzyl	73–74[c,i]	32.7
23	6443-81-8	3-Phenyl-1-propyl	76–77[c,j]	70.6

[a] Based on phenylacetoacetonitrile sodium salt 2. [b] Since the alkylation failed according to procedure B, a mixture of 0.1 mol of phenylacetoacetonitrile sodium salt and 0.3 mol of alcohol was heated for 3 hr. [c] Melting point. [d] Colorless needles (from ethanol). [e] Colorless platelets (from methanol), literature mp 58°: M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **80**, 493 (1958). *Anal.* Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.50; H, 6.86; N, 6.52. [f] Colorless platelets (from ethanol), literature mp 86–87°: H. Lettré, W. Haede, and L. Schäfer, *Hoppe-Seyler's Z. Physiol. Chem.*, **289**, 298 (1952). *Anal.* Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.92; H, 6.29; N, 5.96. [g] Colorless platelets (from ethanol), literature mp 113–114°: M. Avramoff and Y. Sprinzak, *J. Amer. Chem. Soc.*, **80**, 493 (1958). *Anal.* Calcd for $C_{15}H_{12}NCl$: C, 74.53; H, 5.00; N, 5.80. Found: C, 74.85; H, 5.19; N, 5.54. [h] Colorless needles (from methanol), literature mp 98°: P. C. Jocelyn, *J. Chem. Soc.*, 1640 (1954). *Anal.* Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 75.98; H, 6.22; N, 5.34. [i] Colorless prisms (from methanol). No depression of melting point on admixture with authentic sample was observed. [j] Colorless prisms (from methanol), literature mp 79°: W. Borsche, *Ber.*, **45**, 624 (1912). *Anal.* Calcd for $C_{17}H_{17}N$: C, 86.77; H, 7.28; N, 5.95. Found: C, 86.38; H, 7.18; N, 6.01.

However, satisfactory results were obtained when the amount of alcohol was doubled and the reaction period was extended to 3 hr (Table II, expt 9 and 12). According to procedure B alkylations by means of a series of aralkyl alcohols were also successfully achieved (Table II).

In view of the fact that the previous method[1] becomes less attractive for large-scale operation due to the quantities of alcohol that must be employed, it is noteworthy that smaller amount of alcohols; *i.e.*, 1.5 and 3 times the calculated amount of alcohol in alkylations with higher alcohols (procedure B) and with lower alcohols (procedure A), respectively, is required as compared with 4–5 times the calculated amount in the previous method.

Since phenylacetoacetonitrile sodium salt 2 can be readily prepared by condensation between phenylacetonitrile and ethyl acetate in the presence of sodium ethoxide[3] and shows good shelf stability, the present method offers advantage sufficient to compensate for time and cost of producing 2. Thus, the described procedure features low price of the reagents employed and very simple manipulation, and is possibly the most convenient method for the preparation of α-substituted phenylacetonitriles.

(3) P. L. Julian, J. J. Oliver, R. H. Kimball, A. B. Pike, and G. D. Jefferson, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1957, p 487.

Experimental Section

Alkylation with Lower Aliphatic and Alicyclic Alcohols (Procedure A) (Table I, Experiment 1–8).—A mixture of 0.1 mol of **2** and 0.3 mol of alcohol was heated with stirring in an autoclave at 210–220° for 1 hr. Water was added to the content of the autoclave, the resulting suspension was stirred, and the upper clear layer was removed by decantation from the precipitated sodium acetate hydrate. Removal of excess alcohol and ether by distillation gave light brown residual oil which was dissolved in ether. The ethereal solution was washed with several portions of water until the solution became clear, and the ethereal layer was dried (K_2CO_3), concentrated, and distilled, giving α-alkyl phenylacetonitrile.

Akylation with Higher Aliphatic Alcohols (Procedure B), (Table II, Experiment 9–16).—A mixed slurry of 0.05 mol of **2** and 0.075 mol of alcohol was heated at 210° for a few minutes when a vigorous reaction started. This was heated at 210–220° for 30 min. After cooling, water was added to the brownish-yellow cake, the resulting oily layer was extracted with ether, and the ethereal layer was washed with water, dried (K_2CO_3), concentrated, and distilled, giving α-alkylphenylacetonitrile.

Alkylation with Aralkyl Alcohols (Procedure B) (Table II, Experiment 17–23).—A mixed slurry of 0.05 mol of **2** and 0.075 mol of aralkyl alcohol was heated at 200–210° for 20 min. After cooling, water was added to the brownish-yellow cake. The resulting oily layer was extracted with ether, and the ethereal layer was washed with water, dried (K_2CO_3), concentrated, and distilled, giving α-aralkylphenylacetonitrile. The product, which solidified on cooling, was recrystallized from methanol or ethanol. In two cases, expt 20 and 21, crude products were directly obtained as crystals when water was added to the mixture after the reaction was complete.

Registry No.—**2**, 32970-68-6.

Proton Magnetic Resonance and Chemical Evidence for Stereospecificity in the Reaction of *cis*- and *trans*-1-Phenyl-4-*tert*-butylcyclohexanol with HCl. Proton Magnetic Resonance Analysis of the Reaction of Several Substituted 1-Arylcyclohexyl Systems with HCl and FSO_3H–SbF_5–SO_2

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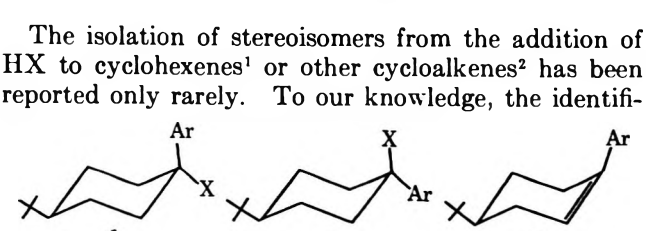
The isolation of stereoisomers from the addition of HX to cyclohexenes[1] or other cycloalkenes[2] has been reported only rarely. To our knowledge, the identification and isolation of similar stereoisomers from substituted cyclohexanols has not been recorded. We selected alcohols *cis*-**1a**, *cis*-**1b**, *trans*-**2a**, and *trans*-**2b** for the study with HCl since the stereomeric chlorides *cis*-**1c** and *trans*-**2c** have been characterized.[1]



	X	Ar
a	OH	C_6H_5
b	OH	p-$CH_3OC_6H_4$
c	Cl	C_6H_5
d	Cl	p-$CH_3OC_6H_4$

a, Ar = C_6H_5

b, Ar = p-$CH_3OC_6H_4$

We have now found that alcohols *cis*-**1a** and *trans*-**2a**[3] react in a stereospecific fashion with HCl(g). Suspended in anhydrous pentane at −30° under N_2, *cis*-**1a** was treated with anhydrous HCl(g) and gave (after 45 min) a ratio of 3.67:1 for the chlorides *cis*-**1c**:*trans*-**2c** as measured from peak areas for the corresponding *tert*-butyl protons (δ 0.74 and 0.92, respectively) in the pmr spectrum of the reaction mixture. These peaks are clearly separated in $DCCl_3$ at 50-Hz sweep width. The complete disappearance of a signal for the proton on oxygen suggested a nearly quantitative conversion of

$$\textit{cis}\text{-}\mathbf{1a} + HCl \xrightarrow[-30°]{\text{pentane}} \underset{(78.6\%)}{\textit{cis}\text{-}\mathbf{1c}} + \underset{(21.4\%)}{\textit{trans}\text{-}\mathbf{2c}}$$

$$\textit{trans}\text{-}\mathbf{2a} + HCl \xrightarrow[-30°]{\text{pentane}} \underset{(19.4\%)}{\textit{cis}\text{-}\mathbf{1c}} + \underset{(80.6\%)}{\textit{trans}\text{-}\mathbf{2c}}$$

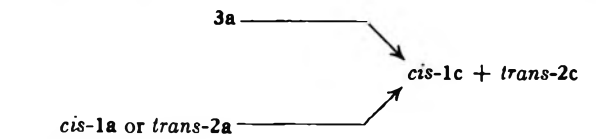
alcohol *cis*-**1a**. The overall phenomenon is surprising in view of the predominance of the chloride *cis*-**2c** at short reaction times (*ca.* 15 min) when **3a** was treated with HCl at −70°.[1] A check on the reaction of *cis*-**1a** at −70° after 45 min did *not* reveal a significant change in the ratio of products (Table I). In contrast, if **3a** was allowed to react with HCl for 45 min, no starting material could be detected in the mixture by pmr, and *cis*-**1c**:*trans*-**2c** was 1.0:2.06. Since the ratio *cis*-**1a**:**3a** in the two separate experiments was only 1.3:1, these above data can be compared, all other reaction conditions being identical. It should be noted (Table I), of course, that there is a dependence of [*cis*-**1c**]:[*trans*-**2c**] upon the initial concentration of **3a** as expected for the same period of time. A similar dependence upon rate of addition of HCl to **3a** was reported.[1]

TABLE I

Compd	Temp, °C	*cis*-**1c**, %	*trans*-**2c**, %	Time, min
cis-**1a** (alcohol)	−30	78.6	21.4	45
(0.0017 mol)[a]	−70	78.6	21.4	45
trans-**2a** (alcohol)	−30	19.4	80.6	45
(0.0022 mol)[a]	−70	28.2	71.8	45
3a (alkene)	−70	48.6	20.5	15[b]
(0.0013 mol)[a]	−70	32.3	67.7	45
3a (alkene)	−70	79.1	20.9	15
(0.0037 mol)[a]	−70	71.8	28.2	45

[a] Per 100 ml of *n*-pentane. [b] Unreacted **3a** detected was 30.9%.

It appears that no common intermediate is formed from the reaction of HCl with either **3a** *or* **1a** *(or* **2a***) in pentane at −70°.* Therefore the mechanisms differ. To our knowledge, this is the first report of the reaction of HCl

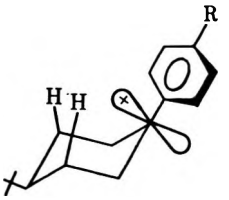


(1) K. D. Berlin, R. O. Lyerla, D. E. Gibbs, and J. P. Devlin, *Chem. Commun.*, 1246 (1970).

(2) P. K. Freeman, F. A. Raymond, and M. F. Raymond, *J. Org. Chem.*, **32**, 24 (1967).

(3) The alcohols were of purity greater than 99.5% by glc analysis. Although the preparation [E. W. Garbisch, Jr., and D. B. Patterson, *J. Amer. Chem. Soc.*, **85**, 3228 (1963)] and purification technique [G. D. Meakins, R. K. Percy, E. E. Richards, and R. N. Young, *J. Chem. Soc. C*, 1106 (1968)] are reported, modification of procedures afforded more pure products in a simpler process; see R. O. Lyerla, Ph.D. Dissertation, Oklahoma State University, 1970.

with epimeric cyclohexanols to give the corresponding epimeric chlorocyclohexanes predominantly with retention of configuration. It is interesting to note that reduction of either *cis*-**1a** or *trans*-**2a** with several silanes has been observed to give the same *cis*:*trans* ratio of hydrocarbons regardless of alcohol used.[4] A common carbonium ion intermediate **4a** was postulated.[4]

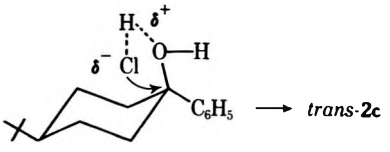


4a, R = H
b, R = OCH_3

In our work this conclusion is untenable in view of the data cited. Interestingly, we *do not* obtain the cis chloride **1c** as the major product from trans alcohol **2a** under conditions comparable (Table I) to the identical reaction of cis alcohol **1a** with HCl. Consequently, a

ion pair

reasonable explanation for retention of configuration may involve ion pairs as shown with *cis*-**1a** → *cis*-**1c** or *via* a type of SNi mechanism as illustrated.



To determine if the stereospecificity of the reactions was preferred under classical ionic conditions, alcohol *trans*-**2a** in hexane was shaken with concentrated HCl at 25° for 5 min. The mixture, *via* pmr analysis, showed *trans*-**2c** (67%) and *cis*-**1c** (33%). However, *cis*-**1a** under identical conditions gave *cis*-**1c** (45%) and *trans*-**2c** (55%). If these reactions are initially stereospecific, isomerization of the chloride *cis*-**1c** to *trans*-**2c** occurs rapidly at 25°. This is in agreement with previous findings[1] that chloride *trans*-**2c** is the thermodynamically more stable isomer. Most interesting was the observation that no alkene **3a** could be detected in either reaction mixture from alcohols *cis*-**1a** or *trans*-**2a**. Under the same conditions at 25°, 1-phenylcyclohexanol gave only 1-phenylcyclohexene. However, it was found that at −10 to 0°, 1-phenylcyclohexanol was converted to 1-chloro-1-phenylcyclohexane (**5**) in a yield of 93% (estimated by pmr). These very fast reactions apparently do not differ in rate strictly because of stability differences in the products, since 1-chloro-1-phenylcyclohexane is unchanged under these conditions at 25°. Also, alkene **3a** and 1-phenylcyclohexene are *not* precursors since they are recovered quantitatively when subjected to the described conditions at 25°. At first glance these results might suggest that the *tert*-butyl group influences the stability of the intermediate formed in conversion of the alcohols *cis*-**1a** and *trans*-**2a** to the respective chlorides under classical ionic conditions at 25°. Differences in partitioning of the individual alcohols between the two phases could explain the results. However, a check of the solubility of the alcohols in water indicates that both are very poorly soluble (estimated <1% at room temperature). Also, since alkenes are not precursors in these reactions, a reasonable interpretation is that ion pairs are involved or an SNi mechanism is operative.

On the assumption that a powerful electron-donating group on the arene might lead to increased stability of the intermediate **4b**, *cis*- (**1b**) and *trans*-1-(*p*-methoxyphenyl)-4-*tert*-butylcyclohexanol (**2b**) were prepared and characterized. Alkene **3b** was obtained *via* dehydration of a mixture of *cis*-**1b** and *trans*-**2b**. At −70° in pentane, **3b** or *cis*-**1b** or *trans*-**2b** and HCl(g) (after 45 min) gave the same ratio of **3b**:*cis*-**1d**:*trans*-**2d**[5] which averaged 5.6:1:7.5. In fact, this apparent equilibrium mixture was observed after 15 min. A small increase in *trans*-**2b**:**3b** was noted as the flow rate of HCl increased. Possibly a common intermediate is formed but this cannot be substantiated in view of the rapid formation of the equilibrium mixture.

When alcohol *cis*-**1a** was added to a mixture of FSO_3H–SbF_5–SO_2 (Olah's solvent) and cooled to −70°, a red solution resulted. Pmr analysis showed a strong singlet at δ 0.67 for *tert*-butyl protons plus the other absorptions already described for this system. Similarly, alcohol *trans*-**2a** gave an almost identical spectrum except for signals at δ 0.70 (*tert*-butyl protons) and at δ 0.95 at −70°. The signal at δ 0.95 disappeared rather quickly while the spectrum was recorded at −60° with no other apparent change in signal shapes or positions. Conceivably, the alcohol *trans*-**2a** was not completely ionized (signal for *tert*-butyl protons in $DCCl_3$ is at δ 0.90 and may be shifted to δ 0.95 in Olah's solvent) or a cation is formed initially which rearranges to a cation with a signal at δ 0.70 for the *tert*-butyl protons. This latter cation from *trans*-**2a** essentially gives the same spectrum as was obtained from the alcohol *cis*-**2a** when dissolved in Olah's solvent and is probably **4a**. Although the extrapolation of these data to that from the addition of HCl to the alcohols is not justified, it is interesting that identical spectra from **1a** and **2a** are not immediately obtained in Olah's solvent. Solvation effects could be operative on the ease of protonation of either alcohol, solvation of the protonated form, or rate of loss of water. In any event, a conformational effect perhaps on some intermediate, such as the immediate cation precursor of **4b**, seems reasonable to explain the data in Olah's solvent.

Experimental Section

Pmr spectra were recorded on a Varian A-60 unit and checked on an HA-100 unit. Chemical shifts are relative to internal TMS. Infrared spectra were recorded on a Beckman IR-5A. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Alcohols **1a** and **2a** were prepared by the literature procedure and purified by chromatography over neutral alumina by the method of Meakins and coworkers.[3] Technical FSO_3H was from City Chemical Corp., New York, N. Y.,

(4) F. A. Carey and H. S. Tremper, *J. Amer. Chem. Soc.*, **90**, 2578 (1968).

(5) All attempts to obtain pure compounds **1d** and **2d** resulted in extensive elimination of HCl. Alkene **3b** was always present in samples as detected by pmr.

and anhydrous SbF_5 was from Research Organic/Inorganic Chemical Co., Sun Valley, Calif. [bp 149.5° (760 mm)]. Reagent grade pentane was dried over a molecular sieve before use. 4-*tert*-Butylcyclohexanone (mp 48–49°) was from International Flavors and Fragrances, Inc. 1-Phenylcyclohexanol[6] and 1-phenylcyclohexene[7] are known compounds.

Preparation of *cis*- (1b) and *trans*-4-*tert*-Butyl-1-(*p*-methoxyphenyl)cyclohexanol (2b).—The Grignard reagent of *p*-bromoanisole (10.0 g, 0.05 mol) was prepared in ether (2 ml) with 1.3 g (0.05 g-atom) of magnesium. 4-*tert*-Butylcyclohexanone (8.24 g, 0.05 mol) was added in ether (*ca.* 20 ml). After 2 hr at reflux, the mixture was decomposed with water (pH 7) to avoid dehydration which occurred at acid pH values. Ether–benzene extracts gave a solution of **1b** and **2b** in the ratio of 36.5:63.5 *via* pmr analysis of the signals for the *tert*-butyl protons. Removal of solvent gave a solid which was treated with *n*-pentane at −70° (two times). The solid, dried at 50° *in vacuo*, melted at 126–127°: yield 1.5 g (10.7%); ir (KBr) 3225 cm^{-1} (OH), 892 (para substitution); pmr ($DCCl_3$) δ 0.77 [s, $(CH_3)_3C$], 1.75 (s, OH), 2.50 (d, 2,6-equatorial ring H), 3.79 (s, CH_3O), and 7.13 (q, ArH). The other ring protons were in a broad signal at *ca.* δ 0.85–1.9.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.80; H, 9.99. Found: C, 77.82; H, 9.99.

The mother liquors from the recrystallizations with *n*-pentane were evaporated to a yellow solid. Dissolving it in low-boiling petroleum ether (bp 30–60°) gave a solution which was chromatographed (neutral alumina) with ether–petroleum ether. The trans alcohol **2b** was eluted with a solvent ratio of 1:19 of ether–petroleum ether (a small amount of cis alcohol **1b** was eluted when the ratio of solvents was 9:1). Purification of **2b** was by the same technique as for **1b**; yield of **2b** was 0.9 g (6.43%) mp 105–107°; ir (KBr) 3333 cm^{-1} (OH), 892 (para substitution); pmr ($DCCl_3$) δ 0.90 [s, $(CH_3)_3C$], 1.60 (s, OH), 3.78 (s, CH_3O), and 7.13 (q, ArH). Again the other ring protons were visible as a broad signal at δ 1.5–2.05, the 2,6-diequatorial protons not being separated in trans alcohol **2b** as in the spectrum of cis alcohol **1b**. Both **1b** and **2b** are hygroscopic but tend to form alkene when left in the atmosphere. An analytical sample of **2b** was obtained only if extreme care was exercised to avoid moisture.

Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.80; H, 9.99. Found: C, 78.18; H, 9.74.

4-*tert*-Butyl-1-(*p*-methoxyphenyl)cyclohexene (3b).—An equimolar mixture of alcohols **1b** and **2b** (5.0 g, 0.019 mol) was dehydrated with a freshly prepared mixture of 5 ml of concentrated H_2SO_4 and 20 ml of glacial CH_3CO_2H (the solution was magnetically stirred for 30 min).[8] A dark red, viscous solution resulted and was added to a mixture of ether–H_2O (100:200 ml). The organic layer was washed (H_2O followed by 10% K_2CO_3) and dried ($MgSO_4$). Removal of the solvent gave a solid which was extracted with *n*-pentane and purified (*n*-hexane): yield 3.8 g (82.6%); mp 77.5–78°; pmr ($DCCl_3$) δ 0.89 [s, $(CH_3)_3C$], 3.74 (s, CH_3), 6.00 (br s, C=CH), and 7.02 (q, ArH). Ring protons were visible in a broad signal at δ 1.2–2.5 for **3b**.

Anal. Calcd fo $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.64; H, 9.90.

Attempted Preparation of 1-Chloro-1-phenylcyclohexane (5).—Hydrogen chloride was bubbled into 1-phenylcyclohexene (3.0 g, 0.019 mol) in pentane (50 ml) at −78° for 1 hr. Distillation gave an oil which partially decomposed. Pmr analysis showed multiplets at δ 1.8 and 7.3 in the ratio of 2:1; $n^{27}D$ 1.5524. Attempted elemental analysis gave inferior results, apparently due to loss of HCl.

Anal. Calcd for $C_{12}H_{15}Cl$: C, 74.01; H, 7.77; Cl, 18.22. Found: C, 74.86; H, 7.51; Cl, 17.52.

For pmr analysis, pentane was simply stripped from the oil at 0.1 mm (25°). A small sample was dissolved in CCl_4. The sample of **5** was deemed relatively free of 1-phenylcyclohexene since the latter has a signal at δ 5.95 for a vinyl proton which was absent in the spectrum of **5**.

Addition of HCl(g) to the Alcohols. General Procedure.—The description given is for the addition of HCl(g) to *trans*-**2a** at −30°; this is quite typical of the procedures employed.

Hydrogen chloride (predried through molecular sieve, Linde grade 3A) was bubbled through a suspension of *trans*-2a (0.5 g, 0.002 mol) in 100 ml of dried *n*-pentane. A Dry Ice–95% ethanol bath maintained the temperature at −30° throughout the addition. Aliquots were removed for analysis at intervals. After 45 min, HCl addition was stopped, the pentane was removed *in vacuo* (aspirator), and the resulting white solid was dissolved in $DCCl_3$ for nmr analysis. Loss of the signal for OH (of *trans*-**2a**) at δ 1.83 and proper integration of the other proton signals demonstrated the essentially complete conversion of *trans*-**2a**. Authentic samples of *trans*-2c[1] and cis-1c[1] were used to confirm the identities of the isomers in the $DCCl_3$. The ratio of *trans*-2c to *cis*-1c was 80.6:19.4 after 45 min as obtained from peak area measurements for the *tert*-butyl protons (δ 0.92 for *trans*-**2c** and 0.74 for *cis*-**1c**).

Reaction of *trans*-4-*tert*-Butyl-1-phenylcyclohexanol (2a) with FSO_3H–SbF_5–SO_2 at −70°.—Samples of FSO_3H (1 g, 0.01 mol) and SbF_5 (2.17 g, 0.01 mol) were mixed in a quartz test tube with vigorous shaking.[9] To a separate quartz test tube was added 0.3 g (0.0013 mol) of **2a**. After cooling (ice), 1.5 ml of liquid SO_2 was pipetted into the tube forming a suspension with **2a**. The tube was then cooled to −70° with stirring.

The total acid solution (2.8 ml) was pipetted into the SO_2-suspended **2a** in three equal portions with vigorous stirring between additions. The dark red solution was added to an nmr tube which was cooled to −70°. Two peaks were discernable in the region for *tert*-butyl protons (δ 0.70 and 0.95) at −70° but one disappeared when the temperature was raised to −60° and did not reappear at the lower temperatures.

A similar experiment with **1a** gave essentially identical results.

Registry No.—*cis*-**1a**, 21024-55-5; *cis*-**1b**, 33066-12-5; *cis*-**1c**, 28140-27-4; *trans*-**2a**, 17807-26-0; *trans*-**2b**, 33066-15-8; *trans*-**2c**, 28140-28-5; **3b**, 33061-20-0; **5**, 29479-98-9; HCl, 7647-01-0; FHO_3S, 7789-21-1; F_5Sb, 7783-70-2; O_2S, 7446-09-5.

Acknowledgment.—We thank the Research Foundation of Oklahoma State University for partial support, Phillips Petroleum Company for a fellowship (R. O. L.), and N. D. E. A. (D. E. G.) for a fellowship.

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(7) R. C. Carlin and H. P. Landerl, *J. Amer. Chem. Soc.*, **75**, 3969 (1953).

(8) The dehydration procedure is similar to that used for the synthesis of **3a** by Garbisch and Patterson (ref 3).

(9) The general procedure used was very similar to that reported in the literature; see G. A. Olah, J. M. Bollinger, C. A. Cupas, and J. Lukas, *J. Amer. Chem. Soc.*, **89**, 2692 (1967).

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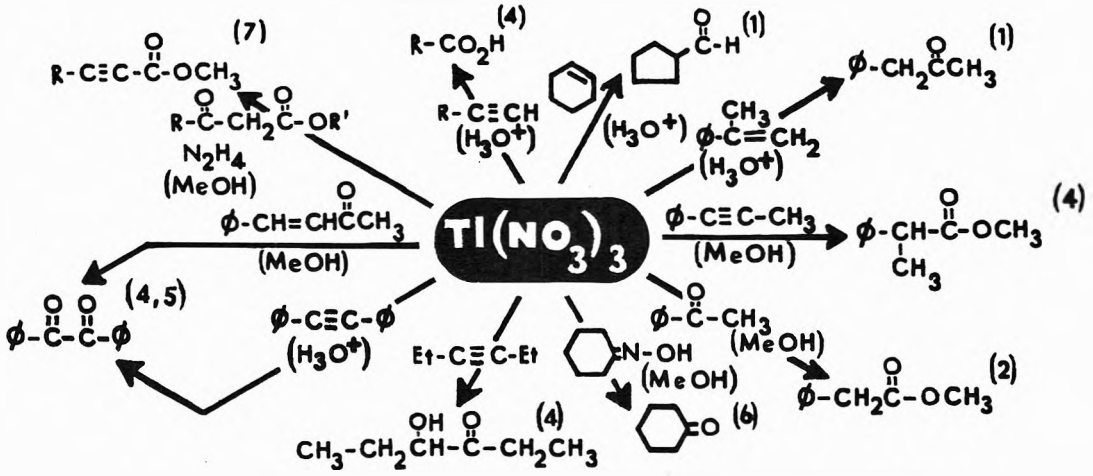

Analogous to oxymercuration, an olefin readily undergoes oxythallation[1] with TTN in methanol but gives a highly unstable thallium compound. The transition state in heterolysis of the C-Tl bond apparently approaches that of a carbonium ion for cyclic olefins and olefins bearing substituents with good migrating properties. The products are ketals and acetals, formed by a Wagner-Meerwein type rearrangement. Acidic workup gives **carbonyl compounds** in high yields. In straight chain olefins, such as 1-decene, participation by solvent in heterolysis increases and substituted glycols predominate. These reactions are completed within minutes at room temperature.

Acetophenones with TTN in acidic methanol undergo oxidative rearrangement[2] to methyl phenylacetates, products which can be obtained only tediously by the conventional Willgerodt-Kindler reaction. In contrast, this TTN reaction can be extended[3] to alkyl aryl ketones for the synthesis of **α-alkyl arylacetates.** The latter can also be prepared **in high yield** by the oxidative rearrangement[4] of arylalkylacetylenes with TTN in methanol.

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1. A. McKillop, J.D. Hunt, E.C. Taylor, and F. Kienzle, Tetrahedron Letters, 5275 (1970).
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